

DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

Report to Congress:

Pediatric Research in Fiscal Year 2017

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DEPARTMENT OF HEALTH AND HUMAN SERVICES
National Institutes of Health
Report to Congress:
The Fiscal Year 2017 Pediatric Research Initiative

TABLE OF CONTENTS

Table of Contents i

PEDIATRIC RESEARCH AT THE NATIONAL INSTITUTES OF HEALTH..... 1

THE PEDIATRIC RESEARCH INITIATIVE..... 2

SELECTED SCIENTIFIC RESEARCH ADVANCES IN PEDIATRICS 3

 Child Development 3

 Environmental and Social Influences 4

 Pregnancy and the Health of the Newborn 7

 Nutrition and Obesity in Pregnancy and Childhood 15

 Diabetes 17

 Structural Congenital Anomalies 18

 Intellectual and Developmental Disabilities 19

 Neurological Disorders and Mental Health 24

 Substance Misuse 27

 Bone and Muscle Health 29

 Hearing 29

 Childhood Disease 30

 Allergies and Immunity 33

 Rare Pediatric Diseases 34

 Pediatric Cancer 35

 Childhood Injuries and Maltreatment 39

 Pain and Pain Management 41

 Pediatric Critical Care and Emergency Care 41

 Clinical Care, Outreach, and Services 43

 Technology and Tools 45

 Global Pediatric Health 46

SELECTED NEW AND EXPANDED RESEARCH EFFORTS IN PEDIATRICS IN FY 2017 48

 Selected New Pediatric Research Efforts 48

 Selected Expanded Pediatric Research Efforts 54

 Funding Opportunities for Pediatric Research 59

SELECTED MAJOR ONGOING NIH PROGRAMS IN PEDIATRIC RESEARCH..... 60

 Child Development 60

Environmental and Social Influences	61
Pregnancy and the Health of the Newborn	63
Nutrition and Obesity in Pregnancy and Childhood	65
Diabetes	66
Structural Anomalies and Birth Defects	67
Intellectual and Developmental Disabilities	68
Neurological Disorders and Mental Health	69
Substance Use	70
Childhood Disease	71
Allergies and Immunity	74
Rare Pediatric Diseases	75
Pediatric Cancer	76
Childhood Injuries and Maltreatment	81
Pain and Pain Management	81
Pediatric Critical Care and Emergency Care	82
Clinical Care, Outreach, and Services	82
Technology and Tools	85
Global Pediatric Health	86
Pediatric Research at the NIH Clinical Center	87
Other Cross-Cutting Areas of Pediatric Research	87
Research Training, Career Development, and Loan Repayment	88
ADDITIONAL PEDIATRIC COLLABORATIONS.....	90
APPENDIX.....	92
Table 1: All NIH Pediatric Research, FY 2017	93
Table 2: NIH Funding Opportunity Announcements That Solicited Applications for Pediatric Research, FY 2017	94
Table 3: Acronyms for NIH Institutes, Centers, and Offices and Other Federal Agencies Referred to in This Report	103

PEDIATRIC RESEARCH AT THE NATIONAL INSTITUTES OF HEALTH

Research advances at the National Institutes of Health (NIH) have transformed the diagnosis, treatment, and prevention of disease. Children have benefitted greatly from revolutionary progress in biomedical research. Infant death rates have dropped precipitously in the United States over the past 50 years. Survival rates for respiratory distress syndrome have 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. 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) 2017, the NIH funded research grants and projects directed specifically at pediatric research for a total of \$4,175,953,984, as detailed in Table 1 in the Appendix. The *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) funds the largest portion of pediatric research among the NIH Institutes, Centers, and Offices (ICOs), taking a leadership role in many pediatric research efforts that involve trans-NIH collaborations. However, all of the ICOs support various aspects of pediatric research, such that the NICHD alone accounts for only 18 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.

In FY 2017, several projects originally supported by NIH facilitated product approvals from the Food and Drug Administration (FDA), including a newborn screening device to detect lysosomal disorders, and therapies to combat acute lymphoblastic leukemia and Merkel cell carcinoma. The strategic plan for cerebral palsy research was released. NIH launched nearly \$100 million to support the Autism Centers of Excellence. Neuroimaging studies shed light on autism spectrum disorders, showing methods of early detection in at-risk families.

THE PEDIATRIC RESEARCH INITIATIVE

In the Public Health Service Act (the Act), Congress directed the Secretary of Health and Human Services (HHS) to establish a Pediatric Research Initiative (PRI) in the 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 2017. The overall purpose of the PRI is to “conduct and support research that is directly related to diseases, disorders, and other conditions in children” (Section 409D(a), Public Health Service Act). More specifically, the purpose of the PRI is

(1) “to increase support for pediatric biomedical research within the National Institutes of Health to realize the expanding opportunities for advancement in scientific investigations and care for children;

(2) to enhance collaborative efforts among the Institutes to conduct and support multidisciplinary research in the areas that the Director deems most promising; and

(3) in coordination with the Food and Drug Administration (FDA), to increase the development of adequate pediatric clinical trials and pediatric use information to promote the safer and more effective use of prescription drugs in the pediatric population.”

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

The NIH has funded the initiative through (1) a one-time, \$5 million distribution from the NIH Director’s Discretionary Fund (FY 2002); and (2) individual and collaboratively funded ICO grants and contracts (FY 2002 and thereafter). For reporting purposes, the NIH has defined PRI research as including new or significantly expanded pediatric research projects funded in the reporting year. It should be noted that the PRI reporting definition provides an incomplete picture of the NIH’s total investments in pediatric research. Table 1 in the Appendix of this report provides funding amounts for the NIH’s total investment in pediatric research by ICO.

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 pediatrics research report.

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

Child Development

Infants exposed to multiple languages show enhanced skills

Scientists studied whether a multilingual environment can influence communication skills even before infants are able to speak. The researchers assessed visual communication with infants aged 14 to 17 months, with boys and girls divided equally between those exposed to English only and those exposed to more than one language. An adult sat across a table from an infant. Between them were two identical objects: one that both could see, and the other visible only to the infant. When the researcher asked for the object, the infants from multilingual backgrounds were more likely to hand the researcher the object that both could see, rather than the one that only the infant could see. Compared to the monolingual infants, multilingual infants realized that the adult could only see one object, and they were aware enough to reach for the one that the adult could see. The monolingual infants randomly chose between the two props, making no distinction. The study suggests that infants from multilingual backgrounds appear more adept at picking up nonverbal cues and better able to see a situation from another point of view.

Supported by NICHD

Article: <https://www.ncbi.nlm.nih.gov/pubmed/27002779> [Jan 2017]

Bilingual infants control their languages as they listen

Children who grow up in bilingual homes learn two languages at a pace fairly similar to children who learn only one language, but how this happens is not clear. Scientists reported that bilingual infants as young as 20 months of age understand that they are listening to two different languages. The team found that if languages switched at a natural point between complete sentences, the infants' comprehension was seamless. However, if a single sentence used two languages, infants had to process this switch. According to the study team, bilinguals speed their understanding of two languages by capitalizing on the tendency for words in each language to occur in specific sequences.

Supported by NICHD

Article: <https://www.ncbi.nlm.nih.gov/pubmed/28784802> [Aug 2017]

Preterm children are at risk for difficulties with language development over time

Babies born before 32 weeks in the womb often have more difficulty acquiring language skills than their full-term peers. To understand how prematurity affects children's language learning, researchers tracked language development from infancy to age 8 in nearly 750 children. The researchers divided the children into three groups based on when they were born: very preterm (before 32 weeks), moderate to late preterm (32 to 36 weeks), or full term (37 weeks or later). They tracked the children's language development from infancy through age 8. The researchers found that the very preterm children had the lowest average language scores, followed by moderate to late preterm children, and finally children born at term. The scientists then analyzed the results from each group to see how consistent the individuals' scores were from one assessment to the next. They found that children's language skills scores at age 20 months were a strong indicator of their language ability when they got older, and scores in the very preterm group were the most stable over time. These findings—poorer language skills combined with less change—indicate that it may be difficult for the most premature infants to catch up over time.

Supported by NICHD

Article: <https://www.ncbi.nlm.nih.gov/pubmed/27745750> [Feb 2017]

Sample composition alters associations between age and brain structure

Many neuroimaging research studies are conducted in small, non-representative samples. Researchers report that when neuroimaging data from a large cohort study were weighted to match the socioeconomic status, race/ethnicity, and sex distribution of the United States, the observed pattern of brain development and the ages of developmental milestones were shifted dramatically from the non-weighted average. This finding suggests that many commonly accepted ideas about neurodevelopment are not as broadly generalizable as previously thought, and may not accurately characterize the patterns of brain maturation across typically developing children.

Supported by NIMH, NICHD, NIDA, NIAAA

Article: <https://www.ncbi.nlm.nih.gov/pubmed/29026076> [Oct 2017]

Environmental and Social Influences

Parental obesity linked to delays in child development

When compared to children whose mothers' weight fell within a normal range, researchers found that children of mothers with obesity were more likely to fail tests of fine motor skill—the ability to control movement of small muscles, such as those in the fingers and hands. Children of fathers with obesity were more likely to fail measures of social competence, and those born to couples of extreme obesity were more likely to fail tests of problem-solving ability. If additional research confirms these links, physicians may need to consider parental weight when screening young children for delays and early intervention.

Supported by NICHD

Article: <https://www.ncbi.nlm.nih.gov/pubmed/28044047> [Feb 2017]

NICHD News Release: <https://www.nichd.nih.gov/news/releases/010317-obesity-child-development>

Epigenetic mechanisms may link childhood socioeconomic disadvantage with adult obesity

Childhood socioeconomic disadvantage is associated with an increased risk for obesity in adulthood; however, the mechanisms underlying this association remain poorly understood. Researchers measured DNA methylation – a mechanism that is involved in “turning off” gene expression – in blood and adipose (fat) tissue in participants in the New England Family Study. They found a strong association between low childhood SES, midlife obesity, and DNA methylation at a number of genes in adipose tissue (but not blood). Many of these genes are biologically relevant for the development of obesity.

Supported by NIA

Article: <https://www.ncbi.nlm.nih.gov/pubmed/27768648> [Nov / Dec 2016]

Metal exposure and development of autism

A study of twins—one with and one without Autism Spectrum Disorder (ASD)—used tooth-matrix biomarkers to explore the role of metal exposure in the development of ASD. The data showed that the children with ASD had reduced uptake of essential elements manganese and zinc, and higher uptake of lead compared with their twins, but only during certain developmental periods.

Supported by NIEHS, NINDS, NICHD, NIMH, National Genomics Infrastructure (NGI) Sweden, Innovative Medicines Initiatives Joint Undertaking, Mindich Child Health and Development Institute, Swedish Foundation for Strategic Research, Jeansson's Foundation, Beatrice and Samuel A. Seaver Foundation

Article: <https://www.ncbi.nlm.nih.gov/pubmed/28569757> [Jun 2017]

Impacts of agricultural pesticide use and poverty on childhood cognitive functioning

Residential proximity to organophosphate and carbamate pesticide use during pregnancy, and both household- and neighborhood-level poverty during childhood, were independently associated with poorer cognitive functioning in children at 10 years of age.

Supported by NIEHS

Article: <https://www.ncbi.nlm.nih.gov/pubmed/27281690> [Oct 2016]

Environmental factors in disease flare of juvenile dermatomyositis

Researchers assessed factors for disease flares in juvenile and adult dermatomyositis, systemic autoimmune diseases in which the immune system attacks skeletal muscle, skin and other organ systems. Subjects more often reported disease flares after sun exposure, although use of photo-protective measures did not differ between those with and without a flare. Urinary tract infections and gastroenteritis were more frequent in the preceding 6 months in those who reported disease flares.

Supported by NIEHS, Cure JM Foundation

Article: <https://www.ncbi.nlm.nih.gov/pubmed/28444299> [Aug 2017]

Oral microbe diversity and transmission in children

Streptococcus mutans (*S. mutans*), the primary bacterium that causes dental caries, is easily transmitted between people via saliva. Scientists developed a genotype reference library to study *S. mutans* infection and transmission in 117 children and family members in one town. Researchers identified 34 unique *S. mutans* genotypes from the mouths of ~600 people. Children had 1-9 genotypes, acquired from sources within and outside their families, and those with multiple genotypes were more than twice as likely to have dental caries. In a related study, researchers profiled patterns of bacteria in over 450 dizygotic and monozygotic twin children aged 5-11. The scientists found that highly heritable taxa acquired from parents tended to be beneficial, while taxa obtained from the environment (and likely not controlled by genetic factors) were more likely to be harmful. Identifying how these bacteria are transmitted between individuals, and understanding the impact of the genetic diversity of bacteria on oral health could lead to improved risk assessment and prevention strategies for dental caries.

Supported by NIDCR

Article: <https://www.ncbi.nlm.nih.gov/pubmed/27432341> [Sep 2016]

<https://www.ncbi.nlm.nih.gov/pubmed/28910633> [Sep 2017]

E-cigarettes may be leading more students to smoke

E-cigarette use is rapidly increasing among adolescents in the United States, with some suggesting that e-cigarettes are the cause of declining youth cigarette smoking. In an analysis of the self-reported smoking behaviors of thousands of schoolkids nationwide, researchers found no evidence that the availability of e-cigarettes has served to accelerate the decline in youth smoking. In fact, the researchers concluded the opposite: the popularity of e-cigarettes has led more kids—not fewer—to get hooked on nicotine.

Supported by NCI

Article: <https://www.ncbi.nlm.nih.gov/pubmed/28115540> [Feb 2017]

NIH Director's Blog: <https://directorsblog.nih.gov/2017/01/>

Supportive parenting intervention ameliorated the association between poverty and adverse brain development

Researchers followed up with children who previously took part in a randomized clinical trial to test a parenting support program. The participants underwent brain scans at age 25. The results showed that those receiving the intervention did not experience diminished left dentate gyrus and CA3 hippocampal subfields and left amygdalar volumes despite a history of poverty, in contrast to those who did not receive the intervention.

Supported by NIDA

Article: <https://www.ncbi.nlm.nih.gov/pubmed/27893880> [Jan 2017]

Long parental military deployment is associated with social, behavioral, and psychological issues in children and parents

Researchers surveyed over 1,000 families with children who were 12-13 years of age. The results showed that when parents had military deployments greater than 180 days, their teens experienced decreases in independence, school performance, and responsibility. Parents with these relatively long deployments had diminished psychological health. These effects were stronger for boys and military fathers.

Supported by NICHD

Article: <https://www.ncbi.nlm.nih.gov/pubmed/28005475> [Jan 2017]

Adolescent violence spreads across social networks

Youth violence is a serious problem both in the United States and in other countries. However, the rates at which youth in the United States commit and experience violence are very high compared to rates of youths in many other developed nations. Researchers conducted a study investigating whether violence among adolescents in the United States can spread within a social network, similar to a contagious disease. Using a nationally representative sample of students in the United States aged 12 to 18, researchers assessed violent behavior by asking the participants to report on the number of times in the prior 12 months they had been involved in a serious fight, had hurt someone badly (enough to need bandages or medical care), and if they had drawn a weapon (knife or gun) on someone. The study participants were 48 percent more likely to have been in a serious fight, 183 percent more likely to have hurt someone badly, and 140 percent more likely to have drawn a weapon on someone if they had a friend who had committed the same act than participants who did not have friends engaging in these behaviors. The results showed that it wasn't just close friends, but friends of friends and more distantly connected people that were associated with whether a youth was likely to commit violent acts. The influence spread up to 4 degrees of friend's separation for serious fights, 2 degrees for hurting someone badly, and 3 degrees for drawing a weapon on someone. This study is the first to show that adolescent violence can spread within a social network beyond immediate friends to friends of friends and beyond.

Supported by NICHD

Article: <https://www.ncbi.nlm.nih.gov/pubmed/27997233> [Feb 2017]

Teens drive more safely after being involved in a collision, but effect may be temporary

Motor-vehicle collisions are the leading cause of death among 16- to 24-year-olds in the United States. Previous research had indicated that young driver's risk of collision is high when they start driving, but drops over the first few years, and that age and experience are likely to play a role in this decrease. Scientists conducted a study to investigate the extent to which young drivers learned from the experience of having a collision early in their driving lives, and subsequently engaging in safer driving behavior after that negative experience. The teens' cars were equipped with a device that measured acceleration and cameras that recorded their performance from various angles. The researchers focused on the teen's involvement in collisions identified as very severe and police-reportable, which included any collision resulting in significant damage, airbag deployment, injury, or a rollover. The study data revealed that the rate of high-acceleration events – a sign of risky driving – dropped by 34 percent immediately after a teen was involved in a severe collision and remained unchanged for the following second month. However, the rate of high-acceleration events increased significantly in the following third month, although the rate remained below pre-crash levels. There were no changes in acceleration rate at comparable time points for drivers not involved in a collision. Teens having a serious car collision appear to learn from the experience and considerably decreased risky driving behavior in the following 2 months, but this may be a temporary effect.

Supported by NICHD

Article: <https://www.ncbi.nlm.nih.gov/pubmed/28406372> [Apr 2017]

Pregnancy and the Health of the Newborn

Morning sickness linked to lower risk of pregnancy loss

Nausea and vomiting that occurs in pregnancy is often called "morning sickness," as these symptoms typically begin in the morning and usually resolve as the day progresses. The cause of morning sickness is not known, but researchers have proposed that it protects the fetus against toxins and disease-causing organisms in foods and beverages. Researchers analyzed data from a group of pregnant women who participated in a previous clinical trial. Pregnant women who reported experiencing nausea and/or vomiting were 50 to 75 percent less likely to experience a pregnancy loss, compared with pregnant women who had not reported these symptoms of morning sickness. Unlike previous studies on pregnancy loss, which have relied on women's memories of their symptoms, this study gathered detailed information on symptoms in the early weeks of pregnancy.

Supported by NICHD

Article: <https://www.ncbi.nlm.nih.gov/pubmed/27669539> [Nov 2016]

NICHD News Release: https://www.nichd.nih.gov/news/releases/Pages/92616_nauseapregnancy.aspx

Clinical Trial: <https://clinicaltrials.gov/show/NCT00467363>

Bupropion therapy during pregnancy

A small study of pregnant women taking the medication bupropion has found evidence that the drug and its major active metabolites – that is, compounds created in metabolic processing of a drug—cross the protective tissue (placenta) around the fetus. Bupropion is the generic version of the brand-name antidepressant Wellbutrin; it is also prescribed, as the brand name drug Zyban, for symptoms of nicotine withdrawal in smokers trying to quit. Researchers analyzed samples, collected at delivery, of maternal blood, umbilical cord blood and amniotic fluid, from 22 pregnant women who were being treated with bupropion by their health care providers for depression. Further research is needed to determine the risk of bupropion therapy in pregnancy and assess the neonatal outcomes of infants in-utero exposure to the drug and its metabolites.

Supported by NICHD, NIDA

Article: <https://www.ncbi.nlm.nih.gov/pubmed/27180885> [Oct 2016]

Diet beverages and refined grains during pregnancy could increase child obesity risk by age 7

Obesity now affects 1 in 6 children and adolescents in the United States. Childhood obesity is known to increase the risk for certain health problems later in life, such as diabetes, heart disease, stroke and some cancers. Researchers sought to determine how a woman's diet during pregnancy may affect her child. They focused on women who had gestational diabetes, which affects the way their bodies process sugar during pregnancy. The researchers analyzed data for over 900 pregnancies that were complicated by gestational diabetes, a subset of data collected from over 91,000 women in Denmark between 1996 to 2002. Children born to women who had gestational diabetes and drank at least one artificially sweetened beverage per day during pregnancy were more likely to have overweight or obesity at age 7, compared to children born to women who had gestational diabetes and drank water instead of artificially sweetened beverages. The findings suggest that artificially sweetened beverages during pregnancy are not likely to be any better at reducing the risk for later childhood obesity than sugar-sweetened beverages. Children born to women with gestational diabetes whose diet included high proportions of refined grains (more than 156 grams per day) may also have a higher risk of obesity by age 7, compared to children born to women with gestational diabetes who ate low proportions of refined grains (less than 37 grams per day). The link between maternal grain consumption during pregnancy and obesity by age 7 persisted when the researchers controlled for factors that could potentially influence the children's weight—such as physical activity level and consumption of vegetables, fruit, and sweets.

Supported by NICHD

Article: <https://www.ncbi.nlm.nih.gov/pubmed/28586472> [Oct 2017]

<https://www.ncbi.nlm.nih.gov/pubmed/28592607> [Jul 2017]

NICHHD News Release: <https://www.nichd.nih.gov/news/releases/Pages/060617-diet-beverages-child-obesity.aspx>

NICHHD News Release: <https://www.nichd.nih.gov/news/releases/Pages/060717-grains-child-obesity.aspx>

Association between cesarean delivery and risk of obesity in offspring

A new study adds to emerging evidence that birth by cesarean delivery increases an individual's risk of obesity later in life. The researchers had followed an unusually large group of children born to women in a long-term women's health study, assessing their offspring from ages nine through 10, through ages 20 to 28 years and controlling for factors including maternal obesity. The scientists found the strongest association between cesarean delivery and obesity among individuals whose mothers had delivered by cesarean even though there was no apparent medical reason, such as a complication of labor, for such delivery.

Supported by NICHHD, NIDDK, NCI, NIMH, NHLBI

Article: <https://www.ncbi.nlm.nih.gov/pubmed/27599167> [Nov 2016]

Magnesium exposure during pregnancy does not increase risk of spontaneous intestinal perforation in extremely low birth weight infants

Magnesium is often given to prevent seizures in pregnant mothers with preeclampsia (high blood pressure and/or high amounts of protein in the urine during pregnancy). Magnesium has also been used to prevent premature labor, and may improve neurodevelopment in premature infants. Researchers observed that some infants at their hospital who had been prenatally exposed to magnesium seemed to have an increased risk for spontaneous intestinal perforation (a hole in the stomach or intestine with no demonstrable cause). The researchers therefore conducted a systematic study to examine the association between magnesium and the risk for spontaneous perforation. They reviewed the records of all extremely low birth weight infants (weighing less than 1000 grams) treated in their group of hospitals, from 323 neonatal intensive care units between 2007 to 2013. Of the 28,035 infants studied, over 11,700 were exposed to magnesium in the womb. The researchers found no differences in the risk of spontaneous intestinal perforation in these infants during the neonatal period. In fact, the risk of death was on average 24 percent lower during the first 21 days after birth in the infants exposed to magnesium.

Supported by NICHHD, NHLBI, NCATS, NIAAA, FDA

Article: <https://www.ncbi.nlm.nih.gov/pubmed/28125094> [Jun 2017]

Effects of alcohol exposure in the first trimester

Most women do not realize they are pregnant until about 1 to 2 months after they conceive, so they may expose their fetuses to alcohol in early pregnancy. Drinking alcohol during pregnancy can have severe negative health effects on the fetus. Scientists believe this is partly because alcohol disrupts the flow of blood and nutrients to the fetus through the placenta, but they did not know exactly how alcohol affects the placenta early in pregnancy. Researchers used magnetic resonance imaging (MRI) to study alcohol's effects on blood and oxygen flow within the placenta in pregnant macaques, a type of non-human primate. The researchers found that fetuses in the alcohol-exposed macaques were receiving less blood and oxygen through the placenta midway through the first trimester. Those fetuses also weighed less and had brain abnormalities. The researchers were surprised to note that the alcohol-induced effects became less severe by the end of the trimester. They hypothesize that the placenta can adapt to stress and may try to compensate for reduced blood and oxygen flow by restricting its own growth. Though more research is needed, the researchers suggest that using MRI could potentially help assess placental and fetal health in pregnant women who drank alcohol during early pregnancy, which could ultimately allow health care providers to identify at-risk pregnancies earlier.

Supported by NICHHD, NIAAA, NIH OD

Article: <https://www.ncbi.nlm.nih.gov/pubmed/28153658> [Mar 2017]

Prenatal alcohol exposure is associated with academic difficulty and atypical brain development

Scientists measured general intelligence, behavior, and academic achievement in reading, spelling, numerical operations, and math reasoning among 67 children 8 to 16 years old who had heavy prenatal exposure to alcohol and 61 children who had not. The scientists also used MRI to examine the children's brain structure for correlations to academic performance. Children exposed to alcohol had significantly lower general intelligence and higher behavioral concern scores than the other children, and they also performed worse on all measures of academic function. Moreover, in the children who had not been exposed to alcohol, spelling and math scores increased as brain surface area decreased. In alcohol-exposed children, the researchers found no relationship between spelling and brain surface area, and both simple and complex math ability scores went up as brain surface area increased, suggesting very delayed or atypical brain development. These results highlight a need for additional attention and focused support to help children with heavy prenatal alcohol exposure succeed in school, especially mathematical learning and reasoning.

Supported by NICHD, NIAAA, NIDA

Article: <https://www.ncbi.nlm.nih.gov/pubmed/28340498> [May 2017]

Cigarette smoking during pregnancy linked to changes in baby's immune system

Smoking during pregnancy is linked to pregnancy and birth complications, including miscarriage, premature birth, birth defects, and problems with the placenta, which brings nutrients and oxygen to the fetus. Changes in the immune system are linked to smoking-related conditions such as asthma. However, it's not clear how smoking during pregnancy could affect a baby's immune system. To examine this question, researchers reviewed information from the Upstate KIDS Study, which originally evaluated the effects of parents' infertility treatments on their children's development. About 12 percent of the women in the study had smoked during pregnancy. While some quit smoking during their first trimester, 43 percent of the smokers continued to smoke throughout pregnancy. The study team measured various indicators of immune system functioning in the newborn blood samples. The researchers compared the levels of these immune substances among children grouped by their mother's smoking status: non-smoker, stopped within the first trimester, stopped after the first trimester, or smoked throughout pregnancy. The team also evaluated children exposed to secondhand smoke. Overall, samples from nearly 3,500 children were analyzed. The researchers statistically accounted for a number of factors that could influence their findings, such as the mother's age, race, pre-pregnancy body mass index, education level, marital status, and alcohol use, to help ensure that the findings were associated with smoking and not other issues. They found that infants whose mothers had smoked for their entire pregnancy had elevated levels of interleukin 8 (IL-8), a protein that is known to promote inflammation. Levels of IL-8 tend to be elevated during infections and certain health conditions, including lung disease.

Supported by NICHD

Article: <https://www.ncbi.nlm.nih.gov/pubmed/28011791> [Jul 2017]

Youth perinatally infected with HIV may have severe lung disease complications

Approximately 8,500 women living with HIV give birth annually. Previous research indicated that youth who were exposed to and infected with HIV in the womb have an increased risk for asthma, compared with youth who were exposed to HIV in the womb but uninfected. Asthma is a chronic lung disease that inflames and narrows the airways. Researchers reviewed medical records and reports for 218 HIV-infected youth with asthma, and 152 young people with asthma who had been exposed to HIV before birth but were uninfected. The researchers administered pulmonary function tests to these youths to classify the types of lung disease. To distinguish asthma from other causes of obstructive lung disease, a reversibility test is used to measure the flow of air into the lungs before and after treatment. In asthma, treatment can usually reverse the obstruction of airflow. In this study, the prevalence of obstructive lung disease did not differ by HIV status, but obstruction of airflow was less likely to be reversible in HIV-infected youth, compared to uninfected youth. HIV-infected youth also had lower levels of allergen-associated antibodies and lower ratios of different white blood cells, which indicate an immune

imbalance. These findings indicate that HIV-infected youth may be more prone to a complex combination of asthma and chronic obstructive pulmonary disease, and should be further observed to determine lung disease outcomes in adulthood.

Supported by NICHD

Article: <https://www.ncbi.nlm.nih.gov/pubmed/28279683> [Oct 2017]

Gestational age affects Zika virus transmission to fetus in mouse model

Pregnant women can be infected with the Zika virus (ZIKV) through a mosquito bite or via sexual transmission, which can result in severe birth defects. However, not all pregnant women infected with ZIKV will transmit the virus to the fetus, and not all infected fetuses show signs of the disease. To better understand how the virus causes birth defects, researchers have developed a mouse model showing how gestational age affects ZIKV transmission through the placenta to the fetus. The researchers directly injected ZIKV into the uteruses of mice with healthy immune systems at different stages of their pregnancies. They compared infection at embryonic day 10 (E10), when the placenta was forming (similar to the first trimester of pregnancy in humans), versus embryonic day 14 (E14), when the placenta had stopped growing (similar to the third trimester of pregnancy in humans). ZIKV was detectable in both the mothers' placentas and fetal brains of mice infected at E10, but not E14. Compared to non-infected mice, the mice infected at E10 bore offspring with decreased brain size, more infection-fighting cells, and inflammation in their brains. This mouse model of ZIKV infection shows the effects of the gestational timing on placental transmission and fetal development in mice with intact immune systems that are similar to humans. Infection with the Zika virus during earlier stages of pregnancy appears to have more severe effects on the developing mice, similar to the situation in humans.

Supported by NICHD, NIH OD

Article: <https://www.ncbi.nlm.nih.gov/pubmed/28220786> [Feb 2017]

Outcomes of antenatal corticosteroid treatment in extremely preterm, multiple gestation infants

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

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

Supported by NICHD

Article: <https://www.ncbi.nlm.nih.gov/pubmed/27088897> [Jun 2016]

- Researchers assessed whether a steroid given to women who were in their 34th through 36th week of pregnancy, and at risk for preterm birth, would decrease respiratory and other neonatal complications. The results showed that the steroid decreased the need for substantial respiratory support during the first 72 hours after birth and also resulted in reduced rates of longer term severe respiratory complications.

Supported by NICHD, NHLBI, NCATS

Article: <https://www.ncbi.nlm.nih.gov/pubmed/26842679> [Apr 2016]

NICHD News Release: <https://www.nichd.nih.gov/news/releases/Pages/020416-prenatal-steroids.aspx>

- Because completing the entire course of steroids takes at least 48 hours, health care providers may opt not to begin treatment when premature delivery is imminent. Scientists found that

steroids improve survival and reduce the chances of certain birth defects for extremely premature infants, even if the treatment course is not finished before delivery.

Supported by NICHD

Article: <https://www.ncbi.nlm.nih.gov/pubmed/27723868> [Dec 2016]

NICHD News Release: <https://www.nichd.nih.gov/news/releases/Pages/101016-antenatal-steroids.aspx>

Delayed cord clamping boosted blood volume in full term infants

In 2012, the American College of Obstetricians and Gynecologists recommended a 30 to 60-second delay before clamping the umbilical cord in all preterm deliveries. In 2016, they included this recommendation for term infants. Delaying umbilical cord clamping by 30 to 60 seconds has been shown to be beneficial, though the optimum duration of the delay is not established. Generally, a delayed cord clamping practice is shown to increase the amount of blood flowing from the placenta into the baby's body, which is critical to fill the blood vessels in the infant's lungs, helping them to begin breathing normally and receive oxygen through their lungs. This practice has also been shown to reduce the risk of bleeding in the infant's brain's ventricles, the fluid-filled cavities inside the infant's brain. The overall increase in blood volume and in the number of red blood cells from delayed clamping may also benefit the infant by reducing the risk for developing anemia (low blood iron levels) and the need for blood transfusions. Despite these observations, clamping the umbilical cord soon after an infant's birth has been a standard practice for over 50 years. To identify whether more than just a 60-second delay in cord clamping is safe without increasing any complications (e.g., jaundice during the newborn period), researchers randomly assigned full-term newborn babies to two groups. In the first group, the cord was clamped immediately, and in the second group, cord clamping was delayed for five minutes. In both groups, newborn babies were placed directly on their mother's abdomen after birth. Babies with delayed cord clamping had a higher blood volume and higher levels of hemoglobin (the red blood cell protein that carries oxygen from lungs to tissues). There were no differences between groups in the rates of jaundice or symptoms related to hemoglobin levels. These results suggest that delaying cord clamping by up to five minutes may have some benefit for full term infants without much risk.

Supported by NICHD

Article: <https://www.ncbi.nlm.nih.gov/pubmed/27929530> [Mar 2017]

Role of genetics and maternal depression in infant brain development

Children born to women who experienced depression during pregnancy are at greater risk of depression themselves later in life. It is unclear how much the mother's depression itself influences early brain development, and how much the increased risk reflects shared genetics and family history regardless of the mother's state during pregnancy. Researchers studied these relationships in two groups of mother-infant pairs – one group from Singapore and one group from the United States. The scientists found that prenatal maternal depression and genetic factors interact to influence the unborn developing infant's brain development, particularly in the part of the brain called the amygdala. The amygdala is involved in the processing and expression of emotions, especially anger and fear, and alterations in this area are associated with psychiatric and/or mood disorders.

Supported by NICHD, NIMH

Article: <https://www.ncbi.nlm.nih.gov/pubmed/28334351> [May 2017]

Maternal stress levels in low-risk pregnant women does not affect newborn growth

To determine how maternal mood and maternal stress affect fetal growth during pregnancy, researchers studied over 1900 women who were 18 to 40 years of age. The women underwent six ultrasound examinations throughout their pregnancy and also completed a stress survey. After delivery, ultrasound measurements were correlated with birthweight, length, head circumference, and abdominal circumference. The findings showed similar measurements among women who had been categorized as

low stress, medium stress, and high stress, indicating that the stress perceived by low-risk pregnant women does not affect their newborns' measurements.

Supported by NICHD

Article: <https://www.ncbi.nlm.nih.gov/pubmed/28263750> [Jul 2017]

Placental examination and fetal autopsy can help identify cause of stillbirth

Stillbirth is when a fetus dies any time at or after 20 weeks of pregnancy. Stillbirth affects about 1 in 160 pregnancies in the United States. Even though stillbirth is fairly common, determining why a fetus died is difficult. Researchers compared various tests and methods to determine which were most helpful in identifying the cause of a stillbirth. They analyzed 512 stillbirths in which doctors had performed an autopsy of the fetus and had examined the placenta for abnormalities. Other tests, when available, included genetic testing and various laboratory measurements of both the fetus and the mother. The researchers found that examining the placenta was the most useful test, either confirming or excluding a cause in 64.6 percent of the cases, with fetal autopsy next at 42.4 percent. Genetic testing and a test for a condition that causes the immune system to attack normal proteins, called antiphospholipid syndrome, were each useful in about 10 percent of the cases. Fetal-maternal hemorrhage testing was useful in 6.4 percent of cases. All other tests were useful in fewer than 5 percent of cases. Although the American College of Obstetricians and Gynecologists recommends a wide array of tests to determine the cause of stillbirth, these researchers point out that the potential benefit should be weighed against the cost and yield of the test. The researchers suggest performing fetal autopsy and examining the placenta for all stillbirth cases; using genetic testing and screening for antiphospholipid antibodies for the majority of cases; and utilizing the remaining tests based on the clinical situation surrounding the stillbirth.

Supported by NICHD

Article: <https://www.ncbi.nlm.nih.gov/pubmed/28277368> [Apr 2017]

Common tests for preterm birth are not useful for routine screening of first-time pregnancies

Generally, a normal human pregnancy lasts about 40 weeks. Births that occur before 37 weeks are considered preterm births. Scientists assessed two different methods to see if they could help predict preterm delivery in first-time pregnancies. The study included 9,410 women pregnant with a single fetus. The researchers evaluated routine ultrasound examination of the uterine cervix, the lower part of the uterus that shortens and opens during labor. The researchers also evaluated testing for fetal fibronectin, a glue-like protein that secures the amniotic sac to the inside of the uterus. Previous studies have indicated that a short cervix or the presence of fetal fibronectin in the vagina early in pregnancy could be warning signs of preterm birth or early labor. However, the researchers found that, alone and together, the methods did not identify enough preterm births to support routine screening of first-time pregnancies.

Supported by NICHD, NCATS

Article: <https://www.ncbi.nlm.nih.gov/pubmed/28291893> [Mar 2017]

Extreme temperatures may increase risk for low birth weight at term

Infants may be of low birth weight (less than 5.5 pounds at birth) because they are born prematurely, but some babies are born with low birth weight even though they have completed the 37-40 weeks that is considered to be a full-term pregnancy. Compared to infants of normal weight, low birth weight infants may be at higher risk for infection and developmental delays. Researchers linked medical records from 223,375 births at 12 clinical centers in the United States to hourly temperature records for the region surrounding each center. Their analysis showed that exposure to atypically cold temperature during the entire pregnancy, or just during the second trimester and third trimester, increased the risk for low birth weight. Exposure to atypically hot temperatures during the whole pregnancy, or during the third trimester, also increased this risk. The odds for low term birth weight were highest when the whole pregnancy was exposed to extreme temperatures.

Supported by NICHD

Article: <https://www.ncbi.nlm.nih.gov/pubmed/28258738> [May 2017]

Patterns of brain connectivity in very preterm and full-term infants predict early signs of anxiety and depression

Differences in the strength and pattern of connections within the brain have been associated with mood and anxiety disorders in older children and adults. However, less is known about these relationships in infants. Researchers set out to identify differences in connection patterns across various regions of the brain between full-term infants and very preterm infants and to determine whether these predicted later symptoms associated with risk for mood and anxiety. Using functional connectivity magnetic resonance imaging (MRI), the researchers conducted brain scans in 65 full-term infants, and 57 very preterm infants born at least 10 weeks early. Functional connectivity MRI shows how regions of the brain that function together are also connected. The researchers focused on how the amygdala, a brain structure involved in processing emotion, connects with other brain regions. The scientists found that both the full-term infants and the very preterm infants had amygdala brain connection patterns similar to those found in previous research with older children and adults, but the strength of these connections was decreased in very preterm infants as a group. The researchers conducted a follow-up with a group of study participants at two years of age, finding that the infants who had been very preterm were no more likely than full-term babies to show early signs of anxiety and depression. However, they found that in both full-term and very preterm babies, those with a stronger connection between the amygdala and other structures – like the insula, which is involved in consciousness and emotion, and the medial prefrontal cortex, which plays roles in planning and decision making – were more likely to show internalizing behaviors associated with later affective behavioral abnormalities in infants and children. These findings suggest that risk for future anxiety and depression may be detectable through brain connectivity patterns in infancy.

Supported by NIMH, NICHD, NINDS, NCATS

Article: <https://www.ncbi.nlm.nih.gov/pubmed/28117062> [Feb 2017]

Factors associated with choice of infant sleep position

Sudden infant death syndrome (SIDS) is a leading cause of death of infants in the United States. Putting infants on their backs to sleep can help reduce the risk of SIDS. However, despite widespread recommendations to place infants on their backs, many parents continue to put their children to sleep in other positions. Researchers surveyed over 3,000 mothers about their infant's sleep position. Over three-quarters of mothers reported usually putting their child to sleep on his or her back, and nearly half indicated that they always did so. Women who received advice from their doctor to place the infant on his or her back were more likely to do so. Compared with Caucasian women, African American women were more likely to say they intended to put an infant to sleep in a prone position (on his or her stomach). Women who expressed beliefs that the prone position was healthy for the infant or would make the baby more comfortable were more likely to use that position. The results suggest that targeting these beliefs might be useful in increasing the number of women who place infants to sleep on their backs, ultimately reducing the rates of SIDS.

Supported by NICHD

Article: <https://www.ncbi.nlm.nih.gov/pubmed/28827382> [Sep 2017]

Blood of SIDS infants contains high levels of serotonin

Sudden Infant Death Syndrome (SIDS) is the sudden, unexplained death of a baby younger than 1 year of age. Research suggests that infants who die from SIDS are born with abnormalities in a part of the brain that controls breathing, heart rate, blood pressure, temperature, and waking from sleep. These defects are specifically found within neurons that use serotonin as a chemical signal. Researchers reported that infants who died from SIDS had high blood levels of serotonin, which is primarily produced in the gut, not in the brain. While the results are preliminary, they suggest that the serotonin defect in the brain may be caused by a broader problem with serotonin production and breakdown. Additional research in this area may lead to a screening test that identifies infants at risk for SIDS.

Supported by NICHD

Article: <https://www.ncbi.nlm.nih.gov/pubmed/28674018> [Jul 2017]

Increased levels of human milk doses in very low birth weight infants improves neurodevelopment later in infancy

A recent study carefully tracked the consumption of human milk by a diverse cohort of very low birth weight infants being cared for in the neonatal intensive care unit, and later examined their neurodevelopmental outcomes. The study found that each 10 mL/kg/day increase in human milk consumption was significantly associated with a 0.35 increase in cognitive index score at 20 months of age.

Supported by NINR

Article: <https://www.ncbi.nlm.nih.gov/pubmed/28768286> [Aug 2017]

Healthy bacteria in the gut help protect newborns' lungs from infections

During birth, healthy bacteria from the mother transfer to the gut of her infant. Scientists think that these healthy “normal” bacteria help the newborn’s immune system develop and fight infection. However, it was not clear how bacteria in the gut could affect the immune system in the lungs to fight off infections such as pneumonia, an important cause of illness among infants in low- and middle-income countries. Researchers used mice to study the link between gut bacteria and the immune system. They fed pregnant mice antibiotics, which wiped out the gut bacteria of their offspring, and compared these newborn mice to newborn mice not exposed to antibiotics. The researchers confirmed that healthy gut bacteria were critical to preventing pneumonia in the newborn mice. They also discovered why: bacteria in the gut signaled a type of immune system cell to move out of the gut and into the lung. These cells make a molecule called interleukin-22, which protects the lung from bacteria that cause disease. The researchers found that human infants whose mothers received antibiotics late in pregnancy also had less interleukin-22 in their lungs. The results help explain why antibiotic use during pregnancy and cesarean delivery, which disrupts transfer of healthy bacteria to the newborn gut, can increase the risk for infection in newborns.

Supported by NICHD, NHLBI, NIAID, NIDDK

Article: <https://www.ncbi.nlm.nih.gov/pubmed/28179507> [Feb 2017]

Commonly used antibiotics piperacillin-tazobactam are most likely safe for infants

Health care providers often use combined antibiotics called piperacillin-tazobactam to treat hospital-acquired severe infections in newborns. Although these drugs have been extensively tested in adults, only very limited information is available about whether the drugs are safe to use in infants. One reason for this lack of information is that babies are so small that it is difficult to get enough blood to measure the amount of antibiotics in their blood. Such measurements would show how much antibiotics a baby is exposed to and how long it takes their body to clear the antibiotics, information critical for determining safety. Researchers looked at data from 746 infants who had received piperacillin-tazobactam while hospitalized. They used a mathematical model to calculate the amount of antibiotics in the blood, based on each infant’s weight and age and how much of the antibiotics the infant received. The researchers looked at the infants’ electronic health records to find any adverse reactions, such as seizure or rash, that the infants had after receiving the antibiotics. They then tried to connect the adverse reactions to the predicted blood level of piperacillin-tazobactam. The researchers did not find any association between the piperacillin-tazobactam exposure and infant safety concerns. Because the data are based on simulations rather than direct measurements, additional studies are needed to confirm the safety of piperacillin-tazobactam use in infants.

Supported by NICHD, NCATS, NIAID, FDA

Article: <https://www.ncbi.nlm.nih.gov/pubmed/28410277> [Sep 2017]

Pharmacokinetics of sedation medication in infants

Over 90 percent of infants hospitalized in the intensive care unit undergo multiple painful procedures. Therefore, there is a critical need for safe and effective means to control pain and sedation in this population. Dexmedetomidine is approved for use in adults for sedation in intensive care units or during procedures, but the drug label does not support use in infants and young children, due to limited

pharmacologic data. In spite of this, dexmedetomidine is being used regularly for sedation in infants, a practice called “off-label use.” Researchers aimed to understand how different doses affected the amount of dexmedetomidine in the blood, how long it would take for the drug to clear from an infant’s body, and whether different doses would be needed for different ages. They collected blood samples from 20 infants receiving this pain-controlling medication. The study results showed that the drug cleared from younger infants much more slowly than older infants. Likewise, children recovering from cardiac surgery cleared the drug approximately 40 percent slower than other infants. Based on the study findings, the researchers recommend that younger infants or those receiving the drug for pain control after cardiac surgery may respond to lower doses of dexmedetomidine just as well to achieve adequate pain control.

Supported by NICHD, NIH OD, NHLBI, NIAID, NCATS

Article: <https://www.ncbi.nlm.nih.gov/pubmed/28444697> [Sep 2017]

Prenatal stress, lead, and neurodevelopment

A study of the effects of third trimester lead levels and prenatal stress on children’s cognitive, language, and motor scores at 24 months of age confirmed prenatal stress exposure as a modifier of the well-known neurotoxic effects of prenatal lead. These results add to the existing evidence pointing at the importance of studying the co-exposure of chemical and non-chemical exposures, specifically of considering the emotional environment of children at early developmental stages of life.

Supported by NIEHS, National Institute of Public Health/Ministry of Health of Mexico

Article: <https://www.ncbi.nlm.nih.gov/pubmed/27865525> [Jan 2017]

Nutrition and Obesity in Pregnancy and Childhood

Gut microbial community interactions in childhood malnutrition

Researchers highlighted interactions within the gut microbial community in the context of childhood malnutrition, a leading cause of death in children worldwide. They found that a pathogenic strain of bacteria from an undernourished child living in Bangladesh caused similar weight loss in mice when transplanted along with the undernourished donor’s gut microbial community, but not when transplanted with a healthy donor’s microbial community. This study reveals the importance of microbial community context in influencing metabolism and growth, immune function, and disease.

Supported by NIDDK, Bill and Melinda Gates Foundation

Article: <https://www.ncbi.nlm.nih.gov/pubmed/27881825> [Nov 2016]

Specific bacteria in the gut can protect young mice from gastrointestinal infections

A recent study has found that *Clostridiales* bacteria naturally introduced to the gut shortly after birth can protect young mice from bacterial infections. This result may help explain why newborn humans, who have immature gut microbiomes, are more likely than older people to acquire gastrointestinal infections.

Supported by NIDDK

Article: <https://www.ncbi.nlm.nih.gov/pubmed/28428425> [Apr 2017]

No gender differences in body composition among adolescents with anorexia nervosa

Anorexia nervosa (AN) is potentially life-threatening eating disorder in which an abnormal fear of gaining weight leads and a severe negative body image leads to self-imposed weight loss and malnutrition. AN typically begins in adolescence and is more often found in females. Researchers reviewed electronic medical records of teens and pre-teens, aged 9-20 years, who were diagnosed with AN. This is the first study to assess sex differences in body composition among adolescent boys and girls with AN. The researchers found that once they adjusted for the degree of malnutrition, there were no significant differences in body composition among males and females. In their retrospective analysis, the authors report greater reductions in fat mass compared to lean (muscle) mass. Another observation was that the average age of boys (13.5 yrs.) was significantly younger than the girls (15 yrs.) with the disease.

Supported by NICHD, NIDDK

Article: <https://www.ncbi.nlm.nih.gov/pubmed/28087266> [Apr 2017]

Hypertension in children often goes undiagnosed

Hypertension (high blood pressure) is one of the ten most common chronic diseases in childhood, and predisposes children to adult hypertension. Children with hypertension can also show early signs of cardiovascular disease. Researchers analyzed the electronic health records of 400,000 children from nearly 200 pediatric primary care sites across the country. Only 23 percent of children who had blood pressures consistent with hypertension at multiple primary care visits were diagnosed with the disease, and only 10 percent of patients with symptoms of prehypertension were diagnosed. Of those children and adolescents with diagnoses of hypertension for at least a year, only 6 percent of those who needed anti-hypertension medication received a prescription. Pediatricians were more likely to diagnose hypertension and prehypertension in children who were tall, male, overweight, or obese.

Supported by NICHD

Article: <https://www.ncbi.nlm.nih.gov/pubmed/27940711> [Dec 2016]

Childhood asthma and obesity

Researchers followed 2,171 children who did not have obesity, starting at 5-8 years of age, for 10 years. The results indicated that children with asthma may be at higher risk of obesity, and that asthma rescue medication use appeared to reduce obesity risk independent of physical activity.

Supported by NIEHS, The Hastings Foundation

Article: <https://www.ncbi.nlm.nih.gov/pubmed/28103443> [May 2017]

Modeling the impact of increasing children's physical activity

Using nationally-representative data, researchers created a computational simulation model to assess the benefits of increased physical activity for children between 8 to 11 years of age in the United States. Current physical activity levels indicate that only about 32 percent of children get healthy levels of exercise. According to the researchers' analysis, if 50 percent of children exercised, the number of youth with overweight and obesity would decrease by 4.2 percent, saving \$8.1 billion in direct medical costs and \$13.8 billion that would otherwise be lost productivity. If 75 percent of children exercised, the number of youth with overweight and obesity would decrease by almost 10 percent, saving \$16.6 billion in direct medical costs and \$13.8 billion in lost productivity. Identifying the costs of these different scenarios through a computational simulation model shows how policies encouraging physical activity may save American taxpayers billions of dollars.

Supported by NICHD, AHRQ

Article: <https://www.ncbi.nlm.nih.gov/pubmed/28461358> [May 2017]

Intervention for excess weight gain prevention in adolescent girls

High overweight and obesity rates among adolescent girls are a significant problem in the United States. Interpersonal psychotherapy (IPT) has been shown to be effective in adults with overweight and obesity and binge eating disorder, especially those with increased psychosocial problems. Scientists assessed whether IPT could help prevent weight gain in 113 adolescent girls (12-17 years of age) who were considered at high risk for weight gain because they reported losing control of their eating in the past month. The participants were randomly placed in either an IPT group or a standard health education (HE) group. The researchers found no differences at the 1-year follow-up between the IPT group and the HE group in excess weight gain. The participants were re-contacted 3 years after they started the program. Consistent with the 1-year follow-up, in the 3-year follow-up the IPT group was not superior to the standard HE group in preventing excess weight gain. However, in further analyzing the 3-year assessment data, the researchers found that among girls with greater psychosocial and anxiety problems, those in the IPT group had steeper declines in BMI/weight than girls in the compared to the HE group. These results

suggest a personalized medicine approach for prevention of weight gain – teenage girls with both anxiety and binge eating behaviors may particularly benefit from interpersonal therapy.

Supported by NICHD, NIDDK, NIMH

Article: <https://www.ncbi.nlm.nih.gov/pubmed/27808536> [Mar 2017]

Weight-based dosing suggested for children taking commonly-used antibiotic

Although childhood obesity is common in the United States, for many medications used in children dosing is based on factors other than body weight. For some drugs, this may result in children with overweight or obesity getting less medicine than they need. Clindamycin is an antibiotic that is frequently used in children for serious infections. Researchers combined data from several studies to assess how clindamycin is absorbed, metabolized, and cleared by the body for children who either have or do not have obesity. The results indicated that dosing by total body weight could help ensure that clindamycin is safe and effective for children who either have or do not have obesity.

Supported by NICHD, NIAID, NIAAA, NCATS, FDA

Article: <https://www.ncbi.nlm.nih.gov/pubmed/28137820> [Mar 2017]

Diabetes

SEARCH for Diabetes in Youth study investigates type 1 and type 2 diabetes incidence and complications in youth in the United States

From 2002-2012, the annual increase in type 1 diabetes diagnosis among youth in the United States, when adjusted for age, sex, and racial and/or ethnic group, was 1.8 percent, and the annual increase in type 2 diabetes diagnosis was 4.8 percent. However, researchers found that the increase varied across racial and/or ethnic groups, with type 2 diabetes diagnoses increasing among all racial and ethnic groups except non-Hispanic Whites, and type 1 diabetes incidence increasing significantly more in Hispanic youths than in non-Hispanic White youths (4.2 percent vs. 1.2 percent, respectively). Scientists estimated that by about age 21, approximately 32 percent of study participants with type 1 diabetes and 72 percent of participants with type 2 diabetes would have (or be at high risk for) at least one diabetic complication. These data further demonstrate the critical need to develop strategies to prevent this disease and improve treatment for youth with diabetes.

Supported by NIDDK, NCATS, CDC, Special Statutory Funding Program for Type 1 Diabetes Research

Article: <https://www.ncbi.nlm.nih.gov/pubmed/28402773> [Apr 2017]

<https://www.ncbi.nlm.nih.gov/pubmed/28245334> [Feb 2017]

Artificial pancreas use improves blood glucose of adolescents engaging in vigorous physical activity

Compared to physician-monitored sensor-augmented pump (SAP) therapy, artificial pancreas (AP) use in adolescents (ages 10-16 years) with type 1 diabetes was found to improve glycemic control and reduce hypoglycemia during extended vigorous outdoor exercise at snowboarding camp. To date, AP use has primarily been tested during limited intensity/short duration physical activity and had been found to improve glycemic control; now, researchers have extended that finding to test AP use in 32 adolescents participating in a 5-day ski camp in Virginia or Colorado. AP use increased time in target blood glucose range by 1 h and 40 min per day and halved hypoglycemia compared to SAP; participant feedback was overwhelmingly positive. This study demonstrated the safety and efficacy of the AP even with the added challenges of cold temperature, high altitude, and extended exercise timeframes.

Supported by NIDDK, Special Statutory Funding Program for Type 1 Diabetes Research

Article: <https://www.ncbi.nlm.nih.gov/pubmed/28855239> [Dec 2017]

Vitamin D insufficiency associated with development of autoimmunity in some children at risk for type 1 diabetes

The Environmental Determinants of Diabetes in the Young (TEDDY) study is following over 6,000 newborns at high genetic risk for type 1 diabetes until age 15 to identify environmental factor(s) that may trigger or protect against development of type 1 diabetes. The researchers found that higher childhood 25-hydroxyvitamin D concentration was associated with lower islet autoimmunity; this association was modified by an individual's genetic background (a VDR allele).

Supported by NIDDK, NIAID, NICHD, NIEHS, NCATS, JDRF, CDC, Special Statutory Funding Program for Type 1 Diabetes Research

Article: <https://www.ncbi.nlm.nih.gov/pubmed/29061729> [Oct 2017]

Genetic factors associated with risk of type 2 diabetes in adolescents with obesity

Type 2 diabetes was once rare in children, but this has changed recently. More than 5,000 new cases of type 2 diabetes are estimated to be diagnosed among US youth younger than age 20 each year. For adults, scientists have identified unique genetic factors that raise the risk of developing type 2 diabetes, but it has been unclear if the same genetic factors are related to type 2 diabetes in teens. Researchers investigated variations in the TCF7L2 gene, which has been implicated in adult diabetes, in a group of adolescents with obesity. They found that a specific variation in this gene was associated with a higher risk of impaired glucose tolerance and type 2 diabetes in adolescents.

Supported by NICHD, NIDDK, NCATS

Article: <https://www.ncbi.nlm.nih.gov/pubmed/28611053> [Aug 2017]

Structural Congenital Anomalies

Identification of three genetic variants associated with orofacial clefting

To uncover genetic differences that cause susceptibility to dental, oral, and craniofacial diseases and conditions, scientists used genome-wide association studies (GWAS) to identify three genomic variants associated with cleft lip/palate. Studies in cells grown in the laboratory showed that two of the genetic variants affect DNA interactions with CL/P-associated transcription factor proteins and another disrupts the DNA architecture. Further understanding the biological effects of these variants may lead to novel approaches to diagnose, manage, and treat disease.

Supported by NIDCR

Article: <https://www.ncbi.nlm.nih.gov/pubmed/28287101> [Mar 2017]

Researching Zika virus disruption of fetal craniofacial development

Zika virus infections during pregnancy can disrupt fetal craniofacial development, causing devastating birth defects. Researchers showed that Zika virus can infect cranial neural crest cells, the cells that form most of the craniofacial structures. Infection of cultured cranial neural crest cells disrupted their normal maturation by promoting premature neuronal formation, which may contribute to the disruption of normal fetal craniofacial development. This study expands our understanding of how Zika virus infection disrupts embryonic development so that researchers can devise strategies to prevent birth defects.

Supported by NIDCR, NICHD, NIAID, NIGMS, HHMI

Article: <https://www.ncbi.nlm.nih.gov/pubmed/27693308> [Oct 2016]

Screening for learning deficits in children with craniosynostosis

Children with craniosynostosis, the premature fusion of the fibrous joints (sutures) that separate the bony plates of an infant's skull, are at increased risk for developing learning disabilities, impaired memory, and reduced attention span. Scientists studied cognitive development in these children to identify areas where extra tutoring during early childhood could help close the learning gap. They found that some children with craniosynostosis have challenges with attention and inhibitory control. This study will help identify

subgroups of children with craniosynostosis who might develop learning disabilities and who could benefit from additional support to help them succeed in the classroom.

Supported by NIDCR

Article: <https://www.ncbi.nlm.nih.gov/pubmed/26381123> [Jan 2017]

Cardiovascular risk factors in children with myelomeningocele

Myelomeningocele (MM) is the most common and severe type of spina bifida, occurring in approximately 20-30 of 100,000 live births. MM affects the brain and spinal cord, and can lead to developmental delay, muscle weakness and paralysis, and/or loss of sensation. Children with MM often experience prolonged periods of inactivity, leading to a higher incidence of obesity. Researchers conducted a study to identify pre-clinical signs of disease in 86 children age 6 to 13, where 38 had MM and 58 did not. Children in the MM group showed abnormal biochemical markers for cardiovascular disease, insulin resistance, and bone and mineral metabolism. They also had elevated and/or adverse blood serum levels, higher body fat, higher prevalence of vitamin D deficiency, and significantly lower levels of calcium and alkaline phosphatase. Some of the adverse blood serum levels of the MM group, such as high-density lipoproteins, insulin, and aspartate aminotransferase, were related to higher body fat. However, other markers such as alkaline phosphatase, albumin, creatinine, calcium, PTH and vitamin D, occurred independent of body fat. The children in the MM group had lower parathyroid hormone levels compared to the non-MM group, despite lower calcium, vitamin D and alkaline phosphatase levels. This suggests an alteration in the sensing mechanism or response of the parathyroid gland in children with MM. These findings highlight the importance of screening tests for risk factors in children with MM.

Supported by NICHD

Article: <https://www.ncbi.nlm.nih.gov/pubmed/26666357> [Mar 2017]

Newborn screening allows propionic acidemia to be diagnosed sooner

Propionic acidemia is a rare disease in which the body is unable to process certain parts of proteins and lipids (fats) properly, causing these substances to build up in the blood, urine, and tissues to toxic levels. It affects about 1 in 100,000 people in the United States. The initial symptoms include poor feeding, vomiting, loss of appetite, weak muscle tone (hypotonia), and lack of energy (lethargy). These symptoms can progress to more serious medical problems, including heart abnormalities, seizures, coma, and possibly death. However, the sooner a person is diagnosed, the sooner the disease can be managed by changing their diet. To assess the quickest method for evaluating and treating patients with propionic acidemia, researchers studied 58 individuals who had been diagnosed with propionic acidemia through abnormal newborn screening results, symptoms that occurred in a clinical setting, or the presence of a family history of the disease. The researchers found that, on average, abnormal newborn screening results allowed treatment of the patients within 15 days after birth. By contrast, patients who received a diagnosis based on clinical symptoms were started on treatment around 11 months after birth, and patients who had been diagnosed based on family history went over a year without treatment, on average. In addition, newborn screening was able to identify patients who had excess of ammonia in their blood, a hallmark of the disease requiring rapid intervention and treatment. These findings show that newborn screening is valuable for diagnosing and treating propionic acidemia early in life.

Supported by NICHD

Article: <https://www.ncbi.nlm.nih.gov/pubmed/27776753> [Jan 2017]

Intellectual and Developmental Disabilities

Potential treatment for Fragile X

In a small preliminary clinical trial, researchers tested whether low doses of the drug sertraline (brand name Zoloft) could help with early language development in Fragile X syndrome (FXS) during the period when the brain is developing most rapidly. Since one retrospective study had found positive effects of

sertraline on language development in FXS, researchers thought that the drug should be tested using a randomized control trial in the condition. The trial did not show an apparent effect of sertraline on early language development in children with FXS only; however, other findings indicated that the drug may positively affect certain other aspects of development in FXS, including motor coordination and social participation.

Supported by NICHD, NCATS

Article: <https://www.ncbi.nlm.nih.gov/pubmed/27560971> [Oct 2016]

Study of ganaxolone in children with Fragile X yields mixed results

Ganaxolone is a compound that has been used to reduce anxiety in animal models and to treat epilepsy and traumatic stress disorders in both adults and children. Researchers in Belgium and California conducted a clinical trial to see if treatment with ganaxolone would lead to improvements in behavior in children with Fragile X syndrome (FXS). A total of 60 children with FXS between ages 6-17 were randomly assigned to receive either first ganaxolone then a placebo with no therapeutic effect, or first a placebo then ganaxolone. The researchers did not find significant differences between the children during treatment with ganaxolone versus the placebo. However, when the scientists further analyzed data from only those children who had a higher baseline anxiety or lower cognitive abilities, they found that there may have been improvements in attention, hyperactivity, and anxiety in these subgroups of children with FXS after taking ganaxolone.

Supported by NICHD, NCATS

Article: <https://www.ncbi.nlm.nih.gov/pubmed/28764646> [Aug 2017]

Gene variations may help identify children with Fragile X syndrome most likely to be helped by antidepressant

Researchers sought to characterize whether drugs called selective serotonin reuptake inhibitors (SSRIs) could block how quickly serotonin is removed from neurons, which could prolong the effects of serotonin on these neurons. SSRIs are commonly prescribed to treat depression and anxiety in children and adults. Approximately 50 percent of Fragile X syndrome (FXS) patients over five-years-old are prescribed an SSRI to treat anxiety, irritability, or socialization defects. In this study, researchers aimed to identify biomarkers that might indicate whether a child with FXS was more or less likely to improve when treated with an SSRI called sertraline. The researchers conducted a clinical trial in which 57 children with FXS ages 24 to 72 months old received either low-dose sertraline or a placebo for six months. They measured the children's language development and clinical improvement of any symptoms, and analyzed DNA from collected blood samples. In the trial, children taking sertraline had significant improvements in overall development, cognition, language expression, and social interactions, compared with children taking a placebo. When the researchers examined specific genes in the serotonin pathway, they found that children with certain variations of the BDNF gene in the serotonin pathway were more likely to respond to sertraline than children who did not have these BDNF variations. These results suggest that looking at specific gene variations may help identify children with FXS who are most likely to respond to treatment with an SSRI.

Supported by NICHD

Article: <https://www.ncbi.nlm.nih.gov/pubmed/28242040> [Jun 2017]

Model of Fragile X syndrome shows defects in early neuron development

Researchers studied differences in genetic material generated from cells from individuals who had been diagnosed with Fragile X syndrome (FXS) and autism spectrum disorder (ASD), compared to genetic material in cells from normal subjects. When the researchers analyzed the FXS cells, they found impairments in how neurons matured, how cells communicated with each other, how cells moved into their proper locations during development, and which genes are expressed during development. The results show that differences associated with FXS begin very early. These findings may also help explain some of the similarities between FXS and ASD.

Supported by NICHD, NIGMS, NIDA, NIMH

Article: <https://www.ncbi.nlm.nih.gov/pubmed/28137726> [Mar 2017]

Improving myelin production in a mouse model of tuberous sclerosis complex

Affecting 1 in 6000 newborns worldwide, tuberous sclerosis complex (TSC) is a genetic disorder characterized by the growth of numerous noncancerous tumors in many parts of the body. TSC results from loss of function of either the *TSC1* gene or the *TSC2* gene. TSC often affects the brain, causing seizures, behavioral problems, and, in some people, autism and intellectual disability. TSC patients with autism have problems in their white matter, which coordinates communication between different regions of the brain. Brain cells in white matter are covered by a protective coating called myelin, which is essential for proper brain function. Researchers used a mouse model to show that deleting *TSC1* (one of the genes that can cause TSC) leads to decreased myelin in the brain. Loss of the *TSC1* gene led to increased production of a protein called connective tissue growth factor (CTGF). Treatments that subsequently removed some of this excess CTGF led to better myelin production in this mouse model. These findings suggest that this pathway is a promising target for future therapies in TSC.

Supported by NICHD, NINDS

Article: <https://www.ncbi.nlm.nih.gov/pubmed/28183733> [Mar 2017]

Genomic resource describes molecular changes in tuberous sclerosis complex

The molecular changes underlying tumor growth in tuberous sclerosis complex (TSC) are essential to understanding potential causes and treatments of the disease. Researchers conducted a comprehensive study of the genomics of TSC, evaluating over 100 TSC-associated tissues for mutations in the TSC genes, other DNA mutations, abnormal numbers of genes, and different types of gene expression in specific types of tissue. The scientists have compiled this information to create a molecular catalogue of TSC, which will be a resource for researchers seeking to understand genetic and other biological factors behind the clinical manifestations of TSC.

Supported by NICHD, NINDS, NCI

Article: <https://www.ncbi.nlm.nih.gov/pubmed/28643795> [Jun 2017]

Brain imaging identifies earliest brain network connections in behavior linked to autism

Initiating joint attention (IJA), a phenomenon linked to both language and social development in children, emerges over the first two years of life and occurs when a young child sees an object in their environment and then gets someone else to focus on it by pointing or shifting gaze. Atypical development of IJA is a strong indicator of autism spectrum disorder (ASD). However, the brain systems underlying IJA in early childhood are poorly understood. Researchers used functional Magnetic Resonance Imaging (MRI) scans to identify brain networks involved in IJA in 116 children assessed at 12 months of age, 98 children assessed at 24 months of age, and 37 individuals providing data at both timepoints. The children's brains were scanned while they slept. The next day, the children were assessed to see how often they initiated joint attention. Some of the children had an elevated risk of ASD because they had older siblings who had been diagnosed with the disorder. The study results identified specific networks of brain connectivity associated with IJA at both 12 and 24 months of age, offering the first data on the functional structure associated with the development of IJA from infancy to toddlerhood. This knowledge could lead to interventions that bolster the development of IJA in children at risk for ASD.

Supported by NICHD, NIEHS, NIMH

Article: <https://www.ncbi.nlm.nih.gov/pubmed/28062515> [Mar 2017]

High-risk infants with excess fluid around their brains are more likely to develop autism

Early intervention in autism spectrum disorder (ASD) has been associated with the most positive treatment outcomes. Therefore, diagnosis of ASD at the youngest age possible is important. To identify differences in the brain that could help diagnose ASD sooner, researchers used magnetic resonance imaging (MRI) to examine a potential early marker of ASD, increased cerebrospinal fluid in the brain.

Cerebrospinal fluid cushions the brain and spinal cord. The researchers used MRI images to measure the amount of cerebrospinal fluid in 343 infants at 6 months of age, who were at high or low familial risk for ASD. The researchers then tested the children for ASD at 2 years of age. Infants who later developed ASD had more cerebrospinal fluid in the space around the brain than infants who did not develop ASD. The amount of fluid was related to the symptom severity: infants with more cerebrospinal fluid generally had more severe autistic behaviors than those with less fluid. The findings suggest that increased levels of cerebrospinal fluid in infants could be an important factor contributing to the development of ASD or a biomarker that may allow for earlier diagnosis and intervention.

Supported by NICHD, NIMH, Autism Speaks

Article: <https://www.ncbi.nlm.nih.gov/pubmed/28392081> [Aug 2017]

An enzyme deficiency contributes to disease symptoms in Prader-Willi syndrome

In a recent study of Prader-Willi Syndrome (PWS), which is marked by insatiable appetite leading to obesity in childhood, researchers discovered a critical role for the enzyme, prohormone convertase 1 (PC1). PWS is caused when a part of the genome is missing, resulting in several genes not passing down from a father to a child, leading to many detrimental effects on the infant's body that persist throughout adulthood. Scientists linked this genetic deletion to reduced activity of PC1. While the findings contribute to a growing body of knowledge investigating how the loss of a gene alters hormone levels and function in PWS, more research is necessary to determine if other mechanisms are involved.

Supported by NIDDK

Article: <https://www.ncbi.nlm.nih.gov/pubmed/27941249> [Jan 2017]

Seizure patterns in patients with Rett syndrome change over time

Rett syndrome, a disorder of the brain primarily affecting girls, can cause intellectual disability, seizures, and other symptoms. From 2006 to 2015, researchers monitored almost 1000 children with Rett syndrome to characterize their seizures. The overall lifetime risk of developing seizures was around 90 percent, and the course of seizures was highly variable. The scientists found that the total number of people with seizures increased with age, peaking at 16-19 years old. The development of seizures was associated with frequent hospitalizations, inability to walk, requirement for tube feedings, and more severe clinical features in general. The seizure patterns fell in to three general categories: those that did not develop seizures, those that never stopped having seizures, and most frequently, those that experienced variable relapse and remission during the study. This study provides the largest evaluation of seizures in Rett syndrome to date and may help in developing treatment trials to improve outcomes for girls with Rett syndrome.

Supported by NICHD, NCATS

Article: <https://www.ncbi.nlm.nih.gov/pubmed/28007990> [Feb 2017]

Echocardiogram measurements in children with Rett syndrome

Rett syndrome is a genetic disorder caused by mutations in the *MECP2* gene, predominantly affecting girls. After birth, girls with classic Rett syndrome have 6-18 months of apparently normal development before developing severe problems with language and communication, learning, coordination, and other brain functions. Compared to typically-developing children and adolescents, individuals with Rett syndrome have a higher incidence of sudden, unexpected death, which could be caused by factors such as respiratory failure, seizures, or irregular heart rhythms. Individuals with Rett syndrome often show abnormal recordings on electrocardiograms (ECGs), which display the electrical activity of heart muscles, showing the lengths of different segments of each heartbeat. Researchers analyzed the ECGs from 100 individuals with Rett syndrome aged 1 to 17 years, correlating an ECG measurement called the QTc interval with patient age, clinical severity, and mutation type. Some individuals with Rett syndrome and particular types of mutations showed a relatively high proportion of prolonged QTc, which could indicate a higher risk of sudden cardiac death, but no specific mutation predicted a prolonged QTc. There was a positive relationship between QTc and age, as well as QTc and clinical severity score, among those who

were between 7- and 13-years-old. These findings indicate that individuals with Rett syndrome may benefit from a baseline ECG, with follow-up measurements for those with a prolonged QTc, particularly as they age.

Supported by NICHD, NIGMS

Article: <https://www.ncbi.nlm.nih.gov/pubmed/28394409> [Jun 2017]

Alzheimer's disease in Down syndrome individuals may be affected by flawed system for breaking down proteins

Down syndrome is the most frequent genetic cause of intellectual disability, affecting about 1 in every 700 newborns. Middle-aged adults with Down syndrome have a much higher risk of developing Alzheimer's disease, compared with people of similar age without Down syndrome. Down syndrome and Alzheimer's disease both involve neurodegeneration, or the breakdown of proteins and other structures in the brain. One of the ways that cells degrade proteins is by tagging the protein with a compound called "ubiquitin," a process called "ubiquitinylation." Ubiquitin signals a cell system to find the protein and break it down, so that the cell can reuse the protein's components to build other structures. Researchers examined how this process may be different in the brains of individuals with Down syndrome, and in those with Down syndrome who also have Alzheimer's disease, compared to age-matched controls. They found different patterns of proteins that had been tagged with ubiquitin in the brains in each of these groups. These patterns of ubiquitinated proteins also differed across age. Inefficient breakdown of proteins can result in a build-up of damaged proteins, which can be harmful for brain cells, possibly contributing to symptoms of Alzheimer's disease. The researchers theorize that disruptions in how cells tag proteins with ubiquitin may be an important part of aging and neurodegeneration. Studying this system could lead to insights on how to track or treat disorders like Down syndrome and Alzheimer's disease.

Supported by NICHD

Article: <https://www.ncbi.nlm.nih.gov/pubmed/27627691> [Mar 2017]

Executive function in people with Down syndrome

Down syndrome is the most common cause of developmental delay and intellectual disability, affecting 1 in 700 babies. Compared with typically developing peers, individuals with Down syndrome tend to score lower on measures of executive function, a broad term that includes several different cognitive processes, such as working memory, inhibition, shifting, and planning. These skills are important for an individual to perform goal-directed actions. To understand the specific components of executive function in people with Down syndrome, researchers surveyed parents of individuals with Down syndrome between the ages of 2 to 35 years. They found that across childhood and adulthood, people with Down syndrome exhibited relatively strong emotional control, but had more difficulties with working memory. The ability to move freely from one situation or activity to another tended to be lower in middle childhood (6 to 18 years of age) for people with Down syndrome, compared with Down syndrome individuals in early childhood (2 to 5 years of age) or adulthood (18 to 35 years of age). Understanding specific areas of difficulty and strengths could provide insights on interventions for parents and caregivers of individuals with Down syndrome to improve overall completion of expected tasks.

Article: <https://www.ncbi.nlm.nih.gov/pubmed/28726285> [Sep 2017]

Identifying genetic causes of MEHMO syndrome, a rare intellectual disability condition

MEHMO syndrome (a condition characterized by severe intellectual disabilities, epilepsy, hypogonadism and hypogonadism, microcephaly, and obesity) is a rare condition first described in 1989. To date, researchers have found the full-blown syndrome in only a few families. It is X-linked recessive, which means that it affects only males who inherit it from unaffected women. Scientists have discovered that the syndrome is associated with a specific region on the X chromosome, but they did not know exactly which gene or genes were involved. A team of scientists compared the X chromosome of the affected male children in four families with that of their mothers and other female family members. In all four families,

the children and their mothers had mutations in a gene called EIF2S3, which is important in initiating protein synthesis. In three of the families, the mutation was identical, resulting in a shortened protein with impaired function. In the fourth family, the inherited mutation partially reduced the protein's effectiveness. The three boys with the same mutation all had the full-blown syndrome, had never achieved head control, could not make any voluntary movements, and were not capable of any social interaction. The fourth boy was less severely affected. This work shows the link between mutations in the *EIF2S3* gene and MEHMO syndrome, helping to explain what causes the syndrome, and indicates that different mutations in *EIF2S3* affect function in different ways.

Supported by NICHD

Article: <https://www.ncbi.nlm.nih.gov/pubmed/28055140> [Apr 2017]

Comparing treatments for children with ADHD and reading disabilities

Children with attention-deficit/hyperactivity disorder (ADHD) often are diagnosed with reading disorders. However, researchers do not know if treating one disorder can address problems with reading and attention. An NICHD-supported study published in May found that combining treatments—medication for ADHD and reading intervention—offered the best outcome. The findings show that while both disorders need separate treatments, these interventions can be done effectively at the same time.

Supported by NICHD

Article: <https://www.ncbi.nlm.nih.gov/pubmed/28333510> [May 2017]

Neurological Disorders and Mental Health

Hotspots of missense mutation identify neurodevelopmental disorder genes and functional domains

Using a genome wide approach and publicly available large sample sequencing data, researchers identified 200 genes with significant clustering of novel patient-specific, protein coding missense mutations. Further analysis of the identified hotspot genes showed enrichment for synaptic signaling, and chromatin mediated regulation of transcription pathways both previously implicated in autism and other psychiatric disorders.

Supported by NIMH, NICHD, NCATS, NIDCD, NHGRI, NIGMS

Article: <https://www.ncbi.nlm.nih.gov/pubmed/28628100> [Aug 2017]

Skill training improves hand function in children with unilateral spastic cerebral palsy

Cerebral palsy (CP) represents a range of prenatal and perinatal brain disorders that primarily affect muscle coordination and body movement. In one form of CP, unilateral spastic cerebral palsy, the early damage results in motor difficulties that predominantly affect one side of the body. To help these children recover function in their affected hands and arms, researchers have developed intense training programs to help reshape the circuitry throughout the brain and spinal cord. Similar therapeutic strategies have been effective in promoting arm function in adults who have survived a stroke. This particular study focused on the role of more therapeutically-directed strategies in structured skill training. In a day camp setting, children with unilateral CP spent three weeks of intense therapy using both limbs to practice their movements in play-based activities for six hours a day, five days a week. The children were trained in one of two formats: structured skill training or unstructured play. In the structured skill training group, the children had to accomplish progressively more difficult tasks (like reaching for a game board that was farther away to increase the child's arm extension), perform repeated partial movements of more complicated tasks, and try to complete functional tasks (like dribbling a basketball or tying shoes). In the unstructured play group, the children focused on "having fun" using both hands, but did not have to complete specific therapeutic tasks. The researchers analyzed changes in hand function and performance immediately after and six months after training, as well as how the brain circuitry was affected by the different treatment approaches. The three-week intense training resulted in significant improvements in hand function across both structured and unstructured treatment groups, with somewhat better results in

the structured group. Interestingly, only the structured skill training resulted in positive changes in the brain circuitry, specifically increasing the representation of the brain region that controls the affected hand. The extent of these brain changes was most dramatic in the children who had made the most functional improvements. This study emphasizes the benefit of intense therapeutic training children with unilateral spastic CP, and suggests how the use of skill training may drive brain adaptability and improve hand function.

Supported by NICHD, NINDS, NCATS

Article: <https://www.ncbi.nlm.nih.gov/pubmed/26867559> [Oct 2016]

Mitochondria affect cell membrane repair mechanisms in Duchenne muscular dystrophy

Duchenne muscular dystrophy (DMD) affects approximately 1 in 3500 male births worldwide. Most boys with DMD are unable to walk by age 12 and may later need a respirator to breathe. They usually die in their late teens or early 20s from heart trouble, respiratory complications, or infection. DMD is caused by a dysfunction in the gene that codes for dystrophin, a protein in the muscle; loss of dystrophin causes loss of muscle function and weakness. To understand how muscle cells weaken and atrophy in DMD, researchers analyzed two dystrophin-deficient mouse models of muscular dystrophy. Response to muscle injury is a complex process involving mitochondria traveling to the site of the injury, as well as an increase in membrane proteins regulated by the protein dysferlin. In the muscle fibers of the DMD mice, the number of mitochondria at the injury site was much lower than in normal mice, reducing the ability of the muscle cells to repair the injuries. However, the number of dysferlin-regulated proteins increased over the level in normal muscles, which appeared to compensate for reduced mitochondrial function. The researchers were able to improve muscle repair in the DMD mouse models by restoring dystrophin function through genetic engineering and by increasing mitochondrial function. Therefore, a combined approach of exercise and genetic engineering may be a potential therapy for muscle repair in DMD.

Supported by NICHD, NIAMS, NIH OD

Article: <https://www.ncbi.nlm.nih.gov/pubmed/27834955> [Feb 2017]

New approach offers potential opportunity to those often excluded from Duchenne muscular dystrophy clinical trials

While lower limb magnetic resonance imaging is being used as a biomarker in clinical trials to measure progression of Duchenne muscular dystrophy (DMD), the tool is useful only for boys who retain the ability to walk. Once a DMD patient is confined to a wheelchair, the leg muscles are almost completely replaced by fat and non-functioning connective tissue. Researchers demonstrated that MRI of the arm and shoulder can be followed to track disease progression and response to an intervention during clinical studies involving older patients in the later stages of disease. This could dramatically expand the number of individuals who could participate in clinical trials.

Supported by NIAMS

Article: <https://www.ncbi.nlm.nih.gov/pubmed/27778157> [Jan 2017]

Optimizing steroid treatment for Duchenne muscular dystrophy

Researchers examined cell culture and mouse models to understand how glucocorticoids preserve muscle function in boys who have Duchenne muscular dystrophy. They found that weekly dosing upregulates two genes involved in muscle cell membrane repair, while daily dosing activates cell pathways that cause muscle to shrink and weaken. If the responses also occur in patients, this study could directly inform prescription instructions that would maximize the drugs' therapeutic benefit while minimizing negative side-effects. This work could also extend beyond the muscular dystrophies, as approximately one percent of the entire population in the United States is treated chronically with glucocorticoids for other conditions.

Supported by NIAMS, NINDS, PPMD, MDA, AHA

Article: <https://www.ncbi.nlm.nih.gov/pubmed/28481224> [Jun 2017]

Sex differences in sensitivity to aripiprazole from adolescence to adulthood

In recent years, prescription rates for antipsychotic medications have increased for both males and females; however, many studies on the effectiveness of these drugs have excluded females and focused solely on males. Studies including children at different ages have also been lacking. Researchers used behavioral tests in rats to study long-term effects in adolescent males and females exposed to an antipsychotic medication called aripiprazole. The findings showed that repeated treatment with aripiprazole increased the rats' sensitivity to the medication, which lasted into adulthood. Moreover, females were more sensitive than males to both short- and long-term effects. The scientists then tested rats who had been exposed to aripiprazole for sensitivity to subsequent treatments with two other medications, olanzapine and clozapine. Prior treatment with aripiprazole showed a slight increase in the rats' sensitivity to olanzapine. These findings show that exposure to antipsychotic medications during adolescents can cause long-lasting changes in the behavioral development of animals, with a potential increase or decrease in sensitivity to subsequent treatments with other antipsychotic medications in adulthood.

Supported by NICHD

Article: <https://www.ncbi.nlm.nih.gov/pubmed/28389140> [May 2017]

Common treatments for migraine are ineffective in children and adolescents

NIH-supported researchers tested the effectiveness of two commonly prescribed medications for children and adolescents with migraine, a condition that affects millions children and adolescents in the United States, but for which there is a paucity of evidence to guide treatment decisions. The CHAMP trial was a phase 3 randomized controlled trial in which researchers compared amitriptyline, topiramate, and placebo for prevention of recurrent migraines over a 6-month period in children (ages 8-12) and adolescents (ages 13-17). The trial was stopped early because the results revealed that neither medication was better than placebo in reducing the frequency of migraines, and that both active drugs were associated with adverse events, some of which were serious. This trial suggests that the adult model of headache treatment, where amitriptyline and topiramate have been used effectively, may not apply to pediatric populations, and the study will have important implications for pediatric headache clinical practice.

Supported by NINDS

Article: <https://www.ncbi.nlm.nih.gov/pubmed/27788026> [Jan 2017]

Differences in major depression among adolescent girls and boys

Major depression is a complicated mental health issue that often begins in the teen years. Researchers analyzed a large national survey of over 100,000 12- to 17-year-old American youth to analyze how often teens became depressed, when depression is most likely to start, and how patterns of depression may be different for girls and boys. The data showed higher rates of depression in adolescents compared with previous studies – more than 1 in 5 girls and about 1 in 8 boys reported having experienced depression. At age 12, girls were already more likely to report depression compared with boys, and this difference became wider throughout adolescence. Depression affected the ability to function in school and the community. For girls, persistent depression was more strongly associated with poor functioning compared with depression that began recently; but for boys, the effects of persistent and recent depression were similar. Because both recent and persistent depression were associated with poor academic performance, family issues, and suicide attempts, the researchers suggest treating depression promptly rather than taking a "wait and see" approach.

Supported by NICHD, NIMHD

Article: <https://www.ncbi.nlm.nih.gov/pubmed/28556831> [May 2017]

Scalable, brief interventions for youth with anxiety and depression

While depression and anxiety disorders are prevalent among youth, they are markedly undertreated, especially in Hispanic populations. Researchers showed that that a structured, brief behavioral therapy (BBT) delivered in a pediatrics practice offered much greater benefit to youth (aged 8 to 16) with anxiety

and depression than the more standard referral to mental health care with follow-up approach. Youth in the BBT group showed significantly greater reductions in symptoms, and also showed improvements on measures of functioning. The effects of BBT were even more striking in Hispanic youth, suggesting scalable treatments in pediatric settings may be an effective means of improving access to mental health care and addressing health disparities.

Supported by NIMH

Article: <https://www.ncbi.nlm.nih.gov/pubmed/28423145> [Jun 2017]

NIMH Science Update: <https://www.nimh.nih.gov/news/science-news/2017/pediatrics-based-brief-therapy-outdoes-referral-for-youths-with-anxiety-and-depression.shtml>

Complementary features of attention bias modification therapy and cognitive behavioral therapy in pediatric anxiety disorders

Researchers developed implicit, computer-based techniques to alleviate anxiety in young children. The scientists studied cognitive behavioral therapy, which focuses on developing personal coping strategies and changing unhelpful patterns in thoughts, beliefs, attitudes, behaviors, and emotional regulation. Cognitive behavioral therapy was combined with either placebo or active attention bias modification therapy, where a therapeutic action targets a specific bias in attention. Cognitive behavioral therapy with active attention bias modification therapy showed enhanced benefits.

Supported by NIMH

Article: <https://www.ncbi.nlm.nih.gov/pubmed/28407726> [Aug 2017]

Substance Misuse

NIH Monitoring the Future survey shows teen use of most illicit substances down

The Monitoring the Future (MTF) annual survey measures drug use and attitudes among 8th, 10th, and 12th graders. The results show a continued long-term decline in the use of many illicit substances, including marijuana, as well as alcohol and tobacco, and misuse of some prescription medications, among the nation's teens.

Supported by NIDA

<http://monitoringthefuture.org/>

NIDA Press Release: <https://www.drugabuse.gov/news-events/news-releases/2016/12/teen-substance-use-shows-promising-decline> [Dec 2016]

Substance use and adolescent firearm homicide

Homicide is the third leading cause of death for adolescents in the United States, and the leading cause of death for African American adolescents. To determine the relationship between homicide and exposure to drugs, firearms, and alcohol for individuals, families, and neighborhoods, researchers studied all 13- to 20-year-olds who were homicide victims in Philadelphia from January 2010 to December 2012, using police and medical examiner's reports. Almost all adolescent homicide cases in Philadelphia were committed with a firearm (157 firearm cases within 161 homicide cases overall). Compared to 172 matched control subjects, substance use at the individual, family, and neighborhood levels was associated with increased risk of adolescent firearm homicide. Expanding violence prevention efforts to target substance use may help reduce firearm violence that disproportionately affects adolescents in large cities in the United States.

Supported by NIAAA, NICHD, CDC

Article: <https://www.ncbi.nlm.nih.gov/pubmed/28055064> [Mar 2017]

Adolescents, substance use, and depression

About one-third of high school students in the United States say they currently use alcohol, and about one-quarter use marijuana. Up to one-fifth of adolescents have experienced a depressive episode.

Adolescents who have depression and use alcohol or marijuana are at higher risk for longer depressive episodes, severe mental health issues, and suicide. Substance use and depression often occur at the same time. Using data from a national study on adolescents, a team of researchers set out to study how the frequency of substance use and symptoms of depression could evolve between adolescence and young adulthood, and whether the associations between them were stronger for females or males. The researchers found that both male and female adolescents with symptoms of depression were more likely to use marijuana through young adulthood, but they were not more likely to binge drink. Adolescents—especially young women—who binge drank or used marijuana were more likely to develop symptoms of depression between adolescence and young adulthood than were those who did not. The researchers hope these findings will help with efforts to screen adolescents for substance abuse and depression.

Supported by NICHD, NIDA

Article: <https://www.ncbi.nlm.nih.gov/pubmed/27567065> [Dec 2016]

Relationship violence changes binge drinking patterns of adolescents

Both relationship violence and binge drinking are common among adolescents. To understand how these behaviors may be related, researchers interviewed over 3,600 12- to 17-year-olds at least twice over a three-year period. Patterns of binge drinking and relationship violence were highly variable. However, the data showed that teens tended to engage in binge drinking more often over time as they got older. There were no significant differences in rates of binge drinking among boys and girls. Binge drinking was associated with new reports of relationship violence, but surprisingly, teens exposed to relationship violence generally experienced a significantly faster decline in binge drinking over the course of the study. These findings suggest that teenagers may engage in binge drinking in the short term following a period of violence, but ultimately binge drink less than their non-victim peers, perhaps to reduce their risk of subsequent relationship violence.

Supported by NICHD, NIDA, NIMH

Article: <https://www.ncbi.nlm.nih.gov/pubmed/28494414> [Jul 2017]

Decision tree to identify children affected by prenatal alcohol exposure

Identifying children with prenatal alcohol exposure can be difficult, especially in individuals who lack physical features of Fetal Alcohol Syndrome. A primary screening tool for use by pediatricians to identify children with neurobehavioral impairments attributable to in utero alcohol exposure could distinguish children affected by prenatal alcohol exposure from non-exposed children, including those with other behavioral conditions. The findings provide a novel model for identifying children with prenatal alcohol exposure that requires a limited number of measures and can be obtained easily as part of standard clinical practice.

Supported by NIAAA

Article: <https://www.ncbi.nlm.nih.gov/pubmed/27476634> [Oct 2016]

Effect of peer influence and cost on underage drinking

Researchers sought to learn how much friends' drinking habits and the price of alcohol influence underage drinking. Most research to date has studied one or the other, but not both of these factors together. Using interviews from students at 16 high schools and information from a national survey, the researchers found that high schoolers whose peers drank were much more likely to drink themselves, regardless of the price of alcohol. Peers' influence did not affect how often kids drank or whether they binge drank. Contrary to other studies on underage drinking, this study found that alcohol's cost was not a determining factor in whether high schoolers drank. The researchers concluded that access to alcohol is more of a hurdle for high schoolers than price. They suggested that laws to raise taxes on alcohol would therefore not lower rates of underage drinking.

Supported by NICHD

Article: <https://www.ncbi.nlm.nih.gov/pubmed/27507725> [Dec 2016]

Bone and Muscle Health

Effect of antidepressants and exercise on bone health in adolescents with anorexia

Anorexia nervosa (AN) is a psychiatric illness characterized by a distorted body image, depression, severe malnutrition, abnormal growth and compromised bone health. Individuals with AN often reduce their caloric intake to unhealthy levels, leading to a severely reduced body weight including low muscle and bone mass. Researchers assessed how exercise and use of antidepressant medication affected bone health in adolescent girls with AN and a comparison group of adolescent girls with normal weight. They found that for both groups of girls, exercise helped increase bone mass. However, in girls with AN, use of antidepressant medication was associated with poorer scores on measures of bone health.

Supported by NICHD, NIAMS, NCATS

Article: <https://www.ncbi.nlm.nih.gov/pubmed/27939877> [Feb 2017]

Effect of education program on calcium consumption and bone accrual

Poor nutrition and decreased calcium intake is associated with greater fracture risk and diminished bone density. More than 53 million people either already have osteoporosis, which commonly occurs in older women, or are at high risk as a result of low bone density. The highest rate of growth in bone mineral density occurs during adolescence. Previous studies have shown that calcium supplements in children improve bone density and contribute to bone health throughout childhood and into the adult years. Beneficial effects of supplements appear to last only while taking the supplements, but giving additional calcium through food could increase calcium intake through long-lasting nutrition choices. Researchers found that children who increased calcium in their diets and participated in five nutrition education sessions over a six-week period with their primary caregivers had significantly higher calcium intake even a year later, compared to children and caregivers who only had one visit with a dietician. However, the researchers did not find an increase in bone accrual over 12 months. The study suggests that dietary behavior changes can be long lasting if accompanied by nutritional education.

Supported by NICHD, NCATS, NIDDK

Article: <https://www.ncbi.nlm.nih.gov/pubmed/28225052> [Jun 2017]

Juvenile patients with anti-HMGCR antibodies experience more severe muscle disease

Autoimmune myopathies are muscle diseases associated with muscle inflammation (myositis), weakness, and production of myositis-specific autoantibodies (MSAs) by the body's immune system. MSAs are clinical markers that help predict disease severity and treatment response. Previous research revealed a link between statin exposure and expression of anti-HMGCR autoantibodies in adult myositis patients, and these individuals experience more severe disease and worse prognosis. However, the clinical features of juvenile patients with anti-HMGCR muscle disease are unclear. Scientists evaluated a cohort of juvenile myositis patients and determined that children with anti-HMGCR autoantibodies also experience worse muscle disease, more severe weakness, and limited response to therapy, compared to children with other MSAs. The researchers noted these patients did not have a history of statin exposure, and identified a strong link between the genetic marker HLA-DRB1*07:01 and development of anti-HMGCR autoantibodies in juvenile myositis patients.

Supported by NIAMS

Article: <https://www.ncbi.nlm.nih.gov/pubmed/28129483> [Jul 2017]

Hearing

Cost-effectiveness of newborn screening for cytomegalovirus (CMV) infection

Congenital cytomegalovirus (CMV) infection is a major cause of childhood hearing loss and deafness. An estimated 20,000 infants are born each year with this infection in the United States, and about 3,000 of these infants develop permanent disability. Studies show that treatment of newborns with congenital

CMV with an antiviral drug reduces both the frequency and severity of later hearing loss. This can result not only in long-term benefits for the child, but can also lead to cost savings through decreased need for medical care and special education services. However, children with congenital CMV may or may not show signs of the infection at birth, and as a result CMV-related hearing loss may not be discovered and treated early. A group of scientists wanted to look at whether screening newborns for CMV could be a cost-effective way of identifying more infants with congenital CMV infection. To do this, they estimated the benefits and costs of screening newborns for CMV infection under a wide range of assumptions about which infants would be screened, the cost of screening and the effectiveness of early treatment. The researchers found that if the early treatment is even partially effective in reducing hearing loss in half the treated infants, screening all newborns for CMV would reduce medical and educational costs by more than enough to compensate for the cost of the screening program.

Supported by NICHD, NIDCD, NIAID

Article: <https://www.ncbi.nlm.nih.gov/pubmed/27723885> [Dec 2016]

Gene therapy treatment for deafness shows promise in mouse model of Usher syndrome

Previous research in animal models suggests that gene therapy delivery to the inner ear may be an approach to correct genetic deafness in humans. Researchers expanded on this previous research by focusing on Usher syndrome, a catastrophic genetic disorder that causes blindness, balance disorders and profound deafness. In a mouse model of Usher syndrome, gene therapy resulted in recovery of hearing and balance behavior to near-normal levels. These study results show remarkable recovery of inner ear function, and suggest that these therapies may be suitable to be adapted for use by humans with genetic inner ear disorders.

Supported by NICHD, NIDCD, NIGMS, NEI, HHMI

Article: <https://www.ncbi.nlm.nih.gov/pubmed/28165476> [Mar 2017]

Childhood Disease

Gene therapy approved to treat retinal degenerative disease

In December 2017, the FDA approved Luxturna (voretigene neparvovec-rzyl), a new gene therapy, to treat children and adult patients with Leber Congenital Amaurosis (LCA), an inherited retinal degenerative disease characterized by severe loss of vision at birth, and progressing to blindness within several years. Luxturna is the first directly administered gene therapy approved in the United States that targets a disease caused by mutations in a specific gene, in this case the RPE65 gene. The RPE65 enzyme was discovered by scientists at the National Eye Institute in 1993, and it is responsible for regenerating the visual pigment necessary for rod and cone cells to respond to light. To translate this research into gene therapy, the team had to develop gene delivery vectors and test them in rodent models. They were then able to stably rescue vision in a naturally occurring dog model of LCA. Three teams conducted clinical trials, testing different vectors and delivery techniques. Early trials demonstrated safety in adult patients who were completely blind. However, the treatment was particularly efficacious on younger patients with greater residual vision. With LCA paving the way for gene therapies, there are now several gene-based therapeutic trials for inherited eye diseases, including retinoschisis, achromatopsia, and a mitochondrial gene mutation, Leber Hereditary Optic Neuropathy.

Supported by NEI

FDA News Release: <https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm589467.htm> [Dec 2017]

Genetic repair of stem cells from patients with chronic disease

Scientists utilized a novel gene-editing method to repair a genetic defect in cells called hematopoietic stem and progenitor cells (HSPCs) that can reconstitute the immune system. HSPCs were derived from patients with X-linked chronic granulomatous disease (X-CGD), an immunodeficiency disorder

diagnosed in childhood, and edited utilizing CRISPR-Cas9 gene repair. These results demonstrate the feasibility of a gene-editing approach for a treatment of X-CGD and possibly other blood cell disorders.

Supported by NIAID

Article: <https://www.ncbi.nlm.nih.gov/pubmed/28077679> [Jan 2017]

Gene sequencing in congenital heart disease

The Pediatric Cardiac Genomics Consortium recently performed gene (exome) sequencing in a cohort of >2,800 patients with congenital heart disease (CHD). The analysis sheds light on rare, transmitted variants associated with CHD as well as causes of isolated CHD:

- A recessive founder mutation in *GDF1* was implicated in ~5 percent of severe CHD in Ashkenazim.
- Recessive *MYH6* mutations accounted for ~11 percent of Shone complex.
- Dominant *FLT4* mutations accounted for 2.3 percent of Tetralogy of Fallot.
- Rare *de novo* mutations were implicated in ~3 percent of children with isolated CHD and ~28 percent with both neurodevelopmental and extra-cardiac congenital anomalies.

Supported by NHLBI, NCATS, NHGRI

Article: <https://www.ncbi.nlm.nih.gov/pubmed/28991257> [Nov 2017]

Personalized medicine treatment plan developed after identification of a rare pathogenic mutation

Diagnosed at 1 year of age with Diamond-Blackfan anemia (DBA), a 6-year old boy subsequently underwent a bone marrow transplant with a fully matched donor. Although expected to be curative, the transplant was not successful and the boy did not survive due to complications of the procedure. Given the unanticipated transplant outcome, researchers wanted to learn the cause of the boy's severe anemia. An analysis of the boy's genes did not reveal mutations known to cause DBA but did identify, for the first time, a mutation in the gene encoding erythropoietin (EPO). The EPO mutation decreased its ability to remain attached to the EPO receptor, resulting in significantly diminished ability to stimulate red blood cell proliferation. While their findings were under review for publication, the researchers learned that the parents of the 6-year old boy had a newborn child who also had anemia. Equipped with the new knowledge gained through research, the clinical scientists developed a treatment strategy consisting of injections of normal EPO produced in the laboratory. After 11 weeks of treatment, the child's red cell production had increased—eliminating the need for blood transfusions.

Supported by NIDDK, NHLBI, and NHGRI

Article: <https://www.ncbi.nlm.nih.gov/pubmed/28283061> [Mar 2017]

Scientists identify single-gene mutations that lead to atopic dermatitis

Scientists discovered novel mutations in the *CARD11* gene in four unrelated families with severe atopic dermatitis, or eczema, a condition most common in babies and children, and studied the resulting cell-signaling defects that contribute to allergic disease. Their findings suggest that some of these defects potentially could be corrected by supplementation with the amino acid glutamine.

Supported by NIAID and NCI

News Release: <https://www.niaid.nih.gov/news-events/scientists-identify-single-gene-mutations-lead-atopic-dermatitis>

Article: <https://www.ncbi.nlm.nih.gov/pubmed/28628108> [Aug 2017]

New response criteria for clinical trials developed for juvenile and adult dermatomyositis and polymyositis

Researchers analyzed the performance of more than 300 candidate response criteria for juvenile dermatomyositis (DM) and adult DM and polymyositis (PM), rare systemic autoimmune diseases in which the immune system attacks skeletal muscle, skin and other organ systems, and reached consensus on a model for determining minimal, moderate, and major improvement. The same criteria were chosen

for juvenile DM, adult DM and PM, with differing thresholds for improvement. These new response criteria should provide a uniform approach for assessing treatment responses in future therapeutic and preventive clinical trials.

Supported by NIEHS, NIAMS, NCATS, American College of Rheumatology, European League Against Rheumatism

Article: <https://www.ncbi.nlm.nih.gov/pubmed/28385804> [May 2017]

<https://www.ncbi.nlm.nih.gov/pubmed/28382778> [May 2017]

<https://www.ncbi.nlm.nih.gov/pubmed/28382787> [May 2017]

<https://www.ncbi.nlm.nih.gov/pubmed/28385805> [May 2017]

<https://www.ncbi.nlm.nih.gov/pubmed/28977549> [May 2017]

Consideration of genotype is essential for achieving optimal dose of the HIV drug efavirenz

Cytochrome P450 enzymes play an important role in the metabolism of many drugs. Genetic variations of these enzymes can affect the efficacy and safety of a therapy, contributing to variations in individual responses to medication. Finding the appropriate dose of the HIV drug efavirenz for very young children can be particularly difficult because slight changes in drug metabolism can have large effects on the effective dose of the drug. The researchers demonstrated that in HIV-infected children 3-36 months old, efavirenz dosing improves when it is based on the child's cytochrome P450 genotype. This method appears to outperform other efavirenz dosing methods.

Supported by NIAID, NICHD, and NIMH

Article: <https://www.ncbi.nlm.nih.gov/pubmed/28323755> [May 2017]

Longer-term health outcomes among youth infected with HIV at birth

Current treatment regimens have all but eliminated HIV transmission from women to their offspring in the United States. However, children and youth who were previously infected at birth must still take medication every day to control the virus. Many in this group have reached adolescence or young adulthood and are entering adult care. Health care providers need updated information to assess these patients' ongoing health risks and improve their care. Researchers studied 1,446 children and youth who became infected with HIV at birth. The researchers measured the participants' immune systems and viral load (which indicates how well the medication is controlling the virus) and assessed health events related to their HIV infection by immune system health, viral load, and age. Over a five-year period, the researchers found that immune system health declined, viral load increased, and sickness increased as the participants got older. The death rate in this population was 5.6-fold higher than the rate in the general population among those aged 15 to 19 years and 12.3-fold higher among those aged 20 to 29 years. The researchers also found that participants had a high viral load during 35 percent of the follow-up time, suggesting that either the participants were not adhering to their treatment regimens or the virus was drug resistant.

Supported by NICHD, NIAID

Article: <https://www.ncbi.nlm.nih.gov/pubmed/28346597> [May 2017]

Short-course treatment for childhood ear infections is less effective than standard treatment

Scientists evaluated shortened antimicrobial treatment for acute otitis media in young children as a potential strategy to reduce the risk of antimicrobial resistance. In children 6 to 23 months of age, reduced-duration antimicrobial treatment resulted in less favorable outcomes than standard-duration treatment without reducing the occurrence of adverse events or the emergence of antimicrobial resistance.

Supported by NIAID

Article: <https://www.ncbi.nlm.nih.gov/pubmed/28002709> [Dec 2016]

NIAID Press Release: <https://www.niaid.nih.gov/news-events/shortened-treatment-middle-ear-infection-less-effective-standard-course>

Improved diagnosis in children with cerebral malaria

Cerebral malaria (CM) is a complication of malaria infection that causes most of the malaria-associated deaths in African children and is a challenging disease to diagnose in low-resource settings. Automated detection of malarial retinopathy, or damage to the retinas, using color images of the retinas has the potential to improve the accuracy of CM diagnosis in children. Scientists developed fully automated software for the detection of retinopathy in children that can be integrated with low-cost, portable retinal cameras and used in resource-limited areas, potentially improving the accuracy of CM diagnosis.

Supported by NIAID

Article: <https://www.ncbi.nlm.nih.gov/pubmed/28198460> [Feb 2017]

Renal outcomes after pediatric cardiac surgery

Postoperative acute kidney injury (AKI) is common in children who undergo cardiac surgery. In a study of renal outcomes after pediatric cardiac surgery, researchers found that regardless of AKI, hypertension and chronic kidney disease are common risks. In a study of 131 patients, 17 percent had hypertension and 18 percent had CKD five years after surgery. Only 4 percent had seen a nephrologist, indicating that more attention to the risks of long-term renal damage is needed for these children.

Supported by NHLBI

Article: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5476457/> [Nov 2016]

TRIBE-AKI: <https://medicine.yale.edu/intmed/patr/projects/tribe.aspx>

Predicting the response to therapy in children with ulcerative colitis

Researchers are evaluating whether a combination of clinical, genetic, and immunologic tests can be used to predict response to standard medical therapy for children newly diagnosed with ulcerative colitis. Recent results from this study found that certain diagnostic criteria, such as standardized measurements of disease severity or the amount of albumin in the blood, can be applied to determine the best course of treatment for ulcerative colitis in children.

Supported by NIDDK

Article: <https://www.ncbi.nlm.nih.gov/pubmed/28939374> [Sep 2017]

Allergies and Immunity

Early exposure to allergens protects children from developing asthma

Inner-City Asthma Consortium (ICAC) researchers recently found that children who are exposed to mouse, cat, or cockroach allergens during infancy have a lower risk of developing asthma by age 7 years. By contrast, ICAC researchers found that older children who already have asthma and were exposed to airborne mouse allergens at school had increased asthma symptoms and reduced lung function.

Supported by NIAID

Article: <https://www.ncbi.nlm.nih.gov/pubmed/28939248> [Sep 2017]

Exposure to parasites does not impair children's response to pneumococcal vaccine

Streptococcus pneumoniae causes meningitis, pneumonia, and sepsis, and it is a leading cause of death worldwide for children under 5 years of age. Vaccination can prevent the disease, but scientists do not know how well children respond to pneumococcal vaccination in developing countries. Many real-world circumstances, such as malnutrition and infections from bacteria or parasites, influence how well vaccinations work in children. Researchers followed a group of mothers and children from Kenya from 2006 to 2010, tracking the mothers' and children's exposures to numerous parasites and other conditions during pregnancy and the first few years of the children's lives. Up to three-years-old, children who had parasitic infestations or whose mothers had parasitic infestations had a poor response to vaccines that were routinely administered during infancy. After the parasitic infestations were treated in the infants and mothers, response to vaccines was restored. In 2014, researchers retested 281 of these children (now four-

to seven-years-old) for infections, vaccinated them for *S. pneumoniae*, and monitored them for vaccine response, to determine whether the children still responded poorly to vaccines. The researchers found that chronic exposure to parasites during early life does not appear to harm children's response to the pneumococcal vaccine in mid-childhood; however, when these exposures create growth stunting, children are more likely to have a poor response to pneumococcal vaccines. To be effective, immunization campaigns must consider treating parasites and improving overall nutrition to ensure vaccine responses in vulnerable populations.

Supported by NICHD, NIAID, NCATS

Article: <https://www.ncbi.nlm.nih.gov/pubmed/28302673> [Apr 2017]

Rare Pediatric Diseases

FDA-approved newborn screening device can detect lysosomal storage disorders

In February, a newborn screening device received de novo clearance from the FDA for the detection of lysosomal storage disorders. From a single blood spot obtained via newborn screening, the device detects four types of lysosomal storage disorders, which injure the brain and nervous system and can affect learning, development, and movement. Early screening and detection can help physicians treat these disorders before they cause permanent harm.

Supported by NICHD

NICHD News Release: https://www.nichd.nih.gov/news/releases/Pages/sbir_ma_020617.aspx

Cyclodextrin for Niemann-Pick type C1 disease

Niemann-Pick disease type C1 is a fatal genetic disease characterized by a failure to metabolize and dispose of cholesterol and lipids, causing progressively impaired movement and intellectual function. It strikes in early childhood, and with no therapies currently approved by FDA, is lethal within a decade of diagnosis. The molecule 2-hydroxypropyl-beta-cyclodextrin (HPBCD) was shown to reduce cholesterol and lipid storage and to prolong survival in two animal models of disease. An interdisciplinary team of scientists from NIH, academia and industry, as well as patient advocates, is working to advance the development of HPBCD. Preclinical studies were completed and first-in-human trials began at the NIH Clinical Center in January 2013. Due to the strong early data, the program was licensed by a biotechnology company, Vtesse, Inc. In September 2015, Vtesse initiated a multicenter, multinational Phase 2b/3 trial, and subsequently achieved "Breakthrough Therapy" and "Rare Pediatric Disease" designations from the FDA. In 2017, a phase 1-2a study showed that NPC1 treated with intrathecal HPβCD had slowed disease progression with an acceptable safety profile.

Supported by NCATS, NICHD, Dana's Angels Research Trust, Ara Parseghian Medical Research Foundation, Hope for Haley, Samantha's Search for the Cure Foundation, National Niemann-Pick Disease Foundation, Support of Accelerated Research for NPC Disease, Vtesse, Janssen Research and Development, and Johnson & Johnson

Article: <https://www.ncbi.nlm.nih.gov/pubmed/?term=28803710> [Oct 2017]

Identifying a potential new strategy to treat neurodegenerative diseases

In some neurodegenerative disorders, cells have difficulty disposing of waste material, which builds up in a portion of the cell called the lysosome. One such neurodegenerative disorder is Batten disease, which results in progressive blindness and loss of skills in children with mutations in the gene involved in lysosomal function. Previous research has shown that a protein called TFEB in cells stimulates the lysosome to dispose of cellular waste. Researchers used a mouse model of Batten disease to explore possible ways of activating TFEB more effectively. They gave the mice a specific kind of sugar called trehalose, and showed that this treatment helps activate TFEB in the brains of the mice. These changes resulted in the mice living significantly longer, with brains that showed improved clearance of waste

material. The findings of this study are a good start towards a new approach to designing treatments that could improve the lives of people with Batten disease, as well as other neurodegenerative disorders.

Supported by NICHD, NEI, NCI, NIGMS, NEI, NINDS

Article: <https://www.ncbi.nlm.nih.gov/pubmed/28165011> [Feb 2017]

Microcephaly in Angelman syndrome caused by reduced white matter volume and fiber size

Angelman syndrome affects 1 in 12,000 to 20,000 infants, resulting in intellectual disability, delays in development, speech impairment, seizures, problems with balance, and microcephaly, a condition where a baby's head is much smaller than expected. Children with Angelman syndrome receive two versions of the *UBE3A* gene, one from each parent. However, in children with Angelman syndrome, the *UBE3A* gene from their mother is not functioning or is missing; as a result, certain cells in the brain, such as neurons that depend on this maternal copy of *UBE3A*, do not function properly. To determine how microcephaly occurs in Angelman syndrome, researchers created a mouse model that lacked the maternal *Ube3a* gene. Using MRI, the researchers found that the overall amount of white matter and the white matter tracts, or fiber pathways that form connections between nerve cells, was disproportionately reduced in these mice. Microcephaly, therefore, most likely results from deficits in white matter development, leading to impaired brain growth. These smaller fiber tracts may result in slower signaling between nerve cells, which could contribute to the behavioral deficits and impaired movements in Angelman syndrome.

Supported by NICHD, NINDS

Article: <https://www.ncbi.nlm.nih.gov/pubmed/28663201> [Aug 2017]

CRKL gene is likely involved in kidney defects seen in DiGeorge syndrome

DiGeorge syndrome, also called 22q11.2 deletion syndrome, is a rare disorder that occurs when a small portion of chromosome 22 is missing. It can affect nearly any part of the body, including the heart and kidneys. The region of chromosome 22 that is typically deleted contains 30 to 40 genes, but scientists do not know the exact gene or genes involved in the syndrome, including those driving kidney and urinary tract problems. To uncover what gene or genes might cause kidney problems in DiGeorge syndrome, a large team of scientists studied the genetic makeup of 2,080 patients with kidney and urinary tract anomalies and 22,094 control subjects. The researchers found that patients with kidney defects typically had a deletion that included the gene *CRKL*. These findings are a step toward determining genetic causes and identifying potential therapeutic targets for patients with DiGeorge syndrome.

Supported by NICHD, NIDDK, NHGRI, NIGMS, NCATS

Article: <https://www.ncbi.nlm.nih.gov/pubmed/28121514> [Feb 2017]

Pediatric Cancer

Selumetinib identified as a promising treatment in children with low-grade gliomas

Selumetinib is an anticancer agent that blocks a signaling pathway that is activated in most low-grade gliomas. The Pediatric Brain Tumor Consortium (PBTC) conducted a phase 1 clinical trial of selumetinib and identified a dose that is suitable for further testing. Twenty percent of children treated with selumetinib showed sustained reductions in tumor volume meeting criteria for partial response. Most of these children's tumors had gene changes that had been thought to predict sensitivity to selumetinib. These positive results led to a follow-on phase 2 study of selumetinib for children with low-grade glioma, and now a phase 3 evaluation of selumetinib is in development.

Supported by NCI

Article: <https://www.ncbi.nlm.nih.gov/pubmed/28339824> [Aug 2017]

A novel brain-penetrant inhibitor for the noncanonical BRAF oncoprotein mutation of pediatric low-grade astrocytomas

Approximately 75 percent of pediatric low-grade astrocytomas (PLGAs) harbor activating mutations or structural rearrangements in the BRAF proto-oncogene. First generation BRAF inhibitors that target the BRAFV600E mutation are ineffective in PLGAs. A team of researchers composed of experts in chemistry, BRAF signaling, and pediatric brain cancers, discovered a BRAF inhibitor that is active in PLGAs and in cells that harbor the BRAFV600E mutation. The inhibitor (MLN2480) penetrates the blood-brain barrier and is active in human PLGA cells in brain organotypic cultures. Future studies will test whether MLN2480 is also effective in adult BRAF-mutant tumors that metastasize to the brain.

Supported by NCI

Article: <https://www.ncbi.nlm.nih.gov/pubmed/28082416> [Jan 2017]

Nerve tumor characteristics differ in children and adults

Paraganglioma is a type of nerve tumor that forms near certain blood vessels and nerves. When paraganglioma occurs within the adrenal gland, it is called pheochromocytoma. Around 30 percent of these rare tumors occur in patients with a set of inherited traits, and around 10 percent of people diagnosed with them are children. Patients with the inherited traits that increase the risk of these tumors have mutations in genes called tumor susceptibility genes. When those genes have a mutation, the patient has an increased risk for cancer. In paraganglioma and pheochromocytoma, the genes can be divided into two distinct groups based on whether the tumor cells make a hormone called epinephrine. Researchers looked at data from 748 patients with paraganglioma or pheochromocytoma, 95 of whom were children at the time of diagnosis. Children had a higher prevalence of tumor susceptibility gene mutations compared with adults. The children's tumors were more likely to form outside the adrenal gland and to have tumor susceptibility gene mutations that blocked epinephrine production. This pattern of mutation was also associated with cancer that spread to other parts of the body, which was more prevalent in children than in adults. These results suggest that there are important differences in the way the disease affects children compared with adults. Young adults have symptoms more similar to children's, suggesting that some pediatric tumors go undetected until adulthood. These differences in disease patterns in adults versus children can guide patient care. The researchers urge that medical monitoring programs be tailored to the patient's diagnosis and genetic background, with diligent follow-up during the transition from pediatric to adult care for children with inherited traits.

Supported by NICHD

Article: <https://www.ncbi.nlm.nih.gov/pubmed/28324046> [Apr 2017]

Early-phase trial demonstrates shrinkage in pediatric neural tumors

Plexiform neurofibromas develop in up to 50 percent of people with neurofibromatosis type 1 (NF1). The majority of these tumors, which can cause significant pain, disability, and disfigurement, are diagnosed in early childhood and grow most rapidly prior to adolescence. Complete surgical removal of the tumors is rarely feasible, and incompletely resected tumors tend to grow back. In an early-phase clinical trial of a new oral drug, selumetinib, children with NF1 and plexiform neurofibromas tolerated selumetinib and, in most cases, responded to it with tumor shrinkage.

Supported by NCI

Article: <https://www.ncbi.nlm.nih.gov/pubmed/28029918> [Dec 2016]

Epigenetic screen identifies SETD8 as a target in high-risk neuroblastoma

Despite intense treatment, current therapy for neuroblastoma is still inadequate for 50 percent of high-risk patients and causes significant toxicities. There are limited targeted drugs for this type of cancer, so identifying molecular inhibitors to block tumor growth is an important goal. This pre-clinical research identified novel epigenetic targets for high-risk neuroblastoma and validated a promising new targeted inhibitor in pre-clinical models.

Supported by NCI

Article: <https://www.ncbi.nlm.nih.gov/pubmed/28073004> [Jan 2017]

NCI News Release: <https://ccr.cancer.gov/news/article/novel-target-for-high-risk-neuroblastoma-identified-in-pre-clinical-research>

Dual ALK and CDK4/6 inhibition demonstrates synergy against neuroblastoma

Neuroblastoma accounts for about 10 percent of all childhood cancers, with 800 new cases diagnosed in the United States each year. The oncogene most frequently mutated in pediatric neuroblastoma is Anaplastic Lymphoma Kinase, or ALK. In a previous clinical trial, ALK inhibitors did not produce objective responses in most patients, suggesting that a combination with another drug may be a more effective therapeutic approach. Researchers have now identified a drug that works in synergy with the ALK inhibitor against neuroblastoma. The combination of ALK and CDK4/6 inhibitors produced complete regressions in xenografts of neuroblastoma with ALK F1174L mutation and prevented the emergence of drug resistance. These results provide the rationale for conducting a clinical trial with this combination of inhibitors in children with ALK-mutated neuroblastoma.

Supported by NCI

Article: <https://www.ncbi.nlm.nih.gov/pubmed/27986745> [Jun 2017]

Targeting ALK with crizotinib in pediatric anaplastic large cell lymphoma and inflammatory myofibroblastic tumor: a Children's Oncology Group study

Fusions involving the ALK gene are the predominant genetic lesion underlying pediatric anaplastic large cell lymphomas (ALCL) and inflammatory myofibroblastic tumors (IMTs). The researchers assessed the activity of the ALK inhibitor crizotinib in patients who had no known curative treatment options at diagnosis or with relapsed/recurrent disease. In this study, 26 patients with relapsed/refractory ALK-positive ALCL and 14 patients with metastatic or inoperable ALK-positive IMT received crizotinib orally twice daily. The overall response rate for patients with ALCL was 90 percent and for IMT was 86 percent. Complete responses were seen in 80 percent of patients with ALCL and 36 percent of patients with IMT. These responses highlight the importance of the ALK pathway in these cancers.

Supported by NCI

Article: <https://www.ncbi.nlm.nih.gov/pubmed/28787259> [Aug 2017]

FDA approves CAR T-cell therapy for acute lymphoblastic leukemia

Acute lymphoblastic leukemia is the most common cancer among children in the United States. Intensive chemotherapy cures more than 80 percent of children with ALL that arises in B cells, which is the predominant type of pediatric ALL. However, there are few treatment options for patients whose cancers do not respond to treatment or go into remission and later relapse. Recently, the FDA approved the first CAR T-cell therapy to treat B-cell acute lymphoblastic leukemia in certain child and young adult patients.

Supported by NCI

Article: <https://www.ncbi.nlm.nih.gov/pubmed/26962747> [Oct 2014]

<https://www.ncbi.nlm.nih.gov/pubmed/23527958> [April 2013]

NCI Press Release: <https://www.cancer.gov/news-events/cancer-currents-blog/2017/tisagenlecleucel-fda-childhood-leukemia> [FDA approval was announced in August 2017]

Results of the first prospective multi-institutional treatment study in children with bilateral Wilms tumor

Despite excellent outcomes for patients with unilateral favorable histology Wilms tumor, children with bilateral Wilms tumor have significantly poorer outcomes. This was the first prospective therapeutic trial conducted in children with bilateral Wilms tumors. The standardized treatment approach studied on this protocol consisted of 3-drug preoperative chemotherapy (vincristine, dactinomycin and doxorubicin), surgical resection within 12 weeks of diagnosis and response and histology-based postoperative therapy. Four-year EFS and OS were 82.1 percent and 94.9 percent for 189 patients evaluated on AREN0534 were improved over historical outcomes for children with bilateral Wilms tumors.

Supported by NCI

Article: <https://www.ncbi.nlm.nih.gov/pubmed/28795993> [Sep 2017]

FDA approves avelumab treatment for Merkel cell carcinoma

On March 23, 2017, the FDA approved the immunotherapy drug avelumab for metastatic Merkel cell carcinoma (MCC) — a rare, aggressive form of skin cancer — for adults and patients 12 years of age and older. Avelumab, marketed as Bavencio, is the first FDA-approved treatment for MCC.

Supported by NCI, Pfizer, Merck, EMD Serono Inc

Article: <https://www.ncbi.nlm.nih.gov/pubmed/28373005> [May 2017]

Article: <https://www.ncbi.nlm.nih.gov/pubmed/27592805> [Oct 2016]

NCI News Release: <https://ccr.cancer.gov/news/article/ccr-plays-key-role-in-first-FDA-approved-drug-for-treatment-of-merkel-cell-carcinoma> [May 2017]

Macrocephaly associated with the DICER1 syndrome

DICER1 syndrome is an inherited disorder that increases the risk of a variety of cancerous and noncancerous (benign) tumors, most commonly certain types of tumors that occur in the lungs, kidneys, ovaries, and thyroid. Researchers analyzed prospectively collected growth data from 67 DICER1 mutation carriers and 43 family controls, and for the first time, established macrocephaly as a common finding in the DICER1 syndrome. Like some other tumor-predisposition disorders, macrocephaly may be a useful, albeit a subtle, clinical clue to the DICER1 syndrome diagnosis.

Supported by NCI:

Article: <https://www.ncbi.nlm.nih.gov/pubmed/27441995> [Feb 2017]

Risk of thyroid nodules in residents of Belarus exposed to Chernobyl fallout as children and adolescents

The Chernobyl nuclear disaster of 1986 has caused about one thousand cases of thyroid cancer up to now and will cause 16 times as much by year 2065. One of the four most harmful radionuclides released by the meltdown was the iodine I-131, which concentrates in the thyroid and increases the risk of thyroid cancer. Although radiation exposure is an important predictor of thyroid cancer on diagnosis of a thyroid nodule, the relationship between childhood radiation exposure and thyroid nodules has not been comprehensively evaluated. The objective of this study was to examine the association between internal I-131 thyroid dose and thyroid nodules in young adults exposed to radiation during childhood. In this cross-sectional study, 11,421 residents of Belarus aged who were 18 years old or younger at the time of the Chernobyl nuclear accident were screened for thyroid disease at a median age of 21 years old. The researchers found that childhood exposure to I-131 is associated with increased risk of any thyroid nodules, including benign and malignant nodules. This association increased in participants who were exposed to I-131 at a younger age.

Supported by NCI

Article: <https://www.ncbi.nlm.nih.gov/pubmed/28368520> [July 2017]

Cancer risk after pediatric solid organ transplantation

Children who undergo solid organ transplantation have an increased risk of developing some cancers compared to the general population. The US transplant registry was linked to 16 cancer registries to identify cancer diagnoses among transplant recipients <18 years old at time of transplantation. Cancer incidence was found to be significantly increased for non-Hodgkin's lymphoma (NHL), Hodgkin's lymphoma, leukemia, myeloma, and cancers of the liver, soft tissue, ovary, vulva, testis, bladder, kidney, and thyroid compared with the general population. NHL constituted the majority of diagnosed cancers, with the highest risk occurring in the first year after transplantation. NHL risk was high in any transplant recipients susceptible to primary Epstein-Barr virus (EBV) infection after transplant and in intestine transplant recipients, perhaps due to EBV transmission in the donor organ.

Supported by NCI

Article: <https://www.ncbi.nlm.nih.gov/pubmed/28557749> [May 2017]

Radiation-associated breast cancer and gonadal hormone exposure

Researchers evaluated how hormonal factors influence breast cancer risk in childhood cancer survivors exposed to chest radiotherapy. By studying patients in the Childhood Cancer Survivors Study (CCSS) cohort, researchers identified an association between hormone exposure and the risk of radiation-associated breast cancer. The findings showed that endogenous hormones, which are naturally produced by the ovaries, are key contributors to breast cancer among childhood cancer survivors who received chest radiotherapy near the onset of menarche. In addition, when these women are given hormone replacement therapy to compensate for premature ovarian insufficiency, they have a moderately increased risk for developing breast cancer. However, their risk remained lower compared to those survivors who did not receive hormone replacement therapy.

Supported by NCI

Article: <https://www.ncbi.nlm.nih.gov/pubmed/28632729> [Jun 2017]

Temporal trends in treatment and subsequent neoplasm risk among five-year survivors of childhood cancer, 1970-2015

Childhood cancer survivors are at risk for development of subsequent neoplasms (SN) as a result of their cancer treatment. Based on these observations, childhood cancer treatments have been modified over time with the aim of reducing subsequent neoplasm risk while maintaining or improving 5-year survival. Researchers used data from the long-term Childhood Cancer Survivor Study cohort to comprehensively assess the temporal changes in SN among individuals diagnosed between 1970-1999. During a mean follow up of 20.5 years, 1,639 survivors experienced 3,115 SN. The most common SN were breast and thyroid cancers. The risk of subsequent malignancies at 15 years after initial cancer diagnosis remained increased for those diagnosed in the 1990s, although the risk was lower compared with those diagnosed in the 1970s. This lower risk was associated with reduction in therapeutic radiation dose.

Supported by NCI, NCATS

Article: <https://www.ncbi.nlm.nih.gov/pubmed/28245323> [Feb 2017]

Childhood Injuries and Maltreatment

Blood test may detect bleeding in the infant brain after head trauma

Scientists developed a new blood test that can help identify bleeding in the infant brain. Failure to diagnose this injury, which can result from physical abuse, could lead to further brain damage or even death. However, many infants do not show obvious signs or may have non-specific symptoms, such as vomiting. The research team developed a scoring system, based on blood levels of specific substances, that estimates the likelihood of bleeding in the brain. High scores indicate that a child should be referred for brain imaging to confirm the bleeding.

Article: <https://www.ncbi.nlm.nih.gov/pubmed/28395008> [Jun 2017]

NICHHD News Release: <https://www.nichd.nih.gov/news/releases/051917-blood-biomarker>

Booster seats and accidental injuries among children 8-12 years

Motor vehicle crashes are the leading cause of death due to injury among children aged 8-12 years in the United States. Booster seats are designed to improve seat belt fit for children who are too big for a harnessed child restraint system, but too small for vehicle seat belts to fit properly. The American Academy of Pediatrics and National Highway Traffic Safety Administration have recommended that children as old as 12 years use a booster seat when riding in a motor vehicle. However, only 10 percent of children in the 8-12 year age group used a booster seat. Researchers examined data from Washington state on 79,859 children 8-12 years of age who were involved in motor vehicle crashes, and compared the children who were in booster seats to the children restrained by a seat belt alone. The study results show

that the use of a booster seat was generally associated with a lower risk of any injury relative to being in a seat belt alone. The use of booster seats was not found to be more effective than seat belts at preventing fatal or incapacitating injuries such as severe lacerations, broken or distorted extremities, unconsciousness, and paralysis. While booster seats may be as effective as seat belts in preventing the most serious type of injuries, the study results suggest encouraging more use of booster seats among children aged 8-12 could lead to fewer overall injuries.

Supported by NICHD

Article: <https://www.ncbi.nlm.nih.gov/pubmed/28427953> [Aug 2017]

Utilization of mental health services after mild pediatric traumatic brain injury

Mild traumatic brain injuries (mTBI), including concussions, account for more than 2 million pediatric emergency department visits each year in the United States. When mental health symptoms emerge after mTBI, it may be unclear if these symptoms are related to the mTBI or if they are a result of previous mental health diagnoses. Using a large national database, researchers assessed whether children seeking mental health care after an mTBI had previous mental health diagnoses, or whether the onset of the disorders was new. The scientists found that 27 percent of the total children in the study had a mental health diagnosis before their mTBI. The researchers found that mTBI injury was associated with increased use of mental health services in all the children, whether or not they had a previous diagnosis. However, 86 percent of the post-mTBI mental health care went to children with previous mental health disorders. Hispanic children were less likely to receive post-mTBI mental health services, compared with non-Hispanic white children.

Supported by NICHD, CDC

Article: <https://www.ncbi.nlm.nih.gov/pubmed/28159872> [Mar 2017]

Home-visit program in child maltreatment cases strengthens parent-child interaction

According to the Administration on Children and Families, state child protective agencies received 3.6 million referrals of possible child maltreatment in 2014. Child maltreatment may have lifelong effects, but removal from the abusive environment may also have negative effects, as the instability of foster care may be stressful and worsen behavioral problems. Researchers studied a program called "Promoting First Relationships," which seeks to help parents become more sensitive to their child's emotional and social cues. The scientists enrolled 247 families with children between the ages of 10 months and two years, all with cases under review by Child Protective Services. Families were randomly assigned to either the home-visit program, which included 1-hour visits over a 10-week period, or a telephone-based service that included three, 30-minute sessions, and packets of resource and referral information mailed to each family. For the intervention, education specialists videotaped parents playing and interacting with their children. The specialists then reviewed the footage with parents to reflect on how they recognized and responded to their children. Parents who received the video intervention scored higher on measures of engagement and sensitivity, compared to parents who received the telephone-based service. Foster care placements also were lower by more than double among parents who received the home-based intervention.

Supported by NICHD

Article: <https://www.ncbi.nlm.nih.gov/pubmed/27646148> [Sep 2016]

Interventions to decrease child abuse in high-risk families

Child abuse is a world-wide problem. Researchers reviewed the existing scientific literature to identify effective interventions designed to prevent child abuse by mothers at high-risk for maltreatment. Factors that place mothers at higher risk for abusing a child include a history of themselves being abused as a child, life stress, mental illness, and substance abuse, among others. Eight randomized controlled trials met the researchers' review criteria. Of the 8 trials, only 3 studies found interventions that showed statistically significant reductions in child abuse and only 2 of these found reductions in child abuse incidents reported to child protective services. The studies did not adequately address the maternal high-

risk factors for child abuse. Evidence on interventions other than home visitation was limited, and data from low and middle-income countries was especially limited.

Supported by NICHD, NIMH

Article: <https://www.ncbi.nlm.nih.gov/pubmed/28110205> [Mar 2017]

Pain and Pain Management

Telephone intervention can help parents of children with functional abdominal pain

Abdominal pain is common in childhood, and it is often difficult to identify a specific cause for the pain. Pediatric abdominal pain disorders, such as functional abdominal pain and irritable bowel syndrome, can lead to missed school, increased health care use, reduced quality of life, and emotional distress in both children and parents. Researchers compared three types of interventions for parents of children with these conditions. The participants, children aged 7-12 with abdominal pain and their parents, were randomly placed into 1 of the 3 groups. One group received social learning and cognitive behavioral therapy (SLCBT) in-person, another received SLCBT by phone, and the third group received general educational and support by phone without the SLCBT component. There were no significant differences in reported pain severity between the 2 SLCBT intervention groups (in-person or by phone). However, both SLCBT groups showed significantly greater improvements, compared with the other group, on several factors, including child health care visits for abdominal pain. In the SLCBT by phone group only, there was significantly greater improvements with parent-reported quality of life and school absenteeism. However, there were no significant differences across the groups for parent and child-reported gastrointestinal symptoms. These findings suggest that for children with abdominal pain, this type of treatment can be effective, whether provided in person or over the phone.

Supported by NICHD

Article: <https://www.ncbi.nlm.nih.gov/pubmed/28301859> [Apr 2017]

Pediatric Critical Care and Emergency Care

Acute kidney injury takes its toll in critically ill children

A multi-national study assessed the kidney function of 4,683 children and young adults who were admitted to pediatric intensive care units and expected to require a stay of 48 hours or longer. Using the Kidney Disease: Improving Global Outcomes criteria to define acute kidney injury (AKI), all patients were evaluated for kidney function over a 28-day period. AKI developed in 1,261 patients or 26.9 percent. Severe AKI developed in 543 patients or 11.6 percent—and 60 of those patients died within the 28-day period. Thus, among critically ill children and young adults, AKI is common and is associated with poor outcomes including increased death.

Supported by NIDDK

Article: <https://www.ncbi.nlm.nih.gov/pubmed/27959707> [Jan 2017]

NICU study highlights need to reduce loud noises, boost beneficial sounds

Premature babies often spend the first several weeks of life in neonatal intensive care units (NICUs). Ideally, the NICU environment would protect these fragile infants from loud noises but also expose them to beneficial sounds, like human voices. However, this could be difficult because many of the life-saving technologies used in the NICUs – like ventilators – can be noisy. Researchers used digital language-processing devices to capture NICU sounds at the bedsides of 58 premature infants. They found that the average noise level in the NICU was just under 59 decibels, with peak noise levels reaching almost 87 decibels. The American Academy of Pediatrics recommends avoiding levels above 45 decibels. Moreover, the researchers also found that preemies may not get enough exposure to beneficial sounds, such as language and music, that can improve early development. In private rooms, which are becoming

more common in the NICU, babies encounter much longer periods of silence than in rooms with more than one crib. In general, premature infants in the NICU had very little exposure to meaningful language.

Supported by NICHD, NCATS

Article: <https://www.ncbi.nlm.nih.gov/pubmed/28189301> [Apr 2017]

Assessing survival and function among children and infants treated with ECMO

Extracorporeal membrane oxygenation (ECMO) is a type of heart and/or lung bypass treatment used to care for infants and children whose lungs and hearts are failing to provide enough oxygen to the organs of the body despite standard intensive care treatments. ECMO circulates the child's blood through an artificial lung before returning it back into the child's body. This treatment is very invasive and carries enormous risks for bleeding, blood clot formation, and infection, as well as long-term neurological problems. Children treated with ECMO are already very sick, and most would die without it. Scientists studied 514 ECMO patients: 267 newborns (no more than 30 days old) and 247 pediatric patients (age 19 or younger). Nearly half (237) of the patients required this life-saving therapy for a severe breathing problem, 207 for a heart problem, and 70 because their heart and lungs completely stopped. Although survival statistics have long been recorded for ECMO patients, much less is known regarding the functional status of survivors. This study was designed to assess the functional status of survivors and the factors that contribute to poor functional recoveries. The scientists used a standard tool to assess the 282 survivors' mental, sensory, communication, motor, feeding, and respiratory function. Of the survivors, nearly three quarters had good (89) or mildly abnormal (112) function at hospital discharge; only 14 had severely or very severely abnormal function. Long-standing health conditions and increased severity of illnesses were associated with worse results. The researchers concluded that treatments focusing on reducing both blood lactate levels and the volume of red blood cell transfusion could improve outcomes for children and infants receiving ECMO.

Supported by NICHD

Article: <https://www.ncbi.nlm.nih.gov/pubmed/28419061> [Jun 2017]

Protein levels predict risk of mortality in children with severe sepsis

Sepsis is a serious medical condition that occurs when the body's response to an infection triggers widespread inflammation. This inflammation can lead to organ damage and even organ failure. In the United States, sepsis is a leading cause of death in children under age 5. Standard treatment seeks to remove the source of infection and support organ function, but largely ignores inflammation. Scientists wondered if monitoring the level of inflammation could help determine a patient's risk of dying from sepsis. To test this idea, researchers measured levels of two proteins that increase with inflammation, C-reactive protein (CRP) and ferritin, in 100 children with sepsis. The scientists developed three risk categories based on the protein levels: low risk (low levels of both CRP and ferritin), intermediate risk (high levels of either CRP or ferritin and low levels of the other), and high risk (high levels of both CRP and ferritin). The researchers measured the protein levels twice a week in 63 of the children. All 24 of the children who were in the low-risk group at the first measurement survived. Nineteen of the 39 children who were in the intermediate- or high-risk groups at the first measurement later moved to the low-risk group, and all 19 also survived. Among the remaining 20 children in the intermediate- or high-risk groups, 7 died. The scientists concluded that measuring CRP and ferritin levels may help assess the risk of death in children with severe sepsis.

Supported by NICHD

Article: <https://www.ncbi.nlm.nih.gov/pubmed/27941423> [Feb 2017]

Clinical Care, Outreach, and Services

Children with multiple complex chronic conditions (MCCCS) have limited use of hospice at end of life

A study examining California Medicaid records over a period of four years found limited pediatric hospice care utilization among children who died during that time period. On average, only 10 percent of all children who died were enrolled in hospice care, with an average stay of 3 days. While almost half of child mortalities in the sample had multiple complex chronic conditions (MCCCs), only a small percentage used hospice care. Of the children with MCCCs who utilized hospice care, they were enrolled for significantly longer periods of time than the 3-day average. More research is needed to determine if any obstacles exist to pediatric palliative care access, especially for children with MCCCs.

Supported by NINR

Article: <https://www.ncbi.nlm.nih.gov/pubmed/27797636> [Mar 2017]

Sexual activity and contraceptive use among teenagers in the United States

Approximately half of the pregnancies in the United States are unintended. Based on data from the National Survey of Family Growth (NSFG), researchers compiled national estimates of sexual activity and contraceptive use among males and females aged 15 to 19, based on in-person interviews conducted with 2,047 females and 2,087 males. Between 2011-2015, approximately 42 percent of never-married female teenagers (4 million) and 44 percent of never-married male teenagers (4.4 million) were sexually experienced; these statistics were similar to those seen in 2002 and 2006-2010. No significant differences were seen among never-married Hispanic, non-Hispanic white, and non-Hispanic black female teenagers; however, over 58 percent of never-married non-Hispanic black male teenagers had ever had sexual intercourse, a significantly higher percentage than never-married Hispanic (46 percent) or non-Hispanic white males (43 percent). Female teenagers using a method of contraception during their first sexual experience increased from about 71 percent in 2002 to 80 percent in 2006-2010, then decreased to 77 percent in 2011-2015. In 2011-2015, almost 6 percent of female teenagers had used a long-acting reversible method, such as an intrauterine device or implant.

Supported by NICHD

Article: <https://www.ncbi.nlm.nih.gov/pubmed/28696201> [Jun 2017]

Burden of hospitalizations for mitochondrial disease in children and adults

Mitochondrial disease is being diagnosed with increasing frequency, but there is very limited information about the impact of mitochondrial disease on healthcare in the United States across the lifespan. Researchers set out to describe the characteristics of inpatient hospitalizations related to mitochondrial disease, identify patient or clinical factors associated with mortality in hospitals, and to estimate the burden of these hospitalizations on individual patients. In 2012, there were approximately 3200 inpatient pediatric hospitalizations and 2000 inpatient adult hospitalizations (about 1.9 and 0.8 per 100,000 hospitalizations, respectively) for mitochondrial disease in the United States, with associated direct medical costs of \$113 million. Mortality rates were 2.4 percent for children and 3.0 percent for adults. Analysis of 2007-2011 data from California showed that 495 individuals had at least one admission with a diagnosis of mitochondrial disease; over up to five years of follow-up, almost 10 percent of these were noted to have an in-hospital death. These findings show the severe health and economic burden of mitochondrial disease for children and adults.

Supported by NICHD, NIDDK

Article: <https://www.ncbi.nlm.nih.gov/pubmed/28442181> [Jun 2017]

Healthcare professionals' preferences and perceived barriers for routine assessment of patient-reported outcomes in pediatric oncology practice: moving toward international processes of change

Using patient-reported outcomes in clinical practice has been shown to enhance detection of health-related quality of life problems and satisfaction with care in children with cancer. A recent study sought to identify which information healthcare professionals find useful and the perceived barriers for routine

assessments. These results should improve the execution and integration of outcomes such that patient-reported problems can be detected and timely referrals made.

Supported by NCI

Article: <https://www.ncbi.nlm.nih.gov/pubmed/27511830> [Dec 2016]

Outcomes of Fontan operation for single ventricle heart disease

Researchers assessed longer-term outcomes for a group of individuals who had undergone Fontan operation for single ventricle heart disease in childhood. The study demonstrated 90 percent transplant-free survival over 12 years of follow-up. The study noted declines in exercise performance that were associated with worse health status. It also characterized the many morbidities that these individuals face, including additional procedures, arrhythmia, and thrombosis.

Supported by NHLBI

Article: <https://www.ncbi.nlm.nih.gov/pubmed/28571639> [Jun 2017]

Body cooling did not improve outcomes for children with cardiac arrest

About 6,000 children suffer in-hospital cardiac arrest each year in the United States. Some clinicians have routinely used body cooling for patients in cardiac arrest because they believed it might lead to better outcomes. Researchers studied 329 children, aged 2 days to 18 years, who suffered in-hospital cardiac arrest. They found no evidence of improved survival or better functional outcome with cooling compared to maintenance of normal body temperature.

Supported by NHLBI, NICHD, NCATS

Article: <https://www.ncbi.nlm.nih.gov/pubmed/28118559> [Jan 2017]

Clear packaging and better tools can decrease parental dosing errors

Research has shown that many children receive incorrect amounts of prescribed liquid medication. In one recent study, researchers found that over 80 percent of parents made at least one error in dosing. To determine the best type of packaging for minimizing dosing mistakes, researchers presented different labels, tools, and instructions to nearly 500 parents with children under 8 years old. They found that adding illustrations of dose volume to medication instructions decreased the likelihood of dosing mistakes. Overall, parents made the fewest mistakes when the volume of the measuring tool was close to the dose. This was especially true for parents with low health literacy. This study shows that dosing accuracy may be improved by using visual aids and/or labeling with metric units only in order to help people understand dosing instructions.

Supported by NICHD

Article: <https://www.ncbi.nlm.nih.gov/pubmed/28759396> [Jul 2017]

Race, sex, age, and insurance: drivers of pediatric emergent gastrointestinal procedures

A study examined the impact of health disparities on emergency gastrointestinal (GI) procedures among children. The study sought to identify risk factors associated with emergent and non-emergent GI care, and characterize the pediatric population receiving GI procedures at one urban healthcare facility. The study found that children under 18 years were less likely to have emergent GI procedures. Racial and ethnic minorities, were more likely to have GI procedures compared to Whites, particularly observed among African Americans. Girls and children with commercial insurance were less likely to have GI procedures. Further research in understanding the association between health disparities and pediatric emergent GI procedures, will be important to inform the development of effective interventions to reduce the rate of emergent GI procedures.

Supported by NIMHD

Article: <https://www.ncbi.nlm.nih.gov/pubmed/27513695> [Jun 2017]

An oral health promotion trial in Navajo Head Start children

In a 3-year trial, the authors tested the effectiveness of a community-based, tribally delivered oral health promotion (OHP) intervention aimed at reducing caries in Navajo children attending Head Start. They developed an OHP intervention with Navajo input that was delivered by trained Navajo lay health workers to children attending Navajo Head Start classrooms. The intervention was designed as a highly-personalized set of oral health-focused interactions along with fluoride varnish applications delivered in Head Start during the academic year. The outcomes included the levels of caries in the children and the oral health-related knowledge and behaviors of caregivers. The findings from the study are mixed and demonstrate the challenges in identifying effective strategies to prevent and treat caries in this population and the need for additional research in partnership with the Navajo community.

Supported by NIDCR

Article: <https://www.ncbi.nlm.nih.gov/pubmed/27439724> [Oct 2016]

Mindfulness-based stress reduction improves quality of life and relief from symptoms in adolescents with widespread chronic pain conditions

Functional somatic syndromes include conditions such as chronic fatigue syndrome, irritable bowel syndrome, fibromyalgia, chronic unexplained pain, and symptoms attributed to chronic Lyme disease. These syndromes are prevalent, costly and may be debilitating, and individuals often have psychiatric comorbidities such as anxiety or depression. Patients with functional somatic syndromes often seek complementary health treatments. Researchers assessed the feasibility of a mindfulness-based stress reduction (MBSR) program for adolescents with widespread chronic pain and other functional somatic syndromes and found that there is evidence of improvements in functional disability, symptom impact, and anxiety. For adolescents with functional somatic pain syndromes, it is possible that therapeutic approaches focusing on quality of life and symptomatic relief may be more relevant than trying to search for an elusive organic disease.

Supported by NCCIH, NCATS

Article: <https://www.ncbi.nlm.nih.gov/pubmed/28088398> [Apr 2017]

Technology and Tools

National Collaborative on Childhood Obesity Research (NCCOR) launches youth compendium of physical activities

In October 2017, the National Collaborative on Childhood Obesity Research (NCCOR) launched the Youth Compendium of Physical Activities to help childhood obesity and physical activity researchers and practitioners estimate the associated energy expenditure of a variety of activities in which youth participate. The Youth Compendium of Physical Activities provides measures of energy expenditure for 196 common youth activities including sedentary activities, standing activities, playing and participating in games, and walking and running.

Supported by NIH, CDC, RWJF, USDA

NCCOR: <http://www.nccor.org/nccor-tools/youthcompendium/>

New MRI coils aim to improve patient comfort and decrease scan time

Scientists have developed 3D printed MRI coils that can be bent and easily wrapped around an infant. The proximity of the coils allows high quality images to be obtained with much shorter MRI scan times and greater comfort for patients. The new coils produced MRI images of similar quality using traditional MRI methods. Not having to experience the trauma of long MRI exams is a significant benefit to pediatric patients and their parents during what are often trying times.

Supported by NIBIB

Article: <https://www.ncbi.nlm.nih.gov/pubmed/27612330> [Aug 2017]

Scientists engineer intestinal tissue with functioning nervous system

Researchers engineered a stem cell-based human tissue culture system with a functioning nervous system for studying gut motility disorders such as Hirschprung's disease. They combined intestinal organoids grown from differentiated human stem cells with neural cell precursors to create the first human intestinal tissue culture model with a functional enteric system.

Supported by NIDDK

Article: <https://www.ncbi.nlm.nih.gov/pubmed/27869805> [Nov 2016]

Normal reference values for standard pediatric ECG measurements

Scientists produced normal reference values for standard pediatric echocardiographic measurements from a dataset on >3,000 infants, children and adolescents from diverse racial and ethnic populations. In growing children, clinicians assess the size of cardiac structures by using reference "z-scores," which represent a range of cardiac sizes appropriate for the child's body size. The challenge is that a number of z-score sets are available based on small studies – which can lead to very different assessments of whether the heart looks normal or not. This dataset is sufficiently large and diverse to eliminate this problem.

Supported by NHLBI

Article: <https://www.ncbi.nlm.nih.gov/pubmed/29138232>

Pediatric nonhuman primate model of HIV/AIDS

Researchers used the pediatric simian immunodeficiency virus (SIV) rhesus macaque model to test the hypothesis that early-life viral infection depletes the neuronal population in the hippocampal cornu ammonis (CA). SIV-infected infant macaques displayed a 75 percent and 67 percent neuronal reduction in the CA1 and CA2 regions, respectively, compared to age-matched uninfected controls. The loss of hippocampal neurons may contribute to the rapid neurocognitive decline associated with pediatric HIV-1 infection with the CA1 and CA2 subregions demonstrating a potentially enhanced vulnerability to the infection. These data underscore the need for early diagnosis and treatment of pediatric patients, including therapeutics targeting the central nervous system. Researchers focused on determining whether SIV infection of monocytes/macrophages contributes to the rapid progression to AIDS in SIV-infected newborn rhesus macaques. Monocytes are white blood cells that can differentiate into macrophages, which engulf and digest foreign substances in the body. Soon after SIV infection, the monocyte turnover dramatically increased and remained high during progression to AIDS in infant macaques. The higher baseline monocyte turnover and subsequent macrophage damage by SIV infection may explain why infants are more prone to rapid disease progression.

Supported by ORIP, NIAID, NIMH, NHLBI

Article: <https://www.ncbi.nlm.nih.gov/pubmed/28394273> [Apr 2017]

<https://www.ncbi.nlm.nih.gov/pubmed/28566378> [Aug 2017]

Global Pediatric Health

Probiotics may prevent life-threatening infections in newborns

Researchers reported that daily oral doses of beneficial bacteria, which cost less than \$1 a week, reduced the rate of sepsis among newborns in India. Sepsis, a life-threatening infection of the bloodstream, remains a major cause of infant death worldwide. Treatment requires intravenous antibiotics for up to 2 weeks and specialized hospital care, which may not be available in resource-limited areas. The study team used a mix called a synbiotic that contained the probiotic *Lactobacillus plantarum* and a sugar that serves as its food source. Newborns who received the synbiotic had lower rates of sepsis, and surprisingly, lower rates of pneumonia and other airway infections. Overall, the results suggest a cost-effective way to prevent newborn sepsis in developing countries.

Supported by NICHD

Article: <https://www.ncbi.nlm.nih.gov/pubmed/28813414> [Aug 2017]
<https://www.ncbi.nlm.nih.gov/pubmed/28813407> [Aug 2017]

Zinc and multivitamin supplements do not enhance development in Tanzanian infants

Each year, millions of children under five years of age suffer from developmental delays due to factors like limited access to health care and poor nutrition. These delays can permanently affect intellectual ability and productivity. This randomized clinical trial sought to determine whether supplementing infants' diets with zinc, zinc and a mixture of other micronutrients, or micronutrients alone could positively impact development for infants in urban Tanzania, compared to a placebo. Developmental outcomes included complexity of play activities, communication, and motor skills measured at 15 months of age. The study did not measure nutrition-specific intake, the nutritional status of any of the nutrients tested, or infant feeding practices (e.g., breastfeeding or complementary foods). After eight months of supplementation, the researchers reported no differences in the developmental measures between the groups at 15 months of age. The researchers pointed out that a limitation of the trial may include a lack of generalizability, because poor nutrition, poor sanitation, and food insecurity may be more prevalent for children living in rural settings than in urban settings. However, this work highlights the importance of adopting a multifaceted approach to tackling developmental deficits in vulnerable populations.

Supported by NICHD, NIDDK

Article: <https://www.ncbi.nlm.nih.gov/pubmed/27189038> [Apr 2017]

Potential sources of high blood lead levels in infants and mothers in Benin

Lead exposure in childhood is associated with poor neurodevelopment. Exposure to lead is a major problem in low-income as well as high-income countries. As part of a study on maternal anemia and offspring neurodevelopment, researchers analyzed the lead levels in the blood samples of 225 mothers and 685 one- to two-year-old offspring in Benin. High lead levels were found in 44 percent of mothers and 58 percent of the children, with a high correlation between maternal and children blood lead levels. Potential sources of lead exposure included drinking water (water that is transported in lead pipes can become contaminated), eating meat from animals killed using ammunition, and exposure to lead paint.

Supported by NICHD

Article: <https://www.ncbi.nlm.nih.gov/pubmed/26978384> [Mar 2016]

Preventive antibiotic treatment does not benefit HIV-uninfected children in non-malarial areas

Co-trimoxazole is a combination antibiotic prescribed to treat pneumonia; bronchitis; and infections of the urinary tract, ears, and intestines. Health care providers also use it to reduce death from infections in young children with HIV. Mother-to-child HIV transmission has decreased, so babies whose mothers are HIV-positive often remain uninfected. In areas where malaria is endemic, such children are less likely to get malaria if they receive co-trimoxazole, but scientists did not know whether co-trimoxazole would benefit such children in non-malarial regions. In a malaria-free region of Botswana, researchers compared daily treatment with co-trimoxazole with placebo in 2,848 children exposed to but not infected with HIV. The researchers stopped the study before completion because there was overwhelming evidence that co-trimoxazole provided no benefit. Virtually equal numbers of deaths and medical problems occurred in the treatment and placebo groups, but children on co-trimoxazole were more likely to have low white blood cell counts, making them more likely to have infections. They also had more co-trimoxazole-resistant *Escherichia coli*. These results suggest that in regions without endemic malaria, infants and small children who are exposed to but not infected with HIV are unlikely to receive benefit from co-trimoxazole, freeing up resources for other, more important interventions.

Supported by NICHD, NIAID

Article: <https://www.ncbi.nlm.nih.gov/pubmed/28395844> [May 2017]

SELECTED NEW AND EXPANDED RESEARCH EFFORTS IN PEDIATRICS IN FY 2017

Selected New Pediatric Research Efforts

NIH ICOs launched a range of new research programs and efforts related to pediatrics in FY 2017. Selected highlights of new initiatives and funding opportunity announcements (FOAs) 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.

Strategic Plan for Cerebral Palsy Research

NINDS and NICHD co-authored a five-year strategic plan for cerebral palsy research, based on two workshops in 2014 and 2016. The workshops brought together thought leaders to discuss prevention, diagnosis, treatment, and research gaps in the cerebral palsy field, and the resulting strategic plan provides numerous specific recommendations for three priority areas (basic and translational research, clinical research, and workforce development).

Supported by NINDS, NICHD

Strategic Plan: <https://www.ninds.nih.gov/About-NINDS/Strategic-Plans-Evaluations/Strategic-Plans/2017-NINDS-NICHD-Strategic-Plan-Cerebral-Palsy>

Typical and Atypical Patterns of Language & Literacy in Dual Language Learners

About one of every five people ages 5 years and older in the United States speaks a language other than English in the home. Children and adolescents who are learning English in addition to a language spoken or signed at home are known as dual language learners (DLLs), and account for greater than 9 percent of enrollment in grades K-12 in schools throughout the United States. Increasing understanding of typical and atypical language and literacy development in DLLs is critical for improving reading skills and ultimate educational achievement and attainment in this population. However, little is known about how best to promote literacy and learning in one or both of the languages of DLLs. The purpose of this FOA is to support investigator-initiated applications that will inform our understanding of the typical and atypical patterns of language and literacy development of dual language learners (DLLs) in the United States. Applicants are encouraged to take advantage of advances in the language sciences and related fields to identify and clarify specific cognitive, linguistic, neurobiological, and sociocultural factors associated with normal and impaired language and literacy acquisition in young DLL populations.

Supported by NICHD, NIDCD

FOA: <https://grants.nih.gov/grants/guide/pa-files/PA-17-443.html>
<https://grants.nih.gov/grants/guide/pa-files/PA-17-443.html>

Prenatal Exposure to Metals and Risk for Autism Spectrum Disorder

Researchers are engaged in the first prospective, longitudinal study to examine the contribution of prenatal exposure to lead, cadmium, mercury, selenium, and manganese on the risk of autism. The study is using data from 456 mother-child pairs from the two largest enriched risk, prospective pregnancy autism cohorts in the United States: the Early Autism Risk Longitudinal Investigation (EARLI) and Markers of Autism Risk in Babies Learning the Early Signs (MARBLES).

Sponsored by: NIEHS

R01ES025531: https://projectreporter.nih.gov/project_info_description.cfm?aid=9128271 [Sep 2016]

Maternal Stress and Diesel Exhaust Interactions in Autism

Multiple prenatal/maternal environmental toxins and exposures have been linked to human autism spectrum disorders), but the associations of single agents are relatively weak, suggesting it is the combination of multiple maternal exposures that increases vulnerability in offspring. Researchers are

using a new mouse model that combines the effects of maternal stress and exposure to diesel exhaust, both of which have been implicated in autism, to establish a causal link between prenatal environmental exposures and dysfunction of neural cells critical for normal brain development.

Supported by NIEHS

R01ES025531: https://projectreporter.nih.gov/project_info_details.cfm?aid=9128271 [Sep 2016]

New Efforts for Earlier Screening for Autism

Universal screening for autism spectrum disorder (ASD) is one approach to achieving early diagnosis and engagement in treatment. In 2016, the United States Preventive Services Task Force (USPSTF) concluded that more research is needed “to assess the balance of benefits and harms of screening for ASD in young children for whom no concerns of ASD have been raised by their parents or a clinician.” In October 2017, NIMH issued a Notice to encourage submissions for administrative supplement requests to PA-16-287 from researchers with relevant active NIMH-supported research project grants to assess the effectiveness of early screening and engagement in services among young children with ASD. NIMH aims to support research activities that focus on the measurement of short-term and intermediate risks and benefits of early ASD screening, and the preliminary validation of broadband screening instruments testing children at age 12 months.

Supported by NIMH

Guide Notice: <https://grants.nih.gov/grants/guide/notice-files/NOT-MH-18-001.html>

Notice of NIMH's Interest in Pediatric Pharmacologic Trials in Autism Spectrum Disorder, directed at testing selective GABAergic agents

NIMH issued a Notice to encourage pharmacokinetic/pharmacodynamic bridging studies to test a drug called AZD7325 in pediatric subjects with autism. Available through the NCATS repurposing program, AZD7325 regulates GABA-A, a type of neurotransmitter. This is a follow-up to the previously funded safety study on AZD7325 in adults (the recently completed FAST-AS trial).

Supported by NIMH

NCATS Repurposing Program: <https://ncats.nih.gov/preclinical/repurpose>

FAST-AS Trial: <https://www.nimh.nih.gov/research-priorities/research-initiatives/fast-fast-fail-trials.shtml>

Guide Notice: <https://grants.nih.gov/grants/guide/notice-files/NOT-MH-17-044.html>

Using Stem Cell Technology to Better Study the Immediate Effects on Genetic Risks for Common Neurodevelopment Disorders

The NIMH Intramural Research Programs' Developmental Neurogenomics Unit is investigating multiple rare genetic disorders caused by the presence of too few or too many sex chromosomes. These tractable models may be used to examine how genetic and brain changes lead to common neurodevelopment disorders (NDDs) such as autism, attention-deficit/hyperactivity disorder, and intellectual disability. The first phase of this study used brain scans in patients to pinpoint when and where genetic risks for NDD impact brain maturation. The scans identified the initial cell types and stages to examine in order to understand how genetic risks impact individual brain cells. Due to advances in stem cell technology, scientists can now create these cells of interest from patients, and start to ask questions about human nerve cells that cannot be done in vivo or post mortem. NIMH researchers are collaborating with Oxford University scientists to create neural tissue from the skin of patients with genetic disorders of interest. They plan to measure genome function from individual cells using new techniques for gene expression analysis. These efforts will identify molecular targets that could be acting at the cellular level, to ultimately give rise to disorders of brain structure and function. Identifying such targets is a key step in translating neuroscientific and genetic knowledge into tools that help improve health.

Supported by NIMH

Understanding the Brain Mechanisms Mediating Chronic, Severe Irritability in Youth to Develop New Treatments

Irritability is one of the most common reasons children present for psychiatric care, and is associated with severe behavioral dyscontrol (including aggression), often in response to frustration. There are no well-established treatments, and antipsychotic medication is frequently used to control irritability, despite significant side-effects and lack of a good evidence base. Researchers in the NIMH Intramural Research Programs are working to understand the brain mechanisms mediating irritability and to use those insights to develop new treatments. Recent findings and initiatives include:

- Data indicate that irritable youth have a bias to interpret ambiguous faces as hostile, and to have abnormal brain responses to angry faces. These data motivated an ongoing clinical trial to determine whether computer-based training designed to address this bias can decrease irritability in children.
Article: <https://www.ncbi.nlm.nih.gov/pubmed/26745832> [Feb 2016]
Article: <https://www.ncbi.nlm.nih.gov/pubmed/27902832> [Jan 2017]
- Irritability is one of several mental illnesses that has clear parallels in lower species (other examples include anxiety and substance abuse). NIMH researchers are developing a new initiative to leverage these parallels by studying responses to frustration in animals.

Supported by NIMH

Mental Health Family Navigator Models

Recent national data indicate that 45 percent of youth ages 4-17 with serious emotional and behavioral difficulties do not receive mental health treatment. Further, among youth with sub-clinical emotional and behavioral difficulties, parents reported that 80 percent do not receive needed mental health treatment. To address these service delivery issues, NIMH issued a pair of FOAs to encourage research applications to develop and test the effectiveness and implementation of family navigator models designed to promote early access, engagement, and coordination of mental health treatment and services for children and adolescents who are experiencing early symptoms of mental health problems.

Supported by NIMH

FOA: <https://grants.nih.gov/grants/guide/pa-files/PAR-17-265.html>
<https://grants.nih.gov/grants/guide/pa-files/PAR-17-266.html>

Non-Invasive Rapid Diagnostics for Respiratory Diseases in Children

The goal of this contract solicitation is to develop rapid, sensitive diagnostics for lower respiratory tract infections (of bacterial, viral, and/or fungal origin). The diagnostics would be suitable for children and utilize non-invasive specimen collection methods.

Supported by NIAID

SBIR Program Solicitation: <https://sbir.nih.gov/sites/default/files/PHS2017-1.pdf>

Pediatric Heart Network

The NHLBI Pediatric Heart Network is collaborating to support a clinical trial evaluating the safety of Apixaban, a new type of anticoagulant, versus more traditionally used anticoagulants in children with congenital or acquired heart disease.

Supported by NHLBI

Clinical Trial: <https://www.clinicaltrials.gov/ct2/show/NCT02981472>

Pumps for Kids, Infants, and Neonates (PumpKIN)

Researchers from NHLBI's Pumps for Kids, Infants, and Neonates (PumpKIN) program have developed a ventricular assist device (VAD) specifically for infants and small children awaiting a heart transplant. The PumpKIN implant is only 15mm wide (about the size of a AA battery) and fully implantable, and thus allows children to remain active and at home. A clinical trial testing the device began in 2017.

Supported by NHLBI

Article: <https://www.ncbi.nlm.nih.gov/pubmed/28007073>

Clinical Trial: <https://clinicaltrials.gov/ct2/show/NCT02954497>

HIV and Hepatitis B Co-Infection: Advancing HBV Functional Cure through Clinical Research

This FOA invites applications proposing clinical research to identify and better understand the unique challenges to achieve a functional cure in HIV and hepatitis B virus positive (HIV/HBV+) co-infected hosts as well as advance the discovery and development of novel strategies to achieve HBV functional cure for HIV/HBV+ co-infected adult and pediatric populations, including children, adolescents and HIV exposed uninfected children.

Supported by NIAID, NCI, NIAAA

FOA: <https://grants.nih.gov/grants/guide/pa-files/PA-17-278.html>

Examining the Effects of Zika Virus on Children

While there is mounting evidence linking prenatal Zika virus infection to microcephaly and Guillain-Barré Syndrome, the full spectrum of clinical effects of postnatal Zika virus infection, particularly as it affects the central nervous system and neurodevelopment in children, is undetermined. Through the NIAID Vaccine and Treatment Evaluation Units, a clinical trials network, researchers in Guatemala and the United States, including NIAID scientists, have launched a natural history and prospective cohort study in rural Guatemala to examine the effects of Zika virus on children infected after birth. This study is evaluating the spectrum of neurological and neurodevelopmental outcomes in children infected perinatally and up to 5 years of age with Zika virus.

Supported by NIAID

NIH News Release: <https://www.nih.gov/news-events/news-releases/study-examine-effects-zika-infection-guatemalan-infants-children>

Exploring the Effects of Zika Virus Infection on Dental and Craniofacial Health

Congenital Zika virus infection is known to cause devastating birth defects. A newly funded project will study the effects of Zika virus infection on embryonic and fetal development of craniofacial skeletal and dental phenotypes in infants. Because maternal oral health status is associated with adverse pregnancy outcomes, this study will also investigate the relationship between the mothers' oral health status and their babies' craniofacial phenotype outcomes to determine whether Zika virus transmission and immunologic response to oral pathogens interact to impact craniofacial development pathways.

Supported by NIDCR

R21DE027235: https://projectreporter.nih.gov/project_info_description.cfm?aid=9381858

Characterization of the Cellular and Molecular Bases of Combined Immunodeficiencies

Combined immune deficiencies (CID) include a group of genetic conditions characterized by impaired development and/or function of T and B cells, white blood cells that fight infection. Infants affected with the most severe form of these disorders, also known as severe combined immune deficiency (SCID), are highly prone to serious infections early after birth, and die within the first few years of life unless the affected immune cells can be replaced with healthy cells, usually after hematopoietic cell transplantation (HCT). Launched in 2017, this research project focuses on identifying the genetic causes of CID, investigating the underlying immune dysfunction associated with CID, and generating preclinical data exploring novel therapeutic approaches for patients with CID.

Supported by NIAID

ZIAAI001222: https://projectreporter.nih.gov/project_info_description.cfm?aid=9566783

Gene Transfer for XSCID Using a Self-Inactivating (SIN) Gammaretroviral Vector

Severe combined immunodeficiencies (SCID) are a heterogeneous group of fatal inherited disorders characterized by a profound reduction or absence of T lymphocyte function. This project will test the

effectiveness of a recently developed vector expressing the *IL-2RG* gene, which has been shown to have reduced mutagenic potential in pre-clinical studies.

Supported by NIAID

U01AI087628: https://projectreporter.nih.gov/project_info_description.cfm?aid=8719920

Gene Therapy for SCID-X1 with Low Dose Busulfan and SIN-Lentiviral Vector

Gene therapy is a promising treatment for primary immunodeficiency. This project will test the efficacy and safety of a new self-inactivating lentiviral vector to treat SCID-X1. The goals of this project focus on the introduction of low-dose busulfan conditioning to improve immune reconstitution and improvement in patient safety with the change in vector type from previous studies.

Supported by NIAID

U01AI125051: https://projectreporter.nih.gov/project_info_description.cfm?aid=9312746

EFS-ADA Lentiviral Vector Transduction of Bone Marrow CD34+ Cells for ADA-SCID

This project will test an alternative therapeutic approach for patients with adenosine deaminase (ADA)-deficient severe combined immune deficiency using lentiviral vector to transfer the relevant normal gene to bone marrow stem cells. It will provide first-in-human information on safety and effectiveness of the proposed treatment and support the development of better treatments for primary immunodeficiency disease and other blood cell diseases.

Supported by NIAID

U01AI100801: https://projectreporter.nih.gov/project_info_description.cfm?aid=8519294

Randomized Study of Low versus Moderate Dose Busulfan in Transplant for Severe Combined Immunodeficiency

Allogeneic hematopoietic cell transplantation (HCT) is the standard treatment for SCID, which is typically fatal by age 2 years if not treated. However, this treatment leads to poor revitalization of humoral immunity in patients. This study will test the efficacy and safety of a treatment regimen consisting of low dose, individualized targeted busulfan compared to moderate dose in SCID patients at risk of poor humoral outcome undergoing non-matched sibling donor HCT.

Supported by NIAID

U01AI126612-01A1: https://projectreporter.nih.gov/project_info_description.cfm?aid=9450413

Pilot Clinical Trials Targeting HIV-1 Reservoirs in Children

This program supports pilot clinical trials that test interventions to limit or reduce HIV-1 reservoirs in children (birth to 18 years of age at the time of enrollment) on effective suppressive antiretroviral therapy.

Supported by NIAID

FOA: <https://grants.nih.gov/grants/guide/rfa-files/RFA-AI-16-086.html>

Biofeedback Approach to Reduce Risk of ACL Re-Injuries

Anterior cruciate ligament (ACL) injuries are common among adolescent athletes and many will sustain secondary ACL injuries following return to sports. This project will evaluate if a novel biofeedback-based rehabilitation approach can decrease the risk of secondary injuries to the ACL.

Supported by NIAMS

R21AR069865: https://projectreporter.nih.gov/project_info_description.cfm?aid=9234619

FIT Teens for Juvenile Fibromyalgia

Juvenile-onset fibromyalgia (JFM) is a chronic, debilitating pain condition that persists into adulthood for the majority of patients. Cognitive-behavioral therapy (CBT) is effective in reducing functional disability in adolescents with JFM. Increasing engagement in moderate-vigorous physical activity is also a crucial component of JFM pain management, yet regular participation in any physical activity is difficult to initiate and maintain in JFM patients. NIAMS-supported researchers have developed a novel intervention

- the Fibromyalgia Integrative Training program for Teens (FIT Teens), which enhances established CBT techniques with specialized neuromuscular exercise training derived from evidence-based pediatric injury prevention research. Pilot studies demonstrated that this intervention is safe, produces excellent patient engagement, has no adverse effects, reduces fear of movement and has a greater impact on pain-related disability than CBT alone. In this project, a 3-arm multi-site randomized clinical trial (RCT) will test whether the FIT Teens intervention is more effective in reducing disability than CBT alone or graded aerobic exercise alone, and whether treatment effects are sustained over 1 year. The RCT will be the largest and most rigorous trial in JFM to date. The project will provide clear direction for the best clinical care for JFM patients as well as the largest registry of well-characterized JFM patients for potential ancillary projects to investigate the pathophysiology of JFM.

Supported by NIAMS

R01AR070474: https://projectreporter.nih.gov/project_info_description.cfm?aid=9306987

NCI Pediatric MATCH (Molecular Analysis for Therapy Choice)

The NCI-Pediatric MATCH trial (NCT03155620), led by Children's Oncology Group (COG), opened in July, 2017 and is enrolling children with advanced solid tumors that have progressed or recurred on standard therapy. As in the adult MATCH trial, genetic sequencing will be used to identify children and adolescents between the ages of 1 to 21 years whose tumors have a genetic abnormality for which either an approved or investigational targeted therapy exists. Patients with all types of solid tumors are eligible for the trial including central nervous system tumors and non-Hodgkin lymphomas as well as histiocytic disorders. The trial opened with seven treatment arms with several more to be added. A minimum of twenty patients will be enrolled on each treatment arm with the ability to expand the enrollment if 3 or more responses are seen on the treatment arm. Approximately 200-300 patients are expected to enroll each year and approximately 1000 pediatric patients will be screened. Several of the treatment arms include agents that have never been tested in children before. One of the unique aspects of Pediatric MATCH is that germline DNA from peripheral blood will be analyzed. Therefore, if a genetic abnormality is identified in the tumor, the treating physician will be informed whether the genetic abnormality is inherited or not and can provide additional recommendations regarding genetic testing/genetic counseling to the family.

Supported by NCI

ClinicalTrials.gov: <https://clinicaltrials.gov/ct2/show/NCT03155620>

NCI Press Release: <https://www.cancer.gov/news-events/press-releases/2017/nci-pediatric-match-trial-opens>

AGCT 1531: A Phase 3 Study of Active Surveillance for Low Risk and a Randomized Trial of Carboplatin vs. Cisplatin for Standard Risk Pediatric and Adult Patients with Germ Cell Tumors

The Children's Oncology Group (COG) is leading this National CTN trial (NCT03067181) for newly diagnosed patients with low risk and standard risk germ cell tumors. This study aims to reduce therapy to minimize toxicity while maintaining current survival rates. The trial will eliminate chemotherapy for low risk patients who are likely cured with surgery and will observe the salvage rates among those who recur. Among standard risk patients the trial will evaluate whether cisplatin, which is the standard-of-care in COG, can be replaced with the less toxic alternative platin analogue, carboplatin.

Supported by NCI

ClinicalTrials.gov: <https://clinicaltrials.gov/ct2/show/NCT03067181>

Phase 3 Trial of One Dose vs. Two Doses of HPV Vaccine

The "ESCUDDO" Study was launched in Costa Rica in November 2017 and will begin recruiting participants in the next few months. The main goal is to evaluate one vs. two doses of the bivalent and nonavalent HPV vaccines. There are two study components: (1) a controlled, randomized, double-blinded non-inferiority clinical trial to compare one-dose to two-dose vaccination (20,000 girls ages 12-16; and (2) a concurrent epidemiologic survey for HPV status among unvaccinated women (4,000 females ages

17-20). Participants in the four vaccination intervention arms will be followed every six months for four years. The survey arm will measure HPV DNA status at two six-month visits with no other follow up; the women will be offered HPV vaccination at enrollment and at two six-month visits.

Supported by NCI, the Bill & Melinda Gates Foundation

ClinicalTrials.gov: <https://clinicaltrials.gov/ct2/show/NCT03180034>

HPV Serology Standards Laboratory

The Human Papillomavirus Serology Standards Laboratory (HPV-SSL) is jointly supported by the NCI and the Bill and Melinda Gates Foundation and was established in January 2017. The HPV Serology Standards lab is part of an international initiative to standardize and harmonize serological assays for HPV antibody testing in the context of vaccine trials. Serology standardization is particularly important as new HPV prophylactic vaccine trials are proposing to use serology data as endpoints for licensure of new vaccine indications or new vaccines. The main goals of the Laboratory include the development of qualified secondary assay standards, critical reagents (HPV Virus-Like Particles) and assays that will be made available to the scientific community. Overall, this initiative will enable comparisons of data across different vaccines and different studies and thus, it will facilitate vaccine development and implementation of new vaccine indications and new vaccine candidates.

Supported by NCI, CDC, Bill and Melinda Gates Foundation, Karolinska Institute, and Public Health England

NCI News Release: <https://frederick.cancer.gov/news/new-hpv-serology-laboratory-aims-standardize-assays-and-contribute-vaccine-implementation-and>

Personal Health Records for Youth Emancipating from Foster Care

There are 427,000 children in the custody of child protective services (i.e., foster care) in the United States; approximately 5,000 youth emancipate from foster care annually. Health care outcomes are poor, in part due to lack of access to medical history. The proposed research will create and distribute a personal health record for foster youth to be distributed at age 18 to improve healthcare knowledge and utilization.

Supported by NLM

R01LM012816: https://projectreporter.nih.gov/project_info_description.cfm?icde=0&aid=9479351

Selected Expanded Pediatric Research Efforts

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

Biomarkers: Bridging Pediatric and Adult Therapeutics

This FOA encourages grant applications that propose adapting adult biomarkers to children. This would include the application and validation of biomarkers developed in adults to pediatric diagnosis, prognosis, and estimation of disease progression, toxicity and response to therapy. Projects supported by this FOA will include those biomarkers that correlate with a clinical observation, have been extensively studied in adults, and for which there is solid evidence that they have pediatric applications. Discovery of new biomarkers for use in new drug development or in preclinical studies is also part of this FOA.

Supported by NICHD

FOA: <https://grants.nih.gov/grants/guide/pa-files/PAR-17-169.html>

Clinical Genome Resource (ClinGen)

The Clinical Genome Resource (ClinGen) aims to build an authoritative central resource that defines the clinical relevance of genes and variants for use in precision medicine and research. To do so, ClinGen scientists are developing standard approaches for sharing genomic and phenotypic data provided by clinicians, researchers, and patients through centralized databases, such as ClinVar, and are working to standardize the clinical annotation and interpretation of genomic variants. NICHD published an FOA to establish expert panels to select genes and genomic variants associated with diseases or conditions of high priority to NICHD. These panels would systematically determine the clinical significance and utility of these gene and genomic variants for diagnosis and treatment. In FY 2017, funded applications covered expert curation of pediatric mitochondrial Leigh-like syndrome genes and variants, genetics of malformations of the central nervous system, and monogenic diabetes.

Supported by NHGRI, NICHD

ClinGen: <https://www.clinicalgenome.org/>

The Environmental Determinants of Diabetes in the Young (TEDDY)

Insights about strategies to prevent type 1 diabetes could be identified through the NIDDK's ongoing study, TEDDY, which is analyzing thousands of samples as part of a case-control study to investigate etiology and pathogenesis of islet autoimmunity and type 1 diabetes. In FY17, TEDDY was expanded to add studies of immune parameters using new technologies applied to TEDDY blood cell samples, serum, and plasma.

Supported by NIDDK, NIAID, Special Statutory Funding Program for Type 1 Diabetes Research

TEDDY: <https://teddy.epi.usf.edu>

FOA: <https://grants.nih.gov/grants/guide/rfa-files/RFA-DK-17-508.html>

Drug-Induced Liver Injury Network Continuation

The NIDDK established the Drug-Induced Liver Injury Network (DILIN) in 2003 to collect and analyze data from people with severe liver injury caused by over-the-counter and prescription drugs, or by alternative medicines such as herbal products and dietary supplements. Past DILIN studies have included pediatric participants, including one showing that liver injury attributed to herbal/dietary supplements used for bodybuilding was more common in younger males. In 2017, the NIDDK announced an initiative to continue the current Network of six clinical centers and a data coordinating center for an additional 5-year period. As part of its next phase, one objective will be to capture cases from a wide range of the population in the United States, including both children and adults, for studies characterizing liver injury resulting from drugs or herbal/dietary supplements.

Supported by NIDDK

Drug-Induced Liver Injury Network: <http://www.dilin.org/>

FOA: <https://grants.nih.gov/grants/guide/rfa-files/RFA-DK-17-509.html>

<https://grants.nih.gov/grants/guide/rfa-files/RFA-DK-17-510.html>

Article: <https://www.ncbi.nlm.nih.gov/pubmed/25043597> [Oct 2014]

The Microbiome and Juvenile Rheumatic Diseases

The NIEHS Twin Sibling Study has enrolled more than 250 twins and same-gender (close in age) sibling pairs discordant for systemic rheumatic diseases to examine environmental risk factors in recently-diagnosed patients with juvenile and adult myositis, rheumatoid arthritis, lupus and scleroderma to examine risk factors common to these systemic rheumatic diseases in recently-diagnosed patients. To date, this study has identified peripheral blood gene and proteomic signatures common to these diseases, found epigenetic changes in a number of immune response genes in systemic lupus erythematosus patients, and identified herpes virus expression to be increased in the peripheral blood of affected patients. In one of the first studies of microbiome in pediatric rheumatic diseases, researchers will examine the oral microbiome in children with juvenile dermatomyositis as compared to their unaffected siblings and parents to see if changes in the microbiome may be associated with oral changes or disease outcomes.

Supported by NIEHS

Twin Sibling Study: <https://www.niehs.nih.gov/research/clinical/studies/twin-sibs/index.cfm>

Clinical Trial of Sodium Thiosulfate to Treat Calcinosis Associated with Juvenile Dermatomyositis

Calcinosis is a debilitating complication of dermatomyositis in up to 40 percent of patients, resulting in increased disability, frequent infections, and impaired quality of life. No known therapy exists to treat calcinosis after it occurs. Based on anecdotal experiences suggesting significant improvement in the calcifications of dermatomyositis with sodium thiosulfate treatment, NIEHS has opened a Phase 1-2 clinical pilot study to evaluate the efficacy of using sodium thiosulfate in juvenile and adult dermatomyositis with moderate to severe calcinosis. Sodium thiosulfate is FDA-approved for the treatment of cyanide poisoning, but it also acts as a calcium chelator, an antioxidant, and a vasodilator. The study will also assess the safety of longer-term use of sodium thiosulfate in children and adults, and evaluate the impacts of treatment on quantitative changes in calcium lesions by imaging, quality of life, functional disability, muscle strength, laboratory values (including biomarkers of inflammation and endothelial activation), as well as overall myositis disease activity and damage.

Supported by NIEHS, CRADA with Hope Pharmaceuticals

Clinical Trial: <https://clinicaltrials.gov/ct2/show/NCT03267277>

Epigenetic Mediation of Adverse Social Context on Stress Response; Socioemotional Development and Health in a Population-based Study of Minority and Low SES Children and Adolescents

This study will assemble epigenome-wide data on 2,000 children at two points in time, to describe methylation patterns among non-Hispanic Black, Hispanics, and low-income groups. The goal of this approach is to be able to explain epigenetic associations with social adversity, biological processes, and socioemotional development. The study will use data from 20 cities to produce a national and city representative sample of children born between 1998 to 2000. The study will provide estimates of population-based epigenome-wide DNA methylation measures for the three groups of participants, association of social adversity development with DNA methylation, associations between DNA methylation and biological measures of stress response, associations between development of stress response behaviors and methylation profiles, and comparisons of these relationships across the three groups.

Supported by NIMHD

R01MD011716: https://projectreporter.nih.gov/project_info_description.cfm?aid=9386217

A Longitudinal Investigation of Minority Stress in a Diverse National Sample of Sexual Minority Adolescents

Sexual minority adolescents (SMA), defined as those who report a same-sex sexual orientation, are at much higher risk for behavioral health concerns than heterosexual adolescents. To examine the causes for this risk and interventions to reduce them, this study will examine the individual and group trajectories of sexual minority adolescents (ages 14 to 17), and how differences in these trajectories predict behavioral health outcomes. The study will use a developmental psychopathology approach and follow participants for three years. The results will inform clinical assessment and the development of targeted behavioral health interventions for SMAs.

Supported by NIMHD

R01MD012252: https://projectreporter.nih.gov/project_info_description.cfm?aid=9424462

Examining the Role of Sleep Disturbances in Contributing to Health Risk Behaviors and Cardiometabolic Outcomes in Urban Native American Youth

Urban AI/ANs constitute over two-thirds of the total AI/AN population and may be at increased risk for adverse cardiometabolic and behavioral health problems. This study investigates the role of sleep disturbances in contributing to health behavior and clinically relevant health outcomes in a culturally sensitive community. The study addresses the multiple dimensions of behavioral health problems such as

tobacco, caffeine, alcohol, and drug use, physical inactivity and electronic media use, and other social and cultural contexts of sleep in urban AI/AN youth.

Supported by NIMHD

R01MD012190: https://projectreporter.nih.gov/project_info_description.cfm?aid=9403031

Exposure to Violence, Epigenetic Variation, and Asthma in Puerto Rican Children

Research has demonstrated that in Puerto Rican children, psychological stressors including exposure to violence are associated with asthma and increased morbidity from asthma. This study will examine the possibility that exposure to violence increases the risk of asthma and asthma morbidity through altered methylation of genes in regulating behavioral, autonomic, neuroendocrine and immunologic responses to stress. The study will examine changes in the respiratory epithelium in 500 Puerto Rican children.

Supported by NIMHD

R01MD011764: https://projectreporter.nih.gov/project_info_description.cfm?aid=9385085

Childhood Obesity Among Low-Income Mexican Americans

Hispanic or Latino children are nearly twice as likely as non-Hispanic White children to have obesity. Mexican Americans have higher risk of obesity than other Hispanic or Latino subgroups. This study will use data from a longitudinal dataset to collect physical health and markers of cardiometabolic risk of children ages 7.5 and 9 years old. The aims of the study are to: 1) chart trajectories of weight gain using objective measures of weight and growth measured at 13 time points from birth through nine years of age; 2) identify critical periods from birth to age 9 at which children diverge from healthy weight gain trajectories; 3) evaluate early life biological susceptibility as a moderator of the impact of environmental influences on child weight gain trajectories and obesity; 4) evaluate the consequences of cultural, economic, maternal and child factors, and weight gain trajectories for emerging physical health and cardiometabolic risk. This study addresses central questions about early life contributors to weight gain and obesity risk in a high-risk ethnic group, and can enhance opportunities for prevention of obesity and associated health problems.

Supported by NIMHD

R01MD011599: https://projectreporter.nih.gov/project_info_description.cfm?aid=9364958

Consortium for Food Allergy Research (CoFAR)

CoFAR was re-awarded in FY 2017 to continue evaluating new approaches to treat and prevent food allergy. CoFAR has demonstrated the clinical benefit of egg oral immunotherapy for treating egg allergy and has identified the most promising routes, doses, and durations of egg and peanut immunotherapy for further study. In addition, the CoFAR has identified genes associated with an increased risk for peanut allergy among Americans of European descent.

Supported by NIAID

News Release: <https://www.niaid.nih.gov/news-events/nih-designates-43-million-food-allergy-research-consortium>

FOA: <https://grants.nih.gov/grants/guide/rfa-files/RFA-AI-15-050.html>
<https://grants.nih.gov/grants/guide/rfa-files/RFA-AI-15-051.html>

The International Maternal Pediatric Adolescent AIDS Clinical Trials (IMPAACT) Network

IMPAACT supports studies on prevention and treatment of HIV and its complications and co-infections, such as tuberculosis (TB), which is a major cause of death for HIV-infected infants, children, adolescents, and pregnant/postpartum women globally. Since 1990, this NIAID-funded network has collaborated closely with the NICHD-funded Domestic & International Pediatric & Maternal HIV Clinical Studies Network. This collaboration has made it possible to conduct an expanded clinical trial portfolio advancing pediatric HIV/AIDS clinical research. IMPAACT is currently enrolling participants in a multi-center study of HIV-1-infected and HIV-1-uninfected pregnant and postpartum women with latent TB infection.

Supported by NIAID

IMPAACT Studies: <http://impaactnetwork.org/studies/IMPAACT2001.asp>
<http://impaactnetwork.org/studies/IMPAACT2001.asp>

- **Clinical Trials to develop a Pediatric Respiratory Syncytial Virus (RSV) Vaccine**
IMPAACT is conducting several trials to evaluate the safety and effectiveness of live-attenuated respiratory syncytial virus (RSV) vaccines delivered as nose drops to infants.

Supported by NIAID

IMPAACT Studies: <http://impaactnetwork.org/studies/IMPAACT2018.asp>
<http://impaactnetwork.org/studies/IMPAACT2013.asp>,
<http://impaactnetwork.org/studies/IMPAACT2012.asp>

- **Clinical Trials to study HIV Treatment and Remission in Infants**
IMPAACT expanded trials to evaluate the safety of drug treatment and potent neutralizing antibodies therapies in HIV-1 exposed infants at risk of acquiring HIV-1 infection. NIAID also expanded studies designed to:
 - explore the effects of early intensive ART, including use of an antibody, to achieve HIV remission in newborns; and
 - determine safety and pharmacokinetic parameters of potent anti-HIV neutralizing monoclonal antibodies in HIV-exposed infants.

Supported by NIAID

IMPAACT Studies: <http://impaactnetwork.org/studies/IMPAACT2007.asp>
<http://impaactnetwork.org/studies/p1112.asp>
<http://impaactnetwork.org/studies/p1115.asp>

- **Clinical trials of new drugs to treat multidrug-resistant TB in children (MDR-TB)**
In FY 2017, IMPAACT initiated a study to evaluate the pharmacokinetics, safety, and tolerability of bedaquiline, a new drug against multi-drug-resistant tuberculosis (MDR-TB), as part of a new drug regimen in HIV-infected and HIV-uninfected children and adolescents with MDR-TB.
IMPAACT Study: <http://impaactnetwork.org/studies/P1108.asp>

NIDCR Oral Health Disparities and Inequities Research Consortium

NIDCR funds a research consortium and data coordinating center aimed at reducing or eliminating inequities in access to care and improving the oral health of children. Research approaches include:

- Use of micro-incentives to increase attendance of oral care visits and improve oral health behaviors
UH3DE025514: https://projectreporter.nih.gov/project_info_description.cfm?aid=9530847
- Multi-level interventions aimed at caregivers and health care providers and practices
UH3DE025487: https://projectreporter.nih.gov/project_info_description.cfm?aid=9530850
- Text-message based interventions to improve oral health
UH3DE025492: https://projectreporter.nih.gov/project_info_description.cfm?aid=9534314
- Family-focused education and support from community health workers
UH3DE025483: https://projectreporter.nih.gov/project_info_description.cfm?aid=9530852

Supported by NIDCR

FOA: <https://grants.nih.gov/grants/guide/rfa-files/RFA-DE-15-006.html>

Pediatric Suicide Prevention in Emergency Departments

In August 2014, NIMH funded the Emergency Department Screen for Teens at Risk for Suicide (ED-STARS) study, taking place in 14 sites across the country. Researchers generated a two minute, personally tailored, computerized screening tool for EDs to assess youth suicide risk. These researchers are now examining adolescents from the ED-STARS cohort who are at immediate elevated risk for suicide to identify warning signs for suicide attempts.

Supported by NIMH

U01MH104311: https://projectreporter.nih.gov/project_info_description.cfm?aid=9203948

NIMH Science Update: <https://www.nimh.nih.gov/news/science-news/2014/personalized-screen-to-id-suicidal-teens-in-14-ers.shtml>

Funding Opportunities for Pediatric Research

In FY 2017, the NIH issued 163 Funding Opportunity Announcements (FOAs) that specifically called for applications related to pediatric research. These FOAs are listed in Table 3 of the Appendix to this report. Much of the NIH's pediatric research portfolio comes from investigator-initiated research, and a large number of funded grants are associated with funding opportunities that do not have a pediatric focus. However, the FOAs listed in Table 3 provide information about the range of areas that NIH ICOs have taken steps to address in pediatric research. In FY 2017, the NIH issued FOAs in research for chronic condition self-management in children and adolescents, developing interventions for HIV prevention and care, determining basic mechanisms of brain development in substance use and dependence, generating animal models for childhood diseases, managing clinical trials in chronic kidney disease, performing longitudinal analyses on health behaviors using new technologies, and reducing health disparities among minority and underserved children, 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 2017, NIH funded approximately 67 pediatric centers programs that supported pediatric research, with an additional 163 programs funded under cooperative agreement mechanisms that are often similar in structure to centers. Many, but not all, pediatric research programs were focused exclusively on child health. For example, the NIH awarded nine research grants totaling nearly \$100 million for the Autism Centers of Excellence (ACE), a longstanding trans-NIH program that supports large research projects aimed at understanding and developing treatments for autism. The center/network programs supporting pediatric research at the NIH include some that are targeted to a specific disease or condition, such as the Centers for Collaborative Research in Fragile X. Others, like the pediatric component of the Clinical and Translational Science Awards, are not specific to any one condition. Other pediatric research programs are funded using non-center research mechanisms, such as R01 research grants. This report highlights selected key ongoing NIH programs in pediatric research, funded through a variety of research grant and contract mechanisms and interagency agreements.

Child Development

Adolescent Brain Cognitive Development Study (ABCD)

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

Initiated by the Collaborative Research on Addiction at NIH (CRAN, consisting of NIDA, NIAAA, NCI), which leads this effort in partnership with NICHD, NIMH, NIMHD, NINDS, and OBSSR

ABCD Study: <https://abcdstudy.org/>

Upstate KIDS Study and Follow-Up Study

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

Supported by NICHD

Upstate KIDS: <https://www.nichd.nih.gov/about/org/diphr/eb/research/pages/infant-development.aspx>

Reducing Health Disparities Among Minority and Underserved Children

Relaunched in January 2017, this initiative encourages research that targets the reduction of health disparities among children. Investing in early childhood development is essential. Specific targeted areas of research include bio-behavioral studies that incorporate multiple factors that influence child health disparities such as biological (e.g., genetics, cellular, organ systems), lifestyle factors, environmental (e.g., physical and family environments) social (e.g., peers), economic, institutional, and cultural and family influences; studies that target the specific health promotion needs of children with a known health condition and/or disability; and studies that test, evaluate, translate, and disseminate health promotion prevention and interventions conducted in traditional and non-traditional settings.

Supported by NINR, NIDCD

FOA: <https://grants.nih.gov/grants/guide/pa-files/PA-17-118.html>

<https://grants.nih.gov/grants/guide/pa-files/PA-17-117.html>

Learning Disabilities Research Centers (LDRC) Consortium

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

NICHD LDRC Consortium: <https://www.nichd.nih.gov/research/supported/Pages/ldrc.aspx>

NICHD Learning Disabilities Innovation Hubs:

<https://www.nichd.nih.gov/research/supported/Pages/ldhubs.aspx>

FOA: <https://grants.nih.gov/grants/guide/rfa-files/RFA-HD-17-006.html>

<https://grants.nih.gov/grants/guide/rfa-files/RFA-HD-17-003.html>

Environmental and Social Influences

Environmental influences on Child Health Outcomes (ECHO)

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

Supported by NIH OD

NIH ECHO: <https://www.nih.gov/echo>

Clinical Sites for the IDeA States Pediatric Clinical Trials Network¹

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

FOA: <https://grants.nih.gov/grants/guide/rfa-files/RFA-OD-16-001.html>

Centers for Children's Environmental Health and Disease Prevention Research

Since 1998, the Children's Environmental Health and Disease Prevention Research Centers have studied individual, regional, national, and global environmental exposures and the effects on children's health. The centers connect basic scientists, behavioral scientists, social scientists, pediatricians and other clinicians, and public health professionals, all working together to improve the health and environments of children.

Supported by NIEHS, EPA

NIEHS Centers: <https://www.niehs.nih.gov/research/supported/centers/prevention/>

Children's Health Exposure Analysis Resource (CHEAR)

This initiative has created a resource to provide the NIH-funded research community with access to laboratory and statistical analyses that will allow for the addition or expansion of environmental exposures as a component of ongoing epidemiological and clinical research, thereby creating a public resource of children's exposures across the country. Exposures measured encompass the breadth of the exposome, the totality of biological, psychosocial, chemical, and physical factors to which humans are exposed.

Supported by NIEHS

FOA: <https://grants.nih.gov/grants/guide/rfa-files/RFA-ES-15-011.html>

<https://grants.nih.gov/grants/guide/rfa-files/RFA-ES-15-009.html>

<https://grants.nih.gov/grants/guide/rfa-files/RFA-ES-15-010.html>

WHO-NIEHS Collaborating Centre for Environmental Health Sciences

Children have a special vulnerability to physical, chemical, and biological environmental threats. According to the World Health Organization (WHO), environmental factors account for one-third of the global disease burden in children. NIEHS provides support for the WHO Collaborating Centres for Children's Environmental Health Network, 10 research institutes around the world, each of which acts as a hub to strengthen national or regional capacity to advance children's environmental health.

Supported by NIEHS

NIEHS Partnerships: <https://www.niehs.nih.gov/research/programs/geh/partnerships/index.cfm>

Centers of Excellence on Environmental Health Disparities

Five centers combine basic and translational research and community involvement to improve understanding of environmental health disparities as well as identify mitigation and prevention strategies to decrease the public health burden.

Supported by NIEHS, NIMHD, EPA

NIMHD Environmental Health: <https://www.nimhd.nih.gov/programs/extramural/coe/environmental.html>

Threat-related Negative Valence Systems, Child Victimization, and Anxiety

Childhood exposure to interpersonal violence (IPV; e.g., sexual or physical abuse, witnessing domestic violence, dating violence) is a well-established risk factor for anxiety and other mental health problems across the lifespan. However, outcomes after exposure are highly variable in individuals. Understanding

¹ This new network partially meets the requirement in Section 409D(d) of the PHS Act for a National Pediatric Research Network as part of the Pediatrics Research Initiative.

how exposure to IPV leads to negative outcomes and identifying individual risk may guide how and when to intervene. NIMH is supporting a longitudinal study of 360 children and their caregivers to assess exposure to IPV and evaluate mental health outcomes. The study aims to investigate developmental changes in children's responses to threatening stimuli at the levels of neurocircuitry, physiology, and behavior/self-report, to clarify the timing and developmental course of vulnerability to adverse mental health outcomes after childhood exposure to IPV.

Supported by NIMH

R01MH112209: https://projectreporter.nih.gov/project_info_description.cfm?aid=9331981

Guided Imagery Lifestyle Intervention to Prevent & Treat Obesity in Latino Youth

The childhood obesity epidemic represents a major health threat to the current generation of youth, and falls disproportionately on urban, Latino adolescents. Data suggests modern inner-city minority youth suffer from elevated levels of psychosocial stress, and that such chronic stress contributes to obesity and insulin resistance, increasing risk of type 2 diabetes, cardiovascular disease, fatty liver disease, and other obesity-related disorders. Guided imagery is a mind-body complementary/alternative medicine (CAM) modality that offers promise as a therapeutic intervention to reduce psychosocial stress, and to promote healthy lifestyle behaviors. In a pilot 12-week lifestyle intervention, Interactive Guided Imagery significantly reduced salivary cortisol, reduced sedentary behavior, and increased moderate physical activity in overweight Latino adolescents. The overall aim of this research is to determine the separate contributions of stress reduction guided imagery and health behavior guided imagery, when delivered in the context of a health-promoting, lifestyle intervention, on short-term and long-term stress-reduction and behavioral outcomes in predominantly Latino high school students. This project directly addresses the role of psychosocial stress in promoting obesity and metabolic disease risk, and investigates the role of the mind-body CAM intervention of guided imagery in both reducing stress and promoting healthy lifestyle behaviors that could dramatically improve the metabolic health of today's youth.

Supported by NCCIH

R01AT008330: https://projectreporter.nih.gov/project_info_description.cfm?aid=9312779

Pregnancy and the Health of the Newborn

Obstetric-Fetal Pharmacology Research Units (OPRU) Network

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

Supported by NICHD

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

Maternal-Fetal Medicines Unit (MFMU) Network

The MFMU Network is designed to conduct rigorous clinical trials in maternal-fetal medicine and obstetrics, particularly with respect to the continuing problem of preterm birth. The aims of the Network are to reduce maternal, fetal, and infant morbidity related to preterm birth, fetal growth abnormalities, and maternal complications, and to provide the rationale for evidence-based, cost-effective obstetric practice. Current projects include an observational study of hepatitis C in pregnancy and a clinical trial to determine whether administering hyperimmune globulin for congenital cytomegalovirus (CMV) can reduce mother-to-child transmission of CMV infection.

Supported by NICHD

MFMU: <https://www.nichd.nih.gov/research/supported/Pages/mfmu.aspx>

The Hunter Kelly Newborn Screening Research Program

This program funds an array of newborn screening related research that focuses on:

- Developing systematic methods to identify additional conditions appropriate for newborn screening;
- Developing and testing innovative interventions and treatments to improve outcomes;
- Educating the provider workforce;
- Developing and implementing appropriate information and communication systems for parents and providers; and
- Sponsoring ongoing programs of research and research training in newborn screening.

Supported by NICHD

<https://www.nichd.nih.gov/health/topics/newborn>

Newborn Screening Translational Research Network (NBSTRN)

The NBSTRN seeks to improve the health outcomes of newborns with genetic or congenital disorders through an infrastructure that provides the research community with access to resources for newborn screening. NBSTRN has developed three tools to facilitate newborn screening research:

- *Virtual Repository of Dried Blood Spots (VRDBS)*. A web-based tool that enables state program personnel to control and manage access to specimens for newborn screening related research. <https://nbstrn.org/research-tools/virtual-repository-of-dried-blood-spots>
- *Longitudinal Pediatric Disease Resource (LPDR)*. A secure informatics system designed to enable enhanced data collection, sharing, management and analysis for conditions identified as part of newborn screening or for conditions that may benefit from newborn screening. <https://nbstrn.org/research-tools/longitudinal-pediatric-data-resource>
- *Laboratory Performance Database (R4S)*. This web-based application for the collection and reporting of analytical results has been developed and widely adopted into the routine practice of newborn screening laboratories worldwide. <https://nbstrn.org/research-tools/lab-performance-database>

Supported by NICHD

NBSTRN: <https://www.nichd.nih.gov/research/supported/Pages/nbstrn.aspx>
<https://nbstrn.org/>

Newborn Screening Coding and Terminology Guide

This online guide uses nationally-accepted vocabulary and electronic messaging standards to enable laboratories, clinicians, public health officials, and researchers to exchange and aggregate newborn screening results from all of the states as a key Big Data resource.

Supported by NLM

NLM Codes: <https://newbornscreeningcodes.nlm.nih.gov/nb/sc/constructingNBSHL7messages>

Neonatal Research Network (NRN)

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

Supported by NICHD, with co-funding from other ICs for specific projects

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

Immunity in Neonates and Infants

Launched in March 2016, this program supports research to advance understanding of immune system development and mechanisms of immune response in neonates and infants. Results from these studies are defining infant-specific immune processes that may be targeted to improve vaccine efficacy in this vulnerable population.

Supported by NIAID, NICHD, NIEHS, ORWH

FOA: <https://grants.nih.gov/grants/guide/rfa-files/RFA-AI-16-001.html>

Understanding HIV Persistence in Infants

Begun in August 2016, the purpose of this program is to stimulate research in the pathogenesis of perinatal HIV-1 infection by elucidating HIV-1 immune responses in the setting of the infant's evolving immune system and mechanisms of establishment and maintenance of HIV-1 latent viral reservoirs. The goal of this FOA is to gain knowledge to be used in the future development of strategies to induce HIV-1 remission.

Supported by NIAID, NICHD, NIMH

FOA: <https://grants.nih.gov/grants/guide/rfa-files/RFA-AI-16-064.html>

Elucidating the Role of the Genetic and Environmental Determinants of Preterm Birth Using Integrative Computational Approaches

Given the wealth and availability of genomic and environmental exposure data, computational methods provide a powerful opportunity to identify population-specific determinants of disease. The goal of this proposal is to develop computational approaches to integrate diverse genetic and environmental exposure datasets to elucidate factors that affect disease in diverse populations and apply them to the study of preterm birth. The methodology developed as part of this proposal can be extended and applied to other phenotypes of interest and inform precise population-specific diagnostic and therapeutic strategies.

Supported by NLM

K01LM012381: https://projectreporter.nih.gov/project_info_description.cfm?icde=0&aid=9324358

Nutrition and Obesity in Pregnancy and Childhood

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.

ODS Database: https://ods.od.nih.gov/Research/Dietary_Supplement_Label_Database.aspx

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

NIH/USDA Database: <https://dietarysupplementdatabase.usda.nih.gov/>

Supported by ODS

Understanding Factors in Infancy and Early Childhood (Birth to 24 months) That Influence Obesity Development

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

Supported by NIDDK and co-sponsored by NICHD, NIMHD, OBSSR

FOA: <https://grants.nih.gov/grants/guide/pa-files/PA-18-032.html>

Molecular Transducers of Physical Activity in Humans

The Common Fund's Molecular Transducers of Physical Activity in Humans is a clinical research study designed to extensively catalogue the biological molecules affected by physical activity in people, identify some of the key molecules that underlie the systemic effects of physical activity, and characterize the function of these key molecules. One of the clinical sites will focus on the molecular changes that occur when children and adolescents exercise. Scientists and clinicians increasingly recognize that physical activity is an essential component of health, growth, and development, and there are critical periods when exercise can lead to long-term improvements in health. When combined with data from the six clinical sites focusing on adults, this research will show whether the molecular transducers of health benefits differ in children and in adults and during different stages of development.

Supported by NIH Common Fund

Molecular Transducers of Physical Activity Website: <https://commonfund.nih.gov/MolecularTransducers>
U01AR071158: https://projectreporter.nih.gov/project_description.cfm?projectnumber=1U01AR071158-01

Diabetes

Consortium for the Study of Chronic Pancreatitis, Diabetes, and Pancreatic Cancer (CPDPC)

This consortium pursues clinical research on pancreatic diseases, including chronic pancreatitis, acute recurring pancreatitis, pancreatic cancer, and the type 3c diabetes that may result from these diseases. The consortium is enabling researchers to make strides towards the goals of earlier diagnosis, targeted treatment, and prevention of pancreatic disease in a diverse population of patients. As a component of the CPDPC, researchers in the INSPPIRE (International Study Group of Pediatric Pancreatitis: In Search for a Cure) consortium found that genetics, birth defects, and ethnicity may play important roles in the occurrence of pancreatitis in children. (PMID 27064572)

Supported by NIDDK, NCI

CPDPC: <http://cpdpc.mdanderson.org/>

Article: <https://www.ncbi.nlm.nih.gov/pubmed/27064572> [Jun 2016]

TrialNet

The NIDDK-led Type 1 Diabetes TrialNet is an international clinical trials network that screens up to 15,000 individuals annually and conducts trials of agents to prevent clinical diagnosis of type 1 diabetes in people with early stage disease and to slow progression of the disease in people who are newly diagnosed. Blood tests can accurately identify relatives of people with type 1 diabetes who are at early stages of disease (at high or moderate risk of developing clinical symptoms within 5 years), which has enabled TrialNet to initiate clinical trials of promising prevention strategies. Two of which (anti-CD3, abatacept) are currently ongoing (both anti-CD3 and abatacept showed efficacy in preserving insulin secretion in new onset type 1 diabetes, and are now being studied earlier in the course of the disease). TrialNet plans to study additional drugs that have shown efficacy in other autoimmune diseases.

Supported by NIDDK, NIAID, Special Statutory Funding Program for Type 1 Diabetes Research

TrialNet: www.trialnet.org

Advanced Clinical Trials to Test Artificial Pancreas Device Systems in Type 1 Diabetes

Advanced clinical trials are 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. The first trials started in February 2017. These trials should generate data able to satisfy safety and efficacy requirements by regulatory agencies regarding the clinical testing of AP device systems.

Supported by NIDDK, Special Statutory Funding Program for Type 1 Diabetes Research

FOA: <https://grants.nih.gov/grants/guide/rfa-files/RFA-DK-14-024.html>

NIH News Release: <https://www.nih.gov/news-events/news-releases/four-pivotal-nih-funded-artificial-pancreas-research-efforts-begin>

SEARCH for Diabetes in Youth Cohort Study

Study provides population-based data on the incidence and prevalence of diabetes and its complications in youth in the United States. SEARCH is jointly led by the CDC and NIDDK.

Supported by NIDDK, CDC, Special Statutory Funding Program for Type 1 Diabetes Research

SEARCH for Diabetes: www.searchfordiabetes.org

Structural Anomalies and Birth Defects

Gabriella Miller Kids First Pediatric Research Program

The Common Fund's Gabriella Miller Kids First Pediatric Research Program (Kids First) is developing a large-scale data resource for the pediatric research community, providing access to vast amounts of genetic and clinical data from childhood cancer and structural birth defects patient cohorts. This resource will allow researchers to examine these conditions together to uncover new connections between them that might not have been uncovered had they been examined independently. This program is anticipated to accelerate scientific discoveries in pediatric research that will improve the lives of the children and families impacted by childhood cancer and structural birth defects. In FYs 2015, 2016, and 2017, the Kids First program supported whole genome sequencing of childhood cancer or structural birth defects patient cohorts; a total of 23 different cohorts, representing over 18,000 samples, were sequenced. The first set of data was made available to the broad research community in FY 2017. Additionally, in FY 2017, Kids First launched the Kids First Data Resource Center, which will serve as a centralized database to aggregate Kids First-generated data together with additional existing data sets, provide easy access to and querying of disparate data sets to all researchers (including those without bioinformatics expertise), and provide tools for analyzing large and complex data sets including genetic and clinical data.

Supported by NIH Common Fund

Kids First Website: <https://commonfund.nih.gov/KidsFirst>

Kids First Funded Research: <https://commonfund.nih.gov/kidsfirst/fundedresearch>

FaceBase: Comprehensive craniofacial data and resources

The FaceBase Consortium generates and compiles data on craniofacial development and the diseases and disorders that lead to birth defects and facial malformations. The Consortium advances craniofacial research by creating, integrating, and disseminating a variety of large datasets via the FaceBase Hub web site, a resource that is free and openly accessible to the scientific community. The third phase of FaceBase will continue to improve the FaceBase data repository and website so that it better serves the craniofacial research community. This effort will include further development of tools for data visualization, integration, and standardization, as well as outreach to the researchers whose projects could benefit from these data.

Supported by NIDCR

FaceBase: <https://www.facebase.org>

Birth Defects Initiative and Working Group

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

Supported by NICHD, NIAAA, NIDCR, NIDDK, NIEHS, NINDS

BDIWG: <https://www.nichd.nih.gov/research/supported/Pages/bdiwg.aspx>

Newborn Sequencing in Genomic Medicine and Public Health (NSIGHT)

The NSIGHT program aims to explore, in a limited but deliberate manner, the implications, challenges and opportunities associated with the possible use of genomic sequence information in the newborn period. Funds are being used to stimulate research in three component projects specifically applicable to newborn screening: acquisition and analysis of genomic datasets that expand considerably the scale of data available for analysis in the newborn period; clinical research that advances understanding of specific disorders identifiable via newborn screening through promising new DNA-based analysis; and research related to the ethical, legal and social implications (ELSI) of the possible implementation of genomic sequencing of newborns. In 2017, the four sites published a marker paper describing the consortium in Pediatrics. The article “Newborn Sequencing in Genomic Medicine and Public Health” examines some of the challenges of newborn sequencing in three distinct clinical settings (diagnostic, preventive, and predictive), describes the four projects, and puts the NSIGHT consortium’s research in the context of current and future strategies for newborn screening and sequencing of newborns in the clinic.

Supported by NHGRI, NICHD

NSIGHT: <https://www.genome.gov/27558493/newborn-sequencing-in-genomic-medicine-and-public-health-nsight/>

Article: <https://www.ncbi.nlm.nih.gov/pubmed/28096516> [Feb 2017]

Intellectual and Developmental Disabilities

Autism Centers of Excellence (ACE)

In September 2017, NIH awarded nine grants to support large research projects aimed at understanding autism spectrum disorder (ASD) and developing interventions. These awards seek to build upon prior knowledge by supporting the most innovative, multidisciplinary science. Among other topics, ACE projects are focused on studying the earliest brain and behavioral markers of ASD, identifying ASD subtypes, understanding the differences between males and females with ASD, evaluating screening practices for ASD, and developing innovative treatments.

Supported by NICHD, NIDCD, NIEHS, NIMH, NINDS

NIH News Release: <https://www.nih.gov/news-events/news-releases/nih-awards-nearly-100-million-autism-centers-excellence-program>

Longitudinal Brain and Behavior Study of Autism from Infancy through School Age

As part of the Autism Centers of Excellence Network, this program is analyzing data on school-age outcomes in infants at familial risk for autism (300 high risk, 100 low risk) who have been examined using detailed brain imaging and behavior assessments from 3 to 36 months of age in hopes of identifying brain and behavior predictors of school-age cognitive, behavioral, and learning problems in high risk

children; and characterizing the dynamics of brain development in children with autism from infancy through school age in order to develop timely and effective interventions.

Supported by NIEHS, NICHD

R01HD055741: https://projectreporter.nih.gov/project_info_details.cfm?aid=9388680 [Sep 2017]

Autism Biomarkers Consortium for Clinical Trials (ABC-CT)

Launched in 2015, this large, multisite project will receive a total of \$28 million over the four years to evaluate EEG and eye-tracking measures as potential biomarkers of social functioning and/or treatment response in children with autism spectrum disorder.

Supported by NIMH, NICHD, NINDS, Simons Foundation Autism Research Initiative

National Database for Autism Research (NDAR)

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

Supported by NIMH, NICHD, NINDS, NIEHS

Article: <https://www.ncbi.nlm.nih.gov/pubmed/26446859> [Feb 2016]

NDAR: <https://ndar.nih.gov/>

Down Syndrome Consortium

This consortium is a public-private collaboration that launched a Down syndrome registry, DS-Connect®, which safely and confidentially facilitates contacts and information among people with Down syndrome and their family members, researchers, parents, and support groups.

Supported by NICHD, NCI, NHLBI, NIMH, NINDS, NIA, NIMHD

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

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

Fragile X Syndrome Research Centers (FXSRC) Program

The FXSRCs program supports research to improve the diagnosis and treatment of Fragile X syndrome (FXS) and its related conditions. The FXSRCs are geared toward stimulating multidisciplinary, multi-institutional research with the common goal of facilitating the translation of basic research findings from bench to bedside and bedside to community.

Supported by NICHD, NINDS, NIMH

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

Neurological Disorders and Mental Health

A Network Approach to Study Brain Plasticity in Children with Cognitive Training

There is a fundamental gap in understanding of the functional and structural reorganization of the brain that takes place because of therapeutic interventions. Continued existence of this gap represents an important problem in mental health research because, until it is filled, design of more effective and efficient interventions will remain largely unguided. The long-term goal of this research is to use non-invasive detection and monitoring of brain reorganization to guide the development and implementation of therapies. The objective in this work is to develop a reliable and sensitive MR imaging indicator of

brain network plasticity and apply it to study the remodeling of structural brain networks in children with cognitive training. The rationale for the proposed network approach is that brain changes resulting from therapies are not confined to a specific brain region but usually involve communication pathways and this is directly addressed by diffusion MRI connectomics that treats the brain as a network of structural connections between brain regions. The research may provide a method for monitoring the efficacy of therapeutic interventions, guide the development of new interventions, and advance our understanding of how the brain reorganizes as a function of intensive practice of specific cognitive functions. Ultimately, such knowledge has the potential to inform the development of treatment for clinical populations, such as children and adolescents with attention deficit hyperactivity disorder (ADHD), depression and anxiety disorders.

Supported by NCCIH

R21AT009173: https://projectreporter.nih.gov/project_info_description.cfm?aid=9189674 [Dec 2015]

Pediatric Chronic Fatigue Syndrome in a Community-Based Sample

In FY17, ORWH supported research to determine the prevalence of pediatric chronic fatigue syndrome (CFS) in a community-based sample, as well as the relative frequency of CFS among various groups (e.g., different age groups, genders, racial and/or ethnic groups). This study will also identify the prevalence of orthostatic abnormalities among youth with CFS and controls and will examine its relationship with neurocognitive functioning.

Supported by ORWH, NICHD

R01HD072208: https://projectreporter.nih.gov/project_info_description.cfm?aid=9315183

Examining Adolescent Outcomes of Severe Temper Outbursts in Childhood

This Academic Research Enhancement Award (AREA; R15) grant will build research infrastructure and support training of new researchers. Severe temper outbursts in young children are a significant source of concern as they are functionally impairing and frequently the primary reason for psychiatric treatment referral. Many such children, particularly boys, are treated with medications adverse effects and unknown consequences of long-term use. Researchers aim to examine psychopathology, and frustration reactivity and regulation in a unique sample of adolescents who exhibited severe temper outbursts in childhood. They also plan to test the putative contribution of brain structures and functional connectivity assessed in early childhood to these adolescent outcomes.

Supported by NIMH

R15MH115356: https://projectreporter.nih.gov/project_info_description.cfm?aid=9438037

Paul D. Wellstone Muscular Dystrophy Cooperative Research Centers (MDCRCs)

The MDCRCs are designed to foster the translation of new scientific findings and technological developments into novel treatments for muscular dystrophies (MDs). The Centers promote basic, translational, and clinical research and provide important resources that can be used by the national muscle biology and neuromuscular research communities. The Centers also engage patients and patient advocates in educational programs. Centers include one or more scientific research resource cores that support the specific projects and serve as a resource for the international research community.

Supported by NICHD, NINDS, NIAMS, NHLBI

MDCRCs: <https://www.nichd.nih.gov/research/supported/Pages/mdcrc.aspx>

Substance Use

Incorporating Gene-Environment Interplay into Understanding the Effects of Preventive Interventions

NIDA is supporting research to understand how genetic predispositions increase or reduce risk within the context of family-based preventive programs, to inform the development of more effective interventions.

K01DA042828: https://projectreporter.nih.gov/project_info_details.cfm?aid=9384460

R01DA030389: https://projectreporter.nih.gov/project_info_details.cfm?aid=8660676

Underlying Cognitive and Brain Mechanisms of Risk for Adolescent Drug Abuse

NIDA supports a variety of research on individual-level risk factors for adolescent drug abuse, to lead to improved preventive interventions. Examples include examining executive control, a set of cognitive abilities for directing attention and behavior, as important and modifiable contributors to adolescent problem behaviors; and assessing the neural substrates of risk-taking and risk-avoidant behavior before and after a family-based preventive intervention.

R01DA041738: https://projectreporter.nih.gov/project_info_details.cfm?aid=9419848

R01DA040966: https://projectreporter.nih.gov/project_info_details.cfm?aid=9251573

Launch of Online, Free, Comprehensive Adolescent Substance Use Screening Tools

NIDAMED has launched two validated screening tools, for free online administration with adolescent patients (ages 12-17) in primary care settings: (a) Brief Screener for Alcohol, Tobacco, and other Drugs (BSTAD) and (b) Screening to Brief Intervention (S2BI). Each screening tool may be either self-administered directly by the patient or administered by a health professional. The tool asks one question per substance (e.g., tobacco, alcohol, or marijuana). Once completed, the guide provides information to the provider on the patient's risk level of substance use and intervention options based on the responses. Supported by CTN Dissemination Initiative

NIDA Tools: <https://www.drugabuse.gov/adolescent-substance-use-screening-tools>

Integrative Research on Polysubstance Abuse and Addiction

The intent of this FOA is two-fold: (1) characterize how the neurobiological alterations, associated behaviors, and public health consequences arising from polysubstance use differ from, or are similar to, those observed in single drug use; (2) promote integrative polysubstance research along a translational pipeline, consisting of basic science research in animals, human-based laboratory investigations, and epidemiological studies.

Supported by Collaborative Research on Addiction (CRAN) at the NIH, composed of NIAAA, NIDA, NCI

PAR-16-291: <https://grants.nih.gov/grants/guide/pa-files/par-16-291.html>

National Consortium on Alcohol and Neurodevelopment in Adolescence (NCANDA)

NCANDA is an accelerated longitudinal study of more than 800 youth ages 12-21 that is aimed at assessing the short- and long-term effects of alcohol exposure on the developing adolescent brain, and identifying brain characteristics that may increase risk for alcohol use disorder.

Supported by NIAAA

NCANDA: <http://www.ncanda.org/>

Childhood Disease

Adolescent Medicine Trials Network for HIV/AIDS Interventions (ATN)

The ATN is the only national, multicenter research network devoted to the health and well-being of HIV-infected and at-risk adolescents and young adults. The ATN has extensive experience in recruiting and retaining understudied youth populations in the United States. Over the past 10 years (2003-2013), they have had over 26,000 enrollments among 88 ATN studies, with enrollment and retention rates among completed studies over 90 percent. The primary mission of the ATN is to conduct both independent and collaborative research that explores promising behavioral, microbicide, prophylactic, therapeutic, and vaccine modalities in HIV-infected and at-risk adolescents, ages 12 years through 24 years. ATN activities encompass the full spectrum of research needs for youth, from primary prevention – including HIV preventive vaccine, microbicide, and pre-exposure prophylaxis trials – for HIV at-risk youth in the

community to secondary and tertiary prevention with clinical management of HIV infection among youth along the entire HIV care continuum. Secondary and tertiary prevention research investigates novel treatment strategies and regimens, drug adherence, risk reduction interventions, and linkage and engagement to care strategies that can lead to optimal antiretroviral therapy initiation and virologic suppression outcomes.

Supported by NICHD, NIDA, NIMH, NIMHD, NIAID, NIH OD

ATN: <https://www.nichd.nih.gov/research/supported/Pages/atn.aspx>

Pediatric HIV/AIDS Cohort Study (PHACS)

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

Supported by NICHD, NIAAA, NIAID, NIDCD, NIDCR, NIDA, NIMH, NINDS

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

Hepatitis B Research Network

The Network, including its seven pediatric study sites in the United States and Canada, is promoting translational research on hepatitis B focusing upon elucidating the pathogenesis and natural history and developing means of treatment and control. The study continued to receive support in 2017 through ongoing projects at several clinical centers.

Supported by NIDDK

HepB Net: <https://www.hepbnet.org/>

Nonalcoholic Steatohepatitis Clinical Research Network (NASH CRN)

This Network focuses on the etiology, contributing factors, natural history, complications, and therapy of this form of nonalcoholic fatty liver disease through studies in children and adults. In a previous study by Network researchers, a specific form of vitamin E was found to improve NASH in some children. A more recent study testing the drug cysteamine bitartrate found that, while it did not reduce nonalcoholic fatty liver disease in children, it did improve liver enzymes and inflammation within the liver.

Supported by NIDDK

NASH CRN: <https://jhuccs1.us/nash/>

Article: <https://www.ncbi.nlm.nih.gov/pubmed/21521847> [Apr 2011]

Article: <https://www.ncbi.nlm.nih.gov/pubmed/27569726> [Dec 2016]

Childhood Liver Disease Research Network (ChiLDReN)

The mission of the Network 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.

Supported by NIDDK

ChiLDReN: <https://childrennetwork.org/>

Cure Glomerulonephropathy (CureGN)

This 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.

Supported by NIDDK

CureGN: <https://curegn.org/>

FOA: <https://grants.nih.gov/grants/guide/rfa-files/RFA-DK-12-014.html>

Projects:

https://projectreporter.nih.gov/Reporter_Viewsh.cfm?sl=12EECB084B8BC4D17598B8961CAA4A01A2FFCEB861BF

Chronic Kidney Disease in Children (CKiD)

This prospective cohort study of kidney disease in children and adolescents that seeks to identify risk factors for progression of disease, as well as the impact of chronic kidney disease on neurocognitive development, cardiovascular disease, and growth. The study has identified several risk factors for pediatric kidney disease as well as early manifestations of disease. An ancillary study to CKiD has been funded to investigate genetic factors associated with progression of kidney disease in the study population. CKiD recently has been renewed through 2018, and expanded to allow for the recruitment of additional patients.

Supported by NIDDK, NICHD, NHLBI

Clinical trial: <https://clinicaltrials.gov/ct2/show/NCT00327860>

FOA: <https://grants.nih.gov/grants/guide/rfa-files/RFA-DK-12-507.html>

<https://grants.nih.gov/grants/guide/rfa-files/RFA-DK-17-034.html>

<https://grants.nih.gov/grants/guide/rfa-files/RFA-DK-17-502.html>

<https://grants.nih.gov/grants/guide/rfa-files/RFA-DK-17-503.html>

Projects:

https://projectreporter.nih.gov/Reporter_Viewsh.cfm?sl=12EECB084B8AC0D47598B8961CAA4A01A2FFCEB861BF

Urinary Stone Disease Research Network (USRDN)

The USDRN was established to a) design and conduct a randomized clinical trial to investigate the impact of increased fluid intake and increased urine output on the rate of recurrence of urinary stones in adults and children, b) conduct clinical research to understand and mitigate ureteral stent-related pain and symptoms, and c) provide data and collect biological samples from the studies to create a resource for future researchers. The Prevention of Urinary Stones With Hydration clinical study is currently recruiting participants (see [here](#) for more information).

Supported by NIDDK

USRDN: <http://www.usdrn.org/>

FOA: <https://grants.nih.gov/grants/guide/rfa-files/RFA-DK-15-005.html>

<https://grants.nih.gov/grants/guide/rfa-files/RFA-DK-15-004.html>

U01DK110988: https://projectreporter.nih.gov/project_info_description.cfm?aid=9339680 and

U01DK110954: https://projectreporter.nih.gov/project_info_details.cfm?aid=9334855

Pediatric Diagnostic Biomarkers for Active Pulmonary TB Disease

This program, begun in November 2015, supports projects that identify and/or validate biomarkers or biomarker combinations leading to improved diagnosis of active pulmonary tuberculosis (TB) in children, including HIV-infected children.

Supported by NIAID

FOA: <https://grants.nih.gov/grants/guide/rfa-files/RFA-AI-15-057.html>

Zika in Infants and Pregnancy (ZIP) Cohort Study

In June 2016, the NIH and Fundação Oswaldo Cruz (Fiocruz), a national scientific research organization linked to the Brazilian Ministry of Health, began a multi-country study to evaluate the magnitude of health risks that Zika virus infection poses to pregnant women and their developing fetuses and infants. The ZIP study has enrolled over 6,000 pregnant women ages 15 years and older at ten sites. The participants will be in their first or early second trimester of pregnancy and will be followed throughout their pregnancies to determine if they become infected with Zika virus and if so, what outcomes result for both mother and child. The participants' infants will be carefully followed for at least one year after birth. Supported by NICHD, NIAID, NIEHS, Fiocruz
ClinicalTrials.gov: <https://clinicaltrials.gov/ct2/show/NCT02856984>

Allergies and Immunity

Asthma and Allergic Diseases Cooperative Research Centers

This initiative supports centers that integrate clinical and basic research to conduct studies on the mechanisms underlying the onset and progression of diseases of interest, including asthma, rhinitis (allergic and non-allergic), chronic rhinosinusitis, atopic dermatitis, food allergy, and drug allergy. It is well established that environmental exposures in early childhood contribute significantly to the expression of many of these diseases later in life. These exposures involve allergens, and possibly bacteria, viruses and environmental pollutants. It is now known that some of these exposures are protective against allergic disease, but much remains to be learned as to the mechanisms of protection.
Supported by NIAID

FOA: <https://grants.nih.gov/grants/guide/rfa-files/RFA-AI-16-065.html>

Sublingual Immunotherapy for Peanut Allergy

Peanut allergy is one of the most common food allergies; most children develop this allergy early in life, do not outgrow it and are at risk for severe and life-ending anaphylactic reactions. There is a critical need for a proactive treatment for peanut allergy and researchers are developing specific types of immunotherapy that will cause these patients to be no longer allergic to peanuts. The significance of this proposal is based on landmark studies that have examined the effects of peanut sublingual immunotherapy (SLIT) showing a substantial increase in the amount of peanut that a peanut allergic patient can ingest while on therapy and in some cases causing long-term clinical tolerance when the therapy is discontinued. SLIT involves the administration of small amounts (micrograms to milligrams) of allergen extract under the tongue and offers a novel means of treatment for food allergy and seems well suited for several reasons, including the superior safety of this approach. These studies will help us identify the mechanism and durability of the desensitized state and then the subsequent development of tolerance to foods after SLIT. A treatment for peanut allergy is critically needed the completion of these studies may provide a strong scientific basis for the development of SLIT and other types of therapy that hope to produce long-term clinical tolerance to peanuts and other foods.

Supported by NCCIH

R01AT004435: https://projectreporter.nih.gov/project_info_description.cfm?aid=9262154

Immune Tolerance Network (ITN)

The ITN develops treatment and prevention strategies by inducing tolerance for food allergy, autoimmune diseases and organ transplantation, in adult and pediatric populations

Supported by NIAID

ITN: <https://www.immunetolerance.org/>

Human Immunology Project Consortium (HIPC)

The HIPC uses systems biology approaches to identify possible biomarkers of immune protection against natural infections, as well as vaccine efficacy in adult and pediatric populations. Originally launched in November 2015, funding recently was provided to two HIPC awards to conduct detailed immune profiling of samples from women enrolled in the Zika in Infants and Pregnancy (ZIP) program.

Supported by NIAID

FOA: <https://grants.nih.gov/grants/guide/rfa-files/RFA-AI-15-041.html>

NIAID Primary Immune Deficiency (PID) Clinic

The PID clinic is the focal point for studies of the genetics, pathophysiology, and treatment of PID diseases which are rare disorders of the immune system, often very severe in nature, that frequently manifest during infancy or childhood. NIAID, NCI, and the NIH Clinical Center conduct joint clinical trials to continuously improve bone marrow transplant and gene therapy for the treatment of PID diseases.

PID: <https://www.niaid.nih.gov/clinical-trials/primary-immune-deficiency-clinic>

Clinical Trials in Organ Transplantation (CTOT) in Children

First launched in December 2011, the CTOT initiative aims to reduce immune-mediated morbidity and mortality and long-term graft dysfunction and/or loss unique to pediatric transplant recipients.

Supported by NIAID

CTOT: <http://www.ctotstudies.org/>

Rare Pediatric Diseases

Rare Diseases Clinical Research Network (RDCRN)

The RDCRN conducts collaborative clinical research in rare diseases, including longitudinal studies of individuals with rare diseases, clinical studies, and/or clinical trials. The RDCRN also aims to provide up-to-date information for patients and to assist in connecting patients with advocacy groups, expert doctors, and clinical research opportunities. Many of the rare diseases studied under this network occur primarily or frequently in children, including primary immune deficiency diseases, urea cycle disorders, mitochondrial diseases, lysosomal diseases, and Rett syndrome.

Supported by NCATS (lead), NICHD, NCI, NHLBI, NIAID, NIAMS, NIDCR, NIDDK, NIMH, NINDS, OD

RDCRN: <https://ncats.nih.gov/rdcrn>

Some examples of consortia include:

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

Supported by NINDS, NICHD, NIMH, NCATS

DSC: <http://www.rarediseasesnetwork.org/cms/dsc>

- ***Rett and MECP2-Related Disorders Consortium (H3)***. This Consortium studies three distinct disorders: Rett syndrome (RTT), MECP2 duplication disorder, and RTT-related disorders that are caused by *CDKL5* and *FOXP1* mutations and have similar phenotypes to RTT.

Supported by NICHD, NINDS

H3: <https://www.rarediseasesnetwork.org/cms/rett>

- ***Sterol & Isoprenoid Research (STAIR) Symposium.*** The STAIR Consortium studies disorders related to cholesterol and other sterol and isoprenoid metabolism, such as Smith-Lemli-Opitz syndrome (SLOS), Niemann-Pick disease type C (NPC), Sjögren-Larsson syndrome (SLS), mevalonate kinase deficiency (MKD), sitosterolemia, and cerebrotendinous xanthomatosis. Supported by NICHD, NCATS
STAIR: <http://www.rarediseasesnetwork.org/cms/STAIR>
- ***Urea Cycle Disorders Consortium.*** This Consortium examines disorders that affect the body's urea cycle, which regulates the metabolic process of converting wastes from the breakdown of food into urea that is excreted in urine. In urea cycle disorders, these wastes build up in the blood and cause neurological and other developmental problems. Supported by NICHD, NCATS
UCDC: <https://www.rarediseasesnetwork.org/cms/UCDC>
- ***The Brittle Bone Disorders (BBD) Consortium.*** The Consortium's goals include enhanced understanding of genetic forms of osteogenesis imperfecta, expanded treatment options and develop quality of care measures, and training of the next generation of physicians and scientists in genetic bone diseases. Supported by NIAMS, NIDCR, NIDCD, NCATS
BBD: <https://www.rarediseasesnetwork.org/cms/BBD>
- ***Primary Immune Deficiency Treatment Consortium (PIDTC).*** The mission of the PIDTC is to foster collaborations across North America among researchers, physicians allied health care workers, and parent advocacy groups with interest and expertise in PID diseases. Currently, four natural history protocols for treatment of SCID, chronic granulomatous disease and Wiskott-Aldrich syndrome are open and enrolling subjects from over 40 participating centers. Supported by NIAID, NCATS
PIDTC: <https://www.rarediseasesnetwork.org/cms/pidtc/>
<https://ncats.nih.gov/pubs/features/rdcrn-pidtc>

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. Approximately 40 percent of patients seen in the Undiagnosed Disease Network are children, many of whom present with complex pediatric genetic disorders. In 2016, work from a UDN clinical site that described a previously unknown developmental disorder resulting in developmental delay, macrocephaly, and dysmorphic features (abnormally formed body structures).

Supported by NIH Common Fund

UDN: <https://commonfund.nih.gov/diseases>

Article: <https://www.ncbi.nlm.nih.gov/pubmed/27693232> [Sep 2016]

Pediatric Cancer

Gabriella Miller Kids First Pediatric Research Program

The Common Fund's Gabriella Miller Kids First Pediatric Research Program (Kids First) is developing a large-scale data resource for the pediatric research community, providing access to vast amounts of genetic and clinical data from childhood cancer and structural birth defects patient cohorts. This resource will allow researchers to examine these conditions together to uncover new connections between them that might not have been uncovered had they been examined independently. This program is anticipated to accelerate scientific discoveries in pediatric research that will improve the lives of the children and families impacted by childhood cancer and structural birth defects. In FYs 2015, 2016, and 2017, the Kids First program supported whole genome sequencing of childhood cancer or structural birth defects patient

cohorts; a total of 23 different cohorts, representing over 18,000 samples, were sequenced. The first set of data was made available to the broad research community in FY 2017. Additionally, in FY 2017, Kids First launched the Kids First Data Resource Center, which will serve as a centralized database to aggregate Kids First-generated data together with additional existing data sets, provide easy access to and querying of disparate data sets to all researchers (including those without bioinformatics expertise), and provide tools for analyzing large and complex data sets including genetic and clinical data.

Supported by NIH Common Fund

Kids First Website: <https://commonfund.nih.gov/KidsFirst>

Kids First Funded Research: <https://commonfund.nih.gov/kidsfirst/fundedresearch>

Specialized Programs of Research Excellence (SPOREs) in Pediatric Oncology

SPOREs are a cornerstone of NCI's efforts to promote collaborative, interdisciplinary translational cancer research. SPORE grants involve both basic and clinical/applied scientists working together and support projects that will result in new and diverse approaches to the prevention, early detection, diagnosis and treatment of human cancers. Each SPORE focuses on a specific organ site and currently nineteen organ sites, systems, or pathway-specific themes are represented in the SPORE portfolio, including: bladder, brain, breast, cervical, gastrointestinal, head and neck, kidney, leukemia, lung, lymphoma, myeloma, neuroendocrine, ovarian, pancreatic, prostate, sarcoma, skin, thyroid, and hyperactive RAS tumors. SPOREs focused on pediatric cancers include: pediatric astrocytoma, pediatric glioma, and pediatric melanoma.

Supported by NCI

SPOREs: <https://trp.cancer.gov/spores/bylocation.htm>

Beau Biden Cancer Moonshot

The Cancer Moonshot to accelerate cancer research aims to make more therapies available to more patients, while also improving our ability to prevent cancer and detect it at an early stage. In 2016, the report of the Cancer Moonshot Blue Ribbon Panel identified two high priority pediatric research opportunities that are uniquely poised for acceleration. The first is fusion oncoproteins in pediatric cancers, as these distinctive proteins are unique to childhood cancers and drive cancer growth and survival. The immediate need is to improve understanding of the abnormal fusion proteins that result from chromosomal translocations and to further elucidate how these proteins drive many pediatric cancers. Areas for emphasis will include the creation of new preclinical models of pediatric cancers driven by these fusion oncoproteins, the identification of their key dependencies, and the application of this knowledge to develop novel therapeutic approaches that target their mechanisms of action. One FOA, RFA-CA-17-049, was published for FY2018 to support these goals. In addition, administrative supplements to promote research collaborations in this area were administered in FY17 (PA-17-138). The second-high priority area is pediatric immunotherapy translational science. This is a critical area for future research as it is likely that many of the immunotherapy treatments being developed for adult cancers will not be applicable to childhood cancers. Hence, a pediatric-specific approach will be essential if children are to benefit from advances in immunotherapy. Two FOAs, RFA-CA-17-051 and RFA-CA-17-050 were published in FY2018 to support these goals.

Supported by NCI

FOA: <https://grants.nih.gov/grants/guide/rfa-files/RFA-CA-17-051.html>

<https://grants.nih.gov/grants/guide/rfa-files/RFA-CA-17-050.html>

<https://grants.nih.gov/grants/guide/rfa-files/RFA-CA-17-049.html>

<https://grants.nih.gov/grants/guide/pa-files/PA-17-138.html>

Therapeutically Applicable Research to Generate Effective Treatments (TARGET) Initiative

The TARGET Initiative applies a comprehensive genomic approach to determine molecular changes that drive childhood cancers and further stratify patients to improve therapeutic outcomes. TARGET project teams study primarily high-risk, often relapsed/refractory leukemias and solid tumors of the kidney,

osteosarcoma, and neuroblastoma. Results from this large-scale characterization and sequencing initiative are made broadly available to the research community through the NCI Genomic Data Commons (gdc.cancer.gov) to promote discovery. The current data available for analysis is from more than 12,000 tumor and normal samples representing nearly 5,000 unique pediatric cancer cases. During this past year, novel drivers were found for T-cell ALL cases and Wilms tumor and a miRNA-signature for poor outcome was found for AML patients.

Supported by NCI

TARGET: <https://ocg.cancer.gov/programs/target>

Article: <https://www.ncbi.nlm.nih.gov/pubmed/28825729> [Oct 2017]

<https://www.ncbi.nlm.nih.gov/pubmed/28671688> [Aug 2017]

<https://www.ncbi.nlm.nih.gov/pubmed/27702824> [Nov 2016]

<http://www.nature.com/articles/nrneph.2017.131> [Feb 2017]

<http://www.natureasia.com/en/nmiddleeast/article/10.1038/nmiddleeast.2017.135> [Sep 2017]

Pediatric Provocative Questions

NCI published a FOA to invite applications for research

projects designed to use sound and innovative strategies to solve specific problems and paradoxes in childhood cancer research identified by the National Cancer Institute (NCI) as the NCI's Pediatric Provocative Questions (Pediatric PQs). The program is meant to challenge cancer researchers to think about and elucidate specific problems in key areas of pediatric cancer research that are deemed important but have not received sufficient attention. The FOA includes 9 Pediatric PQs that represent diverse fields relevant to childhood cancer research ranging from basic research on mechanisms of cancer development to research addressing important issues for survivors of childhood cancers

Supported by NCI

FOA: <https://grants.nih.gov/grants/guide/pa-files/PAR-16-217.html>

<https://grants.nih.gov/grants/guide/pa-files/PAR-16-218.html>

Gene Fusions in Pediatric Sarcomas

The overall goal of this FOA is to encourage the submission of research grant applications to investigate the molecular mechanisms by which oncogenic fusion genes and their gene products contribute to pediatric sarcoma initiation, progression, and metastasis. Better understanding of the molecular pathways activated by chromosomal translocations in pediatric sarcomas, and their relationship to oncogenesis and tumor progression, can elucidate mechanisms of cancer pathogenesis and potentially lead to novel therapeutics.

Supported by NCI

FOA: <https://grants.nih.gov/grants/guide/pa-files/PA-16-251.html>

<https://grants.nih.gov/grants/guide/pa-files/PA-16-252.html>

International Childhood Cancer Cohort Consortium (I4C)

- ***Parental occupational exposure to pesticides, animals, and organic dust***
Using pooled data from birth cohorts in five countries participating in the I4C (United Kingdom, Denmark, Norway, Israel and Australia), researchers are assessing risk for acute lymphoblastic leukemia (ALL), acute myeloid leukemia (AML), and childhood brain tumors (CBT) in relation to maternal and paternal exposures to pesticides, organic dust, and animals on the job during pregnancy.
- ***Residential proximity to agricultural pesticides and childhood cancer in the Danish National Birth Cohort***
Researchers are conducting analyses of agricultural pesticides applied near homes of childhood cancer cases and a 10 percent sample of non-cases in the Danish National Birth Cohort (DNBC), one of the cohorts participating in the International Childhood Cancer Cohort Consortium (I4C).

Researchers are using national pesticide use data to estimate pesticide use near homes during the pregnancy and will be evaluating risk of childhood leukemia and childhood brain tumors.

Supported by NCI

I4C: <https://dceg.cancer.gov/research/cancer-types/leukemia-lymphoproliferative/international-childhood-cancer-cohort-consortium>

Childhood Cancer Survivor Study (CCSS)/NCI Collaborative Studies

In 2011, researchers at the NCI initiated a collaboration with researchers from the CCSS to conduct a genome-wide association study (GWAS) aimed at identifying genetic variants associated with 1) development of second cancers (either independent of treatment exposures or jointly with specific treatments), 2) development of childhood cancer, and 3) development of non-malignant late adverse effects of treatment (e.g., cardiomyopathy, obesity, ototoxicity). The researchers are currently conducting whole exome sequencing of the cohort to identify other types of genetic variants (e.g., rare variants, multi-allelic substitutions, insertions, and deletions) that may be related to the development of childhood cancer and late effects following childhood cancer diagnosis. In addition, the researchers are collaborating on a case-control study of breast cancer occurring after childhood cancer.

Supported by NCI

CCSS: <https://dceg.cancer.gov/research/who-we-study/cohorts/childhood-cancer-survivors>

NCI Ongoing Research Initiatives in Childhood 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: <https://www.pbtc.org/>
- ***The Pediatric Preclinical Testing Consortium (PPTC)***, which identifies new, more effective agents for treating childhood cancers.
NCIPPTC: <http://www.ncipptc.org/>
- ***The Pediatric Oncology Branch (POB)*** conducts high-risk high-impact basic, translational and clinical studies.
POB: <https://ccr.cancer.gov/Pediatric-Oncology-Branch>
- ***The TARGET Initiative***, a public-private partnership harnessing genomics technology to identify molecular changes that drive childhood cancers.
TARGET: <https://ocg.cancer.gov/programs/target>
- A comprehensive program of ***Clinical Studies of Familial Cancer Syndromes***, several of which include children.
Hereditary Cancer Syndromes: <https://dceg.cancer.gov/research/what-we-study/hereditary-cancer-syndromes>
- ***The Children's Oncology Group (COG)***, part of the NCI National Clinical Trials Network, that develops and coordinates pediatric cancer clinical trials that are available at over 200 members institutions, including cancer centers throughout the United States and Canada. NCI is supporting many clinical trials of high-priority novel agents through the NCI clinical trials programs, including trials of targeted therapies and immunotherapies. The types of cancers addressed include relapsed/refractory solid tumors and lymphomas, newly diagnosed high-risk Hodgkin lymphoma, certain relapsed leukemias, osteosarcoma, and Ewing sarcoma, and certain pediatric brain tumors.

COG: <https://childrensoncologygroup.org/>

- **The COG Phase 1 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.

COG Phase 1: <https://www.childrensoncologygroup.org/index.php/phase-1-home>

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

NExT: <https://next.cancer.gov/>

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

LFS: <https://lfs.cancer.gov/>

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

IBMFS: <https://marrowfailure.cancer.gov/index.html>

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

PPB: <https://ppb.cancer.gov/>

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

Retinoblastoma: <https://dceg.cancer.gov/research/cancer-types/retinoblastoma>

Childhood Injuries and Maltreatment

National Center for Medical Rehabilitation Research (NCMRR)

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

Supported by NICHD

NCMRR: <https://www.nichd.nih.gov/about/org/ncmrr/Pages/overview.aspx>

The Medical Rehabilitation Research Infrastructure Network (MRRIN)

This network, funded through the National Center for Medical Rehabilitation Research with additional support from NINDS and NIBIB, builds research infrastructure in medical rehabilitation by providing researchers with access to expertise, courses and workshops, technologies, and collaborative opportunities from allied disciplines, such as neuroscience, engineering, applied behavior, and the social sciences.

Supported by NICHD, NINDS, NIBIB

MRRIN: <https://www.nichd.nih.gov/research/supported/Pages/mrrin.aspx>

CAPSTONE Centers for Multidisciplinary Research in Child Abuse and Neglect

These centers address child maltreatment as a significant public health concern. This program will allow researchers to: assess the efficacy and effectiveness trials of child abuse and neglect interventions; examine the long-term impact of specific and understudied types of maltreatment; study the neurobiology of abuse and neglect and implications for health outcomes; and develop screening tools and assessment measures for early identification and treatment of specific types of abuse and neglect.

Supported by NICHD

FOA: <https://grants.nih.gov/grants/guide/rfa-files/RFA-HD-16-002.html>

Pain and Pain Management

Peppermint Oil Pharmacokinetics/Dynamics and Novel Biological Signatures in Children with Functional Abdominal Pain

Irritable Bowel Syndrome and functional abdominal pain (FAP) affect up to 15 percent of children based on community-based studies from around the world and is associated with significant emotional and economic burdens. There is a critical need to understand what factors contribute to pain in these disorders so that effective management and treatment strategies can be designed. FAP is characterized by chronic, intermittent abdominal pain. Symptoms range from mild to severe and debilitating and result in reduced quality of life. Up to 66 percent of children go on to have similar symptoms as adults. There are few effective treatments because of poor understanding of their mechanism of action (biological signatures) and of the pathophysiology of what are phenotypically and arbitrarily defined disorders. This research is investigating the pharmaco-dynamic/kinetics (PKD) of peppermint oil (PMO), a botanical with some evidence of efficacy in adults with irritable bowel syndrome - a condition like FAP. The results of this work may uncover a treatment likely to help and will provide insight into the factors responsible for abdominal pain symptoms to allow better patient-specific treatment.

Supported by NCCIH

URL: https://projectreporter.nih.gov/project_info_description.cfm?aid=934661

Pediatric Critical Care and Emergency Care

Collaborative Pediatric Critical Care Research Network (CPCCRN)

Focusing on critically ill infants and children, this national resource aims to reduce morbidity and mortality from pediatric critical illness and injury by enhancing knowledge of the scientific bases of pediatric critical care practice. The CPCCRN conducts a wide range of research activities, reaching across traditional disciplinary lines and transcending customary thinking and organizational structures to achieve innovative research in the care of critically ill and injured children. Research topic areas include: bereavement and grief, functional outcomes, intensive care clinical processes and protocols, and infection and sepsis.

Supported by NICHD

CPCCRN: <https://www.nichd.nih.gov/research/supported/Pages/cpccrn.aspx>

Clinical Care, Outreach, and Services

Racial and Ethnic Disparities in Emergency Department Treatment of Pediatric Asthma

Asthma is the most common chronic disease in children, and one of the leading causes of pediatric visits to the Emergency Department (ED). Children from racial and ethnic minority populations have higher rates of physician, hospital, urgent care and ED visits due to asthma. A study of asthma among pediatric patients visiting the ED at six hospitals, looked at variation by race and ethnicity for pediatric patients receiving asthma treatment at the ED. The study found that children from all racial and ethnic minority groups were more likely to receive steroids than White children, with African Americans been the most likely to be treated with steroids, and the least likely to have radiology tests. Asians were the least likely to return to the ED within 30 days. The study points to the importance of additional research to understand the underlying causes of the racial and ethnic variation in treatment which can provide insights into strategies and programs that can help to ensure that pediatric asthma treatment is equally administered to all children.

Supported by NIMHD

Article: <https://www.ncbi.nlm.nih.gov/pubmed/28926508> [Sep 2017]

NIH Pediatric Rheumatology Clinic

The NIH Pediatric Rheumatology Clinic is a specialty-care medical facility dedicated to evaluating and treating children with pediatric rheumatic diseases who are enrolled in clinical trials. Since the causes of these diseases are unknown, the NIH also seeks to gain a better understanding of why some children develop them. The Clinic consists of two major parts: a clinic and a health information resource center. In the clinic, medical staff diagnose and treat children with arthritis, periodic fever syndromes, lupus, and other rheumatic diseases who are enrolled in clinical trials. The health information resource center provides written and oral information on signs and symptoms of arthritis and rheumatic diseases as well as tips for maintaining wellness and managing disease.

Supported by NIAMS

Teen-Longitudinal Assessment of Bariatric Surgery (Teen-LABS)

Teen-LABS was launched to assess the short- and long-term risks and benefits of bariatric surgery among teens with severe obesity. This is an observational study that enrolled teens who were already planning to have bariatric surgery.

Supported by NIDDK

FOA: <https://grants.nih.gov/grants/guide/rfa-files/RFA-DK-15-508.html>

NIDDK News Release: <https://www.niddk.nih.gov/news/research-updates/Pages/teens-achieve-weight-loss-health-benefits-bariatric-surgery.aspx>

NIH News Release: <https://www.nih.gov/news-events/news-releases/nih-launches-study-assess-bariatric-surgery-adolescents>

Chronic Condition Self-Management in Children and Adolescents

Managing a chronic condition is an unremitting responsibility for children and their families. Children with a chronic condition and their families have a long-term responsibility for self-management. Reissued in January 2017, this FOA encourages research that takes into consideration various factors that influence self-management such as individual differences, biological and psychological factors, family/caregivers and sociocultural context, family-community dynamics, healthcare system factors, technological advances, and the role of the environment.

Supported by NINR, NICHD

FOA: <https://grants.nih.gov/grants/guide/pa-files/PA-17-115.html>

<https://grants.nih.gov/grants/guide/pa-files/PA-17-115.html>

Linking the Provider Recommendation to Adolescent HPV Vaccine Uptake

This Funding Opportunity Announcement (FOA) encourages research on how the health care delivery system enhances or inhibits the effectiveness of a provider's recommendation of the adolescent human papillomavirus (HPV) vaccine. Characteristics of the provider, parent/patient, and clinical setting, can all affect whether a provider makes a recommendation, and whether that recommendation results in uptake of the HPV vaccine. This research requires expertise in cancer prevention, adult and childhood behavior, immunization promotion, and health care delivery.

Supported by NCI

FOA: <https://grants.nih.gov/grants/guide/pa-files/PAR-18-008.html>

<https://grants.nih.gov/grants/guide/pa-files/PAR-18-019.html>

<https://grants.nih.gov/grants/guide/pa-files/PAR-16-337.html>

End-of-Life and Palliative Needs of Adolescents and Young Adults (AYA) with Serious Illnesses

The purpose of this FOA is to foster research on the unique perspectives, needs, wishes, and decision-making processes of adolescents and young adults (AYA; defined by the World Health Organization and the Centers for Disease Control and Prevention as youth between 12 – 24 years of age) with serious, advanced illnesses; and research focused on specific end-of-life/palliative care (EOLPC) models that support the physical, psychological, spiritual, and social needs of AYA with serious illness, their families and caregivers.

Supported by NCI

FOA: <https://grants.nih.gov/grants/guide/pa-files/PA-18-137.html>

<https://grants.nih.gov/grants/guide/pa-files/PA-18-155.html>

Development of Pediatric Cancer Drug Delivery Devices

Drug delivery systems are continually advancing and greatly assist the capabilities of cancer therapies and cancer survival. Yet, the pediatric population has not benefited, to the same extent as adult populations, from these advances in cancer therapy delivery device design and technology. In FY 2017, an SBIR request for proposals focused on drug delivery devices for pediatric cancers was issued. This SBIR solicitation aims to aid the development of appropriate cancer therapy delivery devices that reflect pediatric patient specific designs and dosage parameters for pediatrics. Two small businesses were funded under this announcement in FY2017.

Supported by NCI

Small Business Program: <https://sbir.nih.gov/sites/default/files/PHS2017-1.pdf>

Improving Treatment Adherence in HIV-Positive Youth Through Mindfulness Training

Successful treatment of HIV infection requires patient adherence to medication regimens. This health-related behavior relies on individuals' on-going self-regulation, an intertwined process involving coping, psychological function, and cognitive function. Self-regulation can be particularly challenging during adolescence and young adulthood, when self-regulatory abilities are in flux and still developing. Most current HIV treatment adherence interventions are designed to change thoughts and behaviors, based on cognitive behavioral therapy and behavioral theory, but have limited effect on improving HIV medication adherence and appointment keeping. This research will study the ability of mindfulness-based stress reduction (MBSR) to improve HIV-infected adolescent and young adults' HIV medication adherence and self-regulation. This intervention is innovative and significant because it focuses on self-regulatory processes, and it may be used alone or as a complement to current interventions addressing specific behaviors. MBSR is an instructional program of meditation techniques to enhance participants' mindfulness, or present-focused, non-judgmental awareness. If MBSR is effective, these youths would be healthier, less likely to spread HIV, and have improved mental health and quality of life.

Supported by NCCIH

R01AT007888: https://projectreporter.nih.gov/project_info_description.cfm?aid=9262150

Hippocampal plasticity of young adults with childhood adversity after MBSR

Childhood adversity is remarkably prevalent and significantly increases the risk of developing psychiatric symptoms during adulthood, especially depression and anxiety. Preclinical studies found that early-life stress induces excessive release of stress hormones which inhibit neuronal growth, particularly in the hippocampus. Recent research found that young adults with childhood maltreatment have smaller hippocampal subfield volumes compared to age- and education-matched controls that did not have childhood maltreatment. Studies have also found that the Mindfulness-Based Stress Reduction (MBSR) program is associated with increased hippocampal gray matter density. The objective of the proposed research is to evaluate the effect of MBSR in reducing the depression and anxiety symptoms in young adults with childhood adversity, as well as for inducing hippocampal structural and functional changes. This study will improve our understanding about the clinical and neural effects of MBSR for young adults with childhood adversity.

Supported by NCCIH

K01AT009085: https://projectreporter.nih.gov/project_info_description.cfm?aid=9262848

National Child & Maternal Health Education Program (NCMHEP)

This program, involving over 30 federal and non-federal organizations, is designed to identify key challenges in child and maternal health, review relevant research and initiate educational activities that advance the knowledge base of the field, and improve the health of women and children.

Supported by NICHD, ORWH, CDC, IHS, HRSA, HHS OMH, HHS OWH, 28 member organizations
NCMHEP: <https://www.nichd.nih.gov/ncmhpep/Pages/index.aspx>

Safe to Sleep

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

Supported by NICHD

Safe to Sleep: <https://www.nichd.nih.gov/sts/Pages/default.aspx>

Technology and Tools

Pediatric Research using Integrated Sensor Monitoring Systems (PRISMS)

As the most common pediatric chronic disease, asthma affects more than six million children in the United States. To address this complex disease, NIBIB launched the PRISMS program in September 2015 to develop non-invasive health monitoring system for pediatric asthma research. The program covers development of sensors, an informatics platform and data coordination. To date, progress is being made in creating a variety of sensors for use by individuals or in households that could measure air pollution levels, physical activity, breathing patterns, inhaler use, or heart rate. In one example, researchers are working to improve methods to measure physiological factors, such as heart rate, using mobile or desktop face video without any devices or sensors attached to the subject. In small pilot studies researchers are discovering ways to use this type of technology in real life situations where people are moving constantly. Current technology requires the subject to remain still for the video to capture an accurate measurement. Another group of researchers is working to further develop a mobile health system to help self-manage and determine risk of an asthma attack in children. The system uses wireless sensors to measure specific physiological and environmental factors that are analyzed in a cloud-based environment to determine risk. The level of asthma risk (high, medium, or low) is then transmitted to a smart watch using a simple graphic that can be understood by children. Additional testing of this system with children is needed.

Supported by NIBIB

PRISMS: <http://prisms-study.org>

Article: <https://www.ncbi.nlm.nih.gov/pubmed/27812695> [Nov 2016]

<https://www.ncbi.nlm.nih.gov/pubmed/27362754> [May 2017]

<https://www.ncbi.nlm.nih.gov/pubmed/28771168> [Aug 2017]

mHealth Intervention via Mentors: Preventing Substance Use, Sexual Risk and Violence among Inner City Youth through Technology-Enhanced Mentoring

Adolescents growing up in low-income urban areas such as Baltimore are at particularly high risk for unhealthy practices such as substance use, sexual risk, and engagement in violence. This project is leveraging smartphone technology to develop and test a prevention intervention in the form of a smartphone application (app), as well as training materials for using the app, to enhance existing mentoring models for highly vulnerable African American male adolescents in urban Baltimore.

Supported by NIDA

K01DA042138: https://projectreporter.nih.gov/project_info_description.cfm?aid=9314128

Computationally Modeling the Impact of Ontogeny on Drug Metabolic Fate

The impact of age on cytochrome P450 metabolism makes drug disposition and toxic risks moving targets for pediatric patients, such that robust strategies to identify and assess ontogenetic (age-dependent) effects on drug metabolic fate (in vitro kinetics and metabolite structures) are clearly needed to better personalize drug development for pediatric dosing. These researchers will build and test computational models and datasets for individual P450 isozymes that accurately predict drug metabolites and the rate (kinetics) at which they form. They will then combine these models for an effective, low cost approach that simulates hepatic P450 metabolism and takes into account age-dependent contributions from individual isozymes to assess the metabolic fate of drugs during child development.

Supported by NLM

R01LM012482: https://projectreporter.nih.gov/project_info_description.cfm?icde=0&aid=9341387

CloudConnect: Consumer Health IT for Enhanced Treatment of Chronic Illness

The proposed research addresses questions that relate to the design and performance of a self-management approach for Type 1 Diabetes that integrates remote monitoring of both physiological parameters and patient generated data, informatic processing of multiple data types to assess near-term risk of adverse events, computation of risk profiles that identify linkages between behavior and self-treatment outcomes, clinical decision support, and health information communication systems, all with a focus on dyads of adolescent patients and their local care givers. The first of two studies associated with this proposal is a needs assessment study that reveals patients' and primary informal caregivers' needs/preferences for the technology core of Cloud Connect. The second study is a randomized control trial that assesses CloudConnect in terms of patient engagement, dyad engagement, and clinical outcomes as well as the relationships among these outcome measures for adolescents with diabetes. The results of this project will inform the design of information technology that improves engagement and clinical outcomes for patients who require continuous monitoring and who engage informal primary caregivers in self-management outside clinical settings.

Supported by NLM

R01LM012090: https://projectreporter.nih.gov/project_info_description.cfm?icde=0&aid=9274097

Global Pediatric Health

Domestic & International Pediatric & Maternal HIV Clinical Studies Network

Currently composed of 15 domestic sites in 11 states and territories and 14 international sites in Argentina, Brazil, Kenya, Tanzania, and Thailand, plus a Data Coordinating Center (DCC), this network conducts trials related to preventing and treating HIV infection and its complications in newborns, infants, children, adolescents, and pregnant women. Recently, network researchers have broadened their focus to include TB, malaria, hepatitis, and investigation of vaccines to prevent HIV-related or other high-priority infectious diseases in children, adolescents, and pregnant women, in addition to treatment of HIV infection. Since 1990, this NICHD-funded network has collaborated closely with the NIAID-funded International Pediatric Maternal Adolescent AIDS Clinical Trials (IMPAACT) Network. This collaboration has made it possible to conduct an expanded clinical trial portfolio advancing pediatric HIV/AIDS clinical research.

Supported by NICHD

NICHD Network: <https://www.nichd.nih.gov/research/supported/Pages/pphsn.aspx>

Global Network for Women's and Children's Health Research

The Global Network supports and conducts clinical trials in resource-limited countries by pairing foreign and United States researchers, with the goal of evaluating low-cost, sustainable interventions to improve maternal and child health and simultaneously building local research capacity and infrastructure. Today, the Global Network focuses on community-based common protocols, conducted at three or more sites, which address major maternal and newborn health challenges, with the goal of evaluating low-cost, sustainable interventions to improve maternal and child health. This unique position allows scientists to identify gaps between science and practice and disseminate the research findings to inform local and national health policy. Each study examines either a novel evidence-based treatment or an innovative use of a proven treatment to improve the health, well-being, and survival of pregnant women and infants.

Supported by NICHD

Global Network: <https://www.nichd.nih.gov/research/supported/Pages/globalnetwork.aspx>

Understanding and Addressing the Multi-Level Influences on Uptake and Adherence to HIV Prevention Strategies among Adolescent Girls and Young Women in Sub-Saharan Africa

The purpose of these FOAs was to support research to enhance our understanding of the multi-level factors that influence HIV prevention strategy use among adolescent girls and young women in sub-

Saharan Africa. Furthermore, these funding opportunities aim to support the development and testing of novel interventions to address these factors and enhance the uptake and adherence to HIV prevention strategies among adolescent girls and young women in sub-Saharan Africa.

Supported by NIMH, NICHD, FIC

FOA: <https://grants.nih.gov/grants/guide/rfa-files/rfa-mh-17-550.html>

<https://grants.nih.gov/grants/guide/rfa-files/rfa-mh-17-555.html>

<https://grants.nih.gov/grants/guide/rfa-files/rfa-mh-17-560.html>

Pediatric Research at the NIH Clinical Center

The NIH Clinical Center is the clinical research facility of the NIH. It provides patient care, services, training, and the environment in which NIH clinician scientists creatively translate emerging knowledge into better understanding, detection, treatment and prevention of human diseases. In FY 2017, over 3,100 children were treated at the NIH Clinical Center.

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.

To accommodate the growing number of pediatric intramural research subjects, The Children's Inn at the NIH can care for 61 families every night. In FY 2017, 1,719 families stayed at the Children's Inn while their children were being treated at the NIH Clinical Center.

Other Cross-Cutting Areas of Pediatric Research

Pediatric Pharmacology and the Best Pharmaceuticals for Children Act

Testing the safety and efficacy of drugs in children presents considerable scientific, clinical, ethical, technical, and logistical challenges. Over the years, several practical challenges have discouraged the testing of drugs in pediatric populations. These challenges include lack of incentives for companies to study drugs in neonates, infants, and children; lack of necessary technology to monitor patients and assay very small amounts of blood; and lack of a suitable infrastructure for conducting pediatric pharmacology drug trials. As a result, the majority of drugs used in children today are not approved for use in children and therefore are used without adequate understanding of appropriate dose, safety, or efficacy.

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

BPCA: <https://bpca.nichd.nih.gov/>

Specialized Centers in Research in Pediatric Developmental Pharmacology (RPDP)

NICHD supports the 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.

RPDP: <https://www.nichd.nih.gov/research/supported/scrpdp>

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: <https://ncats.nih.gov/ctsa>

Research Training, Career Development, and Loan Repayment

Child Health Research Career Development Award (CHRCDA) Program

The CHRCDA program was created to fill the gap in training for junior faculty who intend to devote their careers to academic pediatrics. The program provides funding for sustained mentoring and laboratory-based training and offers the vital foundation to compete for grant funding.

Supported by NICHD

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

FOA: <https://grants.nih.gov/grants/guide/rfa-files/RFA-HD-18-011.html>

Child Neurologist Career Development Program (CNCDP)

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

Supported by NINDS

FOA: <https://grants.nih.gov/grants/guide/rfa-files/RFA-NS-16-003.html>

Pediatric Scientist Development Program (PSDP)

This program provides scientific research experience (particularly in basic science areas) for pediatricians wishing to pursue careers in academic medicine. The PSDP has provided research training for more than 175 scholars across the country. Many PSDP scholars have gone on to strong research careers and have received subsequent NIH funding in pediatric research.

Supported by NICHD

PSDP: <https://www.cincinnatichildrens.org/education/research/psdp>

Training the Science of Child Mental Health Treatment

This unique training program aims to train researchers in translational intervention science for child mental disorders, and prepare them to become independent transdisciplinary researchers. Trainees will identify specific areas of mental illness and choose research strategies that advance such research at a variety of levels – treatment mechanisms, biomarkers of outcomes, efficacy study methodology, and implementation science.

Supported by NIMH

T32MH073517: https://projectreporter.nih.gov/project_info_description.cfm?aid=9280686

Pediatric Clinical Pharmacology Postdoctoral Research Training Program

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.

FOA: <https://grants.nih.gov/grants/guide/rfa-files/RFA-HD-16-015.html>

New Paths for Biomedical Informatics: A Mini-Symposium for High School Scholars

The future of health care in the United States will depend on a workforce of biomedical informatics professionals. This project aims to develop a mini-symposium for high school scholars and thus provide inspiration for future generations to consider STEM-C careers, especially in health care and biomedicine.

Supported by NLM

R13LM012214: https://projectreporter.nih.gov/project_info_description.cfm?icde=0&aid=9335446

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.

LRP: <https://www.lrp.nih.gov/eligibility-programs>

ADDITIONAL PEDIATRIC COLLABORATIONS

Pediatric research at the NIH involves many diverse collaborative efforts between NIH Institutes, Centers, and Offices (ICOs) and with other HHS and Federal Agencies. During FY 2017, NIH organized three conferences and over 45 committees, working groups, or task forces with a broad span of pediatric emphases. For example, some collaborations were concerned with specific conditions, such as the Interagency Coordinating Committee on Fetal Alcohol Spectrum Disorders. Other collaborations worked on broader pediatric topics, like the Best Pharmaceuticals for Children Act Working Group. A selection of NIH-supported collaborative efforts in pediatrics follows.

Several NIH collaborations are devoted to nutrition and obesity research. The Pregnancy and Birth to 24 Months Project, which brings together the USDA and the Office of Disease Prevention and Health Promotion and NIHCD within the HHS, aims to help formulate dietary and nutritional recommendations and to conduct systematic reviews on diet and health for pregnant women and infants under 2 years old. The National Collaborative on Childhood Obesity Research (NCCOR) is an effort of the CDC and several NIH ICOs (NCI, NHLBI, NICHD, NIDDK, OBSSR, and ODP). The NCCOR seeks to identify obesity intervention needs, improve obesity surveillance, improve obesity research, and to facilitate implementation of evidence-based practices and policies, particularly for children in communities with high obesity rates.

NIH also collaborates to better understand genetic disorders. The Trans-NIH Working Group on Tuberos Sclerosis Complex is a partnership of NIH (participating ICOs are NCI, NHGRI, NHLBI, NIAMS, NICHD, NIDDK, NIGMS, and NIMH), DOD, and patient advocacy groups. The goal of the Working Group is to share advances in understanding disease pathology and treatment and to identify opportunities to further advance relevant research. The Down Syndrome Consortium is a collaboration between NIH (participating ICOs are NCI, NHGRI, NHLBI, NIA, NICHD, NIDCD, NIDCR, NIDDK, NIMH, NIMHD, and NINDS) and external organizations working in pediatrics and Down syndrome. The goal is to foster the exchange of information and ideas between these collaborators and the Down syndrome community. The Trans-NIH Fragile X Working Group (including representatives from NIA, NICHD, NIDDK, NIMH, NINDS, DPCPSI, and ODP) devises recommendations and coordinates research to facilitate detection, diagnosis, treatment, and prevention of Fragile X and associated disorders.

NIH collaborates to promote research on other neurodevelopmental disorders. For example, the NIH Autism Coordinating Committee is an effort supported by NICHD, NIDCD, NIEHS, and NINDS. This trans-NIH working group identifies joint initiatives, monitors the progress of autism spectrum disorder research, and exchanges information among NIH ICOs involved in the NIH Autism Centers of Excellence. In addition, the Interagency Autism Coordinating Committee (IACC) is comprised of 6 NIH ICOs (including NICHD, NIDCD, NIEHS, NIMH, NINDS and the NIH Office of the Director), AHRQ, CDC, CMS, FDA, HRSA, IHS, EPA, the Social Security Administration, and the Departments of Defense and Education. The IACC is a Federal advisory committee that coordinates Federal efforts and provides advice to the HHS Secretary on issues related to autism.

NIH engages in collaborations to address parental issues that impact children's health. The Trans-NIH Child Abuse and Neglect Working Group (CANWG) is a collaboration between NIAAA, NICHD, NIDA, NIMH, NINR, and OBSSR that was created by a House Committee on Appropriations directive to report on NIH efforts, accomplishments, and research on child abuse and neglect. The CANWG is a subcommittee of the Federal Interagency Workgroup on Child Abuse and Neglect (FEDIAWG). FEDIAWG brings together numerous Federal entities (NIAAA, NICHD, NIDA, NIMH, OBSSR, and the ACF at HHS, as well as the USDA, DOD, USAID, USICH, and the Departments of Education, Housing and Urban Development, Interior, Justice, and State) and provides a government-wide forum for discussion of ideas about and funding for child maltreatment-related programs and activities. The

Neonatal Abstinence/Opioid Withdrawal Syndrome (NAS/NOWS) Workgroup for the HHS Behavioral Health Coordinating Committee Subcommittee on Opioids and Controlled Substances is participated in by numerous HHS entities, including NICHD and NIDA at the NIH, CDC, CMS, HRSA, IHS, and SAMHSA. The Work Group meets regularly to coordinate information and develop joint efforts to mitigate the harmful impacts of NAS/NOWS.

Environmental issues are the subject of several NIH collaborations. For example, the Children's HHS Interagency Leadership on Disasters (CHILD) Working Group identifies and integrates activities related to the needs of children across governmental disaster planning and determines how to best deliver care to children impacted by disasters. The CHILD Working Group involves the efforts of 5 NIH ICOs (NIAID, NICHD, NIDA, NIGMS, NIMH), ACF, CDC, HRSA, SAMHSA, and the Assistant Secretary for Preparedness and Response. NICHD and NIGMS at the NIH collaborate on the Public Health Emergency Medical Countermeasures Enterprise Integrated Program Team for Pediatrics and Obstetrics along with CDC, FDA, and the Office of the Assistant Secretary for Health (OASH) within the HHS, as well as the DOD, VA, USDA, and the Department of Homeland Security. This Team develops, stockpiles, and monitors the safety and effectiveness of medical countermeasures for children and pregnant mothers in preparation for immediate or future public health threats. The Trans-NIH Working Group on Household Air Pollution is made up of FIC, NCI, NEI, NHLBI, NICHD, NIEHS, OBSSR, and ORWH at the NIH. This Work Group seeks to integrate and accelerate NIH-sponsored and -administered research in exposure response relationships of particulate matter and other pollutants to childhood pneumonia, low birth weight heart disease, lung cancer, stroke, eye disorders, and other conditions.

NIH brings together subject matter experts to better understand developmental processes. For example, NIH sponsored the conference "Video-Based Communal Data Collection & Coding: Advancing the Science of Infant Learning & Development" with participation from NICHD, NIMH, NINDS, OBSSR, and the NSF. This conference was for the Play and Learning Across A Year (PLAY) Project, which will video-record the natural behavior and surrounding environments of infants in their first year in hopes of better understanding typical and atypical social, cognitive, motor, and emotional development.

APPENDIX

- Table 1: All NIH Pediatric Research, FY 2017
- Table 2: NIH Funding Opportunity Announcements That Solicited Applications for Pediatric Research, FY 2017
- Table 3: Acronyms for NIH Institutes, Centers, and Offices and Other Federal Agencies Referred to in This Report

Table 1: All NIH Pediatric Research, FY 2017

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 2017 NIH-funded grants and projects in pediatric research is available at:

https://report.nih.gov/categorical_spending_project_listing.aspx?FY=2017&ARRA=N&DCat=Pediatric

The term “Common Fund” refers to research funded through the Office of Strategic Coordination, OD, NIH, to address key scientific issues that no one ICO is positioned to address alone.

NIH ICO	Fiscal Year 2017
FIC	\$7,310,148
NCATS	\$42,114,248
NCCIH	\$5,064,144
NCI	\$407,138,966
NEI	\$73,139,455
NHGRI	\$59,703,298
NHLBI	\$397,965,047
NIA	\$15,650,161
NIAAA	\$109,932,010
NIAID	\$356,424,260
NIAMS	\$69,765,215
NIBIB	\$17,976,488
NICHD	\$760,741,544
NIDA	\$164,110,485
NIDCD	\$74,906,827
NIDCR	\$107,966,837
NIDDK	\$242,885,263
NIEHS	\$131,912,606
NIGMS	\$120,564,131
NIMH	\$405,536,745
NIMHD	\$49,225,169
NINDS	\$214,869,935
NINR	\$23,677,311
NLM	\$2,458,188
OD	\$165,182,568
Common Fund	\$43,139,939
Type 1 Diabetes	\$106,592,996
Grand Total	\$4,175,953,984

Table 2: NIH Funding Opportunity Announcements That Solicited Applications for Pediatric Research, FY 2017

Announcement Number	Issuing Organization	Activity Code	Title
PA-17-078	ORWH	333	Administrative Supplement for Research on Sex/Gender Influences (Admin Supp)
PA-17-084	NIMH	R01	Eradication of HIV-1 from Central Nervous system Reservoirs (R01)
PA-17-085	NICHD	R21	Zika Virus (ZIKV) Complications (R21)
PA-17-091	NICHD	R01	Fertility Status as a Marker for Overall Health (R01)
PA-17-092	NICHD	R21	Fertility Status as a Marker for Overall Health (R21)
PA-17-098	NIH	333	Administrative Supplements for Research on Sexual and Gender Minority (SGM) Populations (Admin Supp)
PA-17-101	ORWH	333	Research on the Health of Women of Underrepresented, Understudied and Underreported (U3) Populations An ORWH FY17 Administrative Supplement (Admin Supp)
PA-17-103	NIMH	R21	Strengthening the HIV Pre-Exposure Prophylaxis (PrEP) Care Continuum through Behavioral, Social, and Implementation Science (R21)
PA-17-104	NIMH	R01	Strengthening the HIV Pre-Exposure Prophylaxis (PrEP) Care Continuum through Behavioral, Social, and Implementation Science (R01)
PA-17-105	NIMH	R21	Targeted basic behavioral and social science and intervention development for HIV prevention and care (R21)
PA-17-106	NIMH	R01	Targeted basic behavioral and social science and intervention development for HIV prevention and care (R01)
PA-17-111	NIDA	R01	Neuroscience Research on Drug Abuse (R01)
PA-17-112	NIDA	R21	Neuroscience Research on Drug Abuse (R21)
PA-17-114	NIAID	R01	NK Cells to Induce Immunological Memory to Prevent HIV Infection (R01)
PA-17-115	NINR	R01	Chronic Condition Self-Management in Children and Adolescents (R01)
PA-17-116	NINR	R21	Chronic Condition Self-Management in Children and Adolescents (R21)
PA-17-117	NINR	R21	Reducing Health Disparities Among Minority and Underserved Children (R21)
PA-17-118	NINR	R01	Reducing Health Disparities Among Minority and Underserved Children (R01)
PA-17-119	NIDA	R01	Basic Mechanisms of Brain Development Mediating Substance Use and Dependence (R01)
PA-17-120	NIDA	R01	Discovering Novel Targets: The Molecular Genetics of Drug Addiction and Related Co-Morbidities (R01)

Announcement Number	Issuing Organization	Activity Code	Title
PA-17-132	NIAAA	R21	Public Policy Effects on Alcohol-, Marijuana-, and Other Substance-Related Behaviors and Outcomes (R21)
PA-17-134	NIAAA	R03	Public Policy Effects on Alcohol-, Marijuana-, and Other Substance-Related Behaviors and Outcomes (R03)
PA-17-135	NIAAA	R01	Public Policy Effects on Alcohol-, Marijuana-, and Other Substance-Related Behaviors and Outcomes (R01)
PA-17-136	NIMH	R01	Innovations in Mechanisms and Interventions to Address Mental Health in HIV Prevention and Care Continuum (R01)
PA-17-137	NIMH	R21	Innovations in Mechanisms and Interventions to Address Mental Health in HIV Prevention and Care Continuum (R21)
PA-17-138	NCI	333	Administrative Supplements to Promote Research Collaborations on Fusion Oncoproteins as Drivers of Childhood Cancer (Admin Supp)
PA-17-157	NIDA	R21	Functional Genetics, Epigenetics, and Non-coding RNAs in Substance Use Disorders (R21)
PA-17-166	NIMH	R34	Formative and Pilot Intervention Research for Prevention and Treatment of HIV/AIDS (R34)
PA-17-181	NIMH	R21	Innovations in HIV Testing, Adherence, and Retention to Optimize HIV Care Continuum Outcomes (R21)
PA-17-182	NIMH	R01	Innovations in HIV Testing, Adherence, and Retention to Optimize HIV Care Continuum Outcomes (R01)
PA-17-194	NIMH	R01	Targeted Implementation Science to Achieve 90/90/90 Goals for HIV/AIDS Prevention and Treatment (R01)
PA-17-195	NIMH	R21	Targeted Implementation Science to Achieve 90/90/90 Goals for HIV/AIDS Prevention and Treatment (R21)
PA-17-211	NIAAA	R01	Nutrition and Alcohol-Related Health Outcomes (R01)
PA-17-212	NIAAA	R03	Nutrition and Alcohol-Related Health Outcomes (R03)
PA-17-213	NIAAA	R21	Nutrition and Alcohol-Related Health Outcomes (R21)
PA-17-222	NCI	333	Supplements for Validating the Use of Automated Sources of Residential Histories in Cancer Epidemiology Cohorts (Admin Supp)
PA-17-223	NCI	333	Supplement Opportunity to Support Population-Based Research Studies of Rare Cancers (Admin Supp)
PA-17-224	NCI	333	Research Supplements to Promote Sharing Data in Cancer Epidemiology Studies (Admin Supp)
PA-17-225	NIA	R01	Advancing the Science of Geriatric Palliative Care (R01)
PA-17-226	NIA	R21	Advancing the Science of Geriatric Palliative Care (R21)
PA-17-239	NCI	R01	Secondary Analysis and Integration of Existing Data to Elucidate the Genetic Architecture of Cancer Risk and Related Outcomes (R01)
PA-17-241	NCI	333	Fostering Research Training and Education Programs for Native American Students at NCI-designated Cancer Centers (Admin Supp)

Announcement Number	Issuing Organization	Activity Code	Title
PA-17-243	NCI	R21	Secondary Analysis and Integration of Existing Data to Elucidate the Genetic Architecture of Cancer Risk and Related Outcomes (R21)
PA-17-248	NCI	333	Activities to Promote Research Collaborations on Immune-Related Adverse Events (APRC-irAEs) Associated with Cancer Immunotherapy (Admin Supp)
PA-17-262	NICHD	R01	Promoting NICHD Areas of Research for HIV/AIDS in Maternal and Child Health (R01)
PA-17-278	NIAID	R21	HIV and Hepatitis B Co-Infection: Advancing HBV Functional Cure through Clinical Research (R21)
PA-17-279	NIAID	R01	HIV and Hepatitis B Co-Infection: Advancing HBV Functional Cure through Clinical Research (R01)
PA-17-296	NIAAA	R21	Alcohol-Induced Effects on Tissue Injury and Repair (R21)
PA-17-297	NIAAA	R01	Alcohol-Induced Effects on Tissue Injury and Repair (R01)
PA-17-308	NIEHS	333	Exposure Analysis Services for the Environmental Influences on Child Health Outcomes (ECHO) Program (Admin Supp)
PA-17-323	NHGRI	R21	Ethical, Legal, and Social Implications (ELSI) of Genomics Exploratory/Developmental Research Grant Program (R21)
PA-17-324	NHGRI	R03	Ethical, Legal, and Social Implications (ELSI) of Genomics Small Research Grant Program (R03)
PA-17-325	NHGRI	R01	Ethical, Legal, and Social Implications (ELSI) of Genomics Research Project Grant Program (R01)
PA-17-443	NIDCD	R01	Typical and Atypical Patterns of Language and Literacy in Dual Language Learners (R01)
PA-17-444	NHGRI	R01	Ethical, Legal, and Social Implications (ELSI) of Genomics Research Project Grant Program (R01)
PA-17-445	NHGRI	R03	Ethical, Legal, and Social Implications (ELSI) of Genomics Small Research Grant Program (R03)
PA-17-446	NHGRI	R21	Ethical, Legal, and Social Implications (ELSI) of Genomics Exploratory/Developmental Research Grant Program (R21)
PA-17-448	NIDCD	R21	Typical and Atypical Patterns of Language and Literacy in Dual Language Learners (R21)
PA-17-451	NICHD	R03	Pregnancy in Women with Disabilities (R03)
PA-17-452	NICHD	R01	Pregnancy in Women with Disabilities (R01)
PA-17-467	NIAAA	R01	Secondary Analyses of Existing Alcohol Research Data (R01)
PA-17-468	NIAAA	R03	Secondary Analyses of Existing Alcohol Research Data (R03)
PA-17-477	NICHD	R21	Research on Transgender Health (R21)
PA-17-478	NICHD	R01	Research on Transgender Health (R01)

Announcement Number	Issuing Organization	Activity Code	Title
PAR-17-004	NHLBI	R21	Secondary Analyses of Existing Datasets in Heart, Lung, and Blood Diseases and Sleep Disorders (R21)
PAR-17-005	NICHHD	R01	In-Depth Phenotyping and Research Using IMPC-Generated Knockout Mouse Strains Exhibiting Embryonic or Perinatal Lethality or Subviability (R01)
PAR-17-059	NCI	R25	National Cancer Institute Youth Enjoy Science Research Education Program (R25)
PAR-17-063	Roadmap	X01	Discovery of the Genetic Basis of Childhood Cancers and of Structural Birth Defects: Gabriella Miller Kids First Pediatric Research Program (X01)
PAR-17-071	NIAAA	R21/R33	Leveraging Electronic Health Records for Alcohol Services Research (R21/R33)
PAR-17-126	NIA	R01	Juvenile Protective Factors and Their Effects on Aging (R01)
PAR-17-127	NIA	R03	Juvenile Protective Factors and Their Effects on Aging (R03)
PAR-17-161	NICHHD	R03	NCMRR Early Career Research Award (R03)
PAR-17-169	NICHHD	R21	Biomarkers: Bridging Pediatric and Adult Therapeutics (R21)
PAR-17-183	NICHHD	R25	NICHHD Research Education Programs (R25)
PAR-17-187	NICHHD	R21	Translational Research in Pediatric and Obstetric Pharmacology and Therapeutics (R21)
PAR-17-188	NICHHD	R03	Translational Research in Pediatric and Obstetric Pharmacology and Therapeutics (R03)
PAR-17-189	NICHHD	R01	Translational Research in Pediatric and Obstetric Pharmacology and Therapeutics (R01)
PAR-17-191	NICHHD	R03	Development of Appropriate Pediatric Formulations and Pediatric Drug Delivery Systems (R03)
PAR-17-192	NICHHD	R21	Development of Appropriate Pediatric Formulations and Pediatric Drug Delivery Systems (R21)
PAR-17-193	NICHHD	R01	Development of Appropriate Pediatric Formulations and Pediatric Drug Delivery Systems (R01)
PAR-17-199	NICHHD	R43	Development of Appropriate Pediatric Formulations and Pediatric Drug Delivery Systems (R43)
PAR-17-200	NICHHD	R41	Development of Appropriate Pediatric Formulations and Pediatric Drug Delivery Systems (R41)
PAR-17-217	NCI	R01	U.S. Tobacco Control Policies to Reduce Health Disparities (R01)
PAR-17-218	NCI	R21	U.S. Tobacco Control Policies to Reduce Health Disparities (R21)
PAR-17-228	NICHHD	R24	Resource-Related Research Projects in the Epidemiology and Prevention of Pediatric Injury (R24)
PAR-17-229	NICHHD	R21	Human-Animal Interaction (HAI) Research (R21)

Announcement Number	Issuing Organization	Activity Code	Title
PAR-17-230	NICHD	R03	Human-Animal Interaction (HAI) Research (R03)
PAR-17-231	NICHD	R01	Human-Animal Interaction (HAI) Research (R01)
PAR-17-236	NICHD	R01	Genetic Susceptibility and Variability of Human Structural Birth Defects (R01)
PAR-17-237	NIAID	P30	Centers for AIDS Research (P30)
PAR-17-238	NIAID	P30	Developmental Centers for AIDS Research (P30)
PAR-17-265	NIMH	R01	Initiation of a Mental Health Family Navigator Model to Promote Early Access, Engagement and Coordination of Needed Mental Health Services for Children and Adolescents (R01)
PAR-17-266	NIMH	R34	Pilot Studies to Test the Initiation of a Mental Health Family Navigator to Promote Early Access, Engagement and Coordination of Needed Mental Health Services for Children and Adolescents (R34)
PAR-17-300	NINDS	U44	NeuroNEXT Small Business Innovation in Clinical Trials (U44)
PAR-17-327	NIMH	U01	First in Human and Early Stage Clinical Trials of Novel Investigational Drugs or Devices for Psychiatric Disorders (U01)
PAR-17-454	NICHD	R01	Systems Developmental Biology for Understanding Embryonic Development and the Ontogeny of Structural Birth Defects (R01)
PAR-17-472	ODP	R21	Electronic Nicotine Delivery Systems (ENDS): Population, Clinical and Applied Prevention Research (R21)
PAR-17-473	ODP	R01	Electronic Nicotine Delivery Systems (ENDS): Population, Clinical and Applied Prevention Research (R01)
PAR-17-474	FIC	R21	Reducing Stigma to Improve HIV/AIDS Prevention, Treatment and Care in Low and Middle- Income Countries (R21)
PAR-17-475	ODP	R21	Electronic Nicotine Delivery Systems (ENDS): Basic Mechanisms of Health Effects (R21 - Clinical Trial Not Allowed)
PAR-17-476	ODP	R01	Electronic Nicotine Delivery Systems (ENDS): Basic Mechanisms of Health Effects (R01 - Clinical Trial Not Allowed)
RFA-AI-16-078	NIAID	U01	Limited Competition: Clinical Trials in Organ Transplantation in Children (CTOT-C): Mechanistic Ancillary Studies (U01)
RFA-AI-16-082	NIAID	R01	Revision Applications for U.S.-South Africa Program for Collaborative Biomedical Research (R01)
RFA-AI-16-083	NIAID	U01	Revision Applications for U.S.-South Africa Program for Collaborative Biomedical Research (U01)

Announcement Number	Issuing Organization	Activity Code	Title
RFA-AI-16-086	NIAID	U01	Pilot Clinical Trials Targeting HIV-1 Reservoirs in Children (U01)
RFA-AR-18-001	NIAMS	P50	Senator Paul D. Wellstone Muscular Dystrophy Specialized Research Centers (MRSRCs) (P50)
RFA-CA-17-027	NCI	UM1	Pediatric Early Phase Clinical Trials Network (UM1)
RFA-CA-17-049	NCI	U54	Collaborative Research Network for Fusion Oncoproteins in Childhood Cancers (U54)
RFA-CA-17-050	NCI	U54	Pediatric Immunotherapy Translational Science Network (PI-TSN)(U54)
RFA-CA-17-051	NCI	U01	Pediatric Immunotherapy Translational Science Network (PI-TSN)(U01)
RFA-DA-17-014	NIDA	UG3/UH3	HIV, HCV and Related Comorbidities in Rural Communities Affected by Opioid Injection Drug Epidemics in the United States: Building Systems for Prevention, Treatment and Control (UG3/UH3)
RFA-DK-16-018	NIDDK	U01	Pilot Clinical Trials in Pediatric Chronic Kidney Disease Participating Clinical Centers (U01)
RFA-DK-16-035	NIDDK	U24	Pilot Clinical Trials in Pediatric Chronic Kidney Disease Data Coordinating Center (U24)
RFA-DK-16-504	NIDDK	UC4	Limited Competition: Follow-up on Subjects and Immunological Assessments in The Environmental Determinants of Diabetes In The Young Study (TEDDY) (UC4)
RFA-DK-16-505	NIDDK	UC4	Limited Competition: Data Coordinating Center for Type 1 Diabetes TrialNet (UC4)
RFA-DK-17-007	NIDDK	P30	Cystic Fibrosis Research and Translation Center (P30)
RFA-DK-17-034	NIDDK	U24	Chronic Kidney Disease in Children Central Biochemistry Laboratory (U24)
RFA-DK-17-501	NIDDK	U01	Limited Competition: Revision Application for the Human Islet Research Network Coordinating Center (U01)
RFA-DK-17-502	NIDDK	U01	Limited Competition for Continuation of the Prospective Study of Chronic Kidney Disease in Children Clinical Coordinating Centers (U01)
RFA-DK-17-503	NIDDK	U24	Limited Competition for Continuation of the Prospective Study of Chronic Kidney Disease in Children Data Coordinating Center (U24)
RFA-DK-17-507	NIDDK	UC4	Limited Competition: Data Coordinating Center for Type 1 Diabetes TrialNet (UC4)
RFA-DK-17-508	NIDDK	UC4	Limited Competition: Follow-up on Subjects and Immunological Assessments in The Environmental Determinants of Diabetes In The Young Study (TEDDY) (UC4)
RFA-EB-17-001	NIBIB	R01	BRAIN Initiative: Proof of Concept Development of Early Stage Next Generation Human Brain Imaging (R01)

Announcement Number	Issuing Organization	Activity Code	Title
RFA-EB-17-002	NIBIB	U01	BRAIN Initiative: Development of Next Generation Human Brain Imaging Tools and Technologies (U01)
RFA-ES-17-003	NIEHS	P30	Environmental Health Sciences Core Centers (EHS CC) (P30)
RFA-ES-17-005	NIEHS	R01	Environmental influences on Placental Origins of Development (ePOD) (R01)
RFA-HD-17-001	NICHD	U24	NICHD Genomic Clinical Variant Expert Curation Panels (U24)
RFA-HD-17-007	NICHD	P2C	Population Dynamics Centers Research Infrastructure Program FY 2017 (P2C)
RFA-HD-17-022	NICHD	R24	Coordinating Center for NICHD Population Dynamics Centers Research Infrastructure Program, FY 2017 (R24)
RFA-HD-17-023	NICHD	K12	Pediatric Scientist Development Program (K12)
RFA-HD-18-003	NICHD	R01	Moving Beyond Standard Assessments: Applying Novel Tools to Assess Human Placental Structure and Function in Real Time (R01)
RFA-HD-18-004	NICHD	R21	Moving Beyond Standard Assessments: Applying Novel Tools to Assess Human Placental Structure and Function in Real Time (R21)
RFA-HD-18-007	NICHD	K12	Reproductive Scientist Development Program (RSDP) (K12)
RFA-HD-18-009	NICHD	UG1	Re-Competition of Global Network for Womens and Childrens Health Research (UG1)
RFA-HD-18-010	NICHD	U24	Data Coordinating Center for the NICHD Neonatal Research Network (U24)
RFA-HD-18-011	NICHD	K12	Child Health Research Career Development Award (CHRCDA) Program (K12)
RFA-HD-18-012	NICHD	P50	CAPSTONE Centers for Multidisciplinary Research in Child Abuse and Neglect (P50)
RFA-HD-18-013	NICHD	P2C	Population Dynamics Centers Research Infrastructure Program FY 2018 (P2C)
RFA-HD-18-019	NICHD	R01	Interaction of HIV and Neurodevelopment of Children in Resource-Limited Settings: Improving Assessments (R01)
RFA-HD-18-020	NICHD	R21	Interaction of HIV and Neurodevelopment of Children in Resource-Limited Settings: Improving Assessments (R21)
RFA-HD-18-028	NICHD	R43/R44	Point of Care Technologies for the Evaluation and Management of Obstetrics, Neonatal, and Pediatric Critical Care Patients, and for Patients with Disorders of Reproductive Tract and Infertility (R43)
RFA-HD-18-036	NICHD	R01	Opioid Use Disorder in Pregnancy (R01)
RFA-HG-17-008	NHGRI	U01	Implementing Genomics in Practice (IGNITE) II: Pragmatic Clinical Trials Clinical Groups (U01)

Announcement Number	Issuing Organization	Activity Code	Title
RFA-HG-17-009	NHGRI	U01	Implementing Genomics in Practice (IGNITE) II: Pragmatic Clinical Trials Enhanced Diversity Clinical Groups (U01)
RFA-HG-17-010	NHGRI	U01	Implementing Genomics in Practice (IGNITE) II: Pragmatic Clinical Trials Coordinating Center
RFA-HL-18-014	NHLBI	U54	Establishment of Research Centers to Investigate the FVIII Immune Response in Patients with Hemophilia A (U54)
RFA-HL-18-024	NHLBI	R01	Cardiovascular and Pulmonary Research on E-Cigarettes (R01)
RFA-MD-17-001	NIMHD	R43/R44	Innovations for Healthy Living - Improving Population Health and Eliminating Health Disparities (R43/R44)
RFA-MH-17-200	NIMH	R34	Services Research for Autism Spectrum Disorders across the Lifespan II (ServASD II): Pilot Studies of Services Strategies for Transition-Age Youth (R34)
RFA-MH-17-604	NIMH	R61/R33	Development of Psychosocial Therapeutic and Preventive Interventions for Mental Disorders (R61/R33)
RFA-MH-17-606	NIMH	R33	Development of Psychosocial Therapeutic and Preventive Interventions for Mental Disorders (R33)
RFA-MH-17-608	NIMH	R01	Clinical Trials to Test the Effectiveness of Treatment, Preventive, and Services Interventions (R01)
RFA-MH-17-610	NIMH	R01	Clinical Trials to Test the Effectiveness of Treatment, Preventive, and Services Interventions (Collaborative R01)
RFA-MH-17-612	NIMH	R34	Pilot Effectiveness Trials for Treatment, Preventive and Services Interventions (R34)
RFA-MH-17-650	NIMH	U01	Implementation Science for the Prevention and Treatment of Mental and/or Substance use Disorders in Low- and Middle-income Countries (U01)
RFA-NS-17-024	NINDS	U24	Clinical Research Sites for the Network of Excellence in Neuroscience Clinical Trials (NeuroNEXT sites) (U24)
RFA-NS-18-004	NINDS	R01	Human Studies of Target Identification, Biomarkers and Disease Mechanisms Specific to CNS Small Blood and Lymphatic Vessels (R01)
RFA-OD-17-003	NIH	U54	Tobacco Centers of Regulatory Science for Research Relevant to the Family Smoking Prevention and Tobacco Control Act (U54)
RFA-OD-17-004	OBSSR	U01	Intensive Longitudinal Analysis of Health Behaviors: Leveraging New Technologies to Understand Health Behaviors (U01)
RFA-OD-17-005	OBSSR	U24	Intensive Longitudinal Analysis of Health Behaviors: Leveraging New Technologies to Understand Health Behaviors (U24)

Announcement Number	Issuing Organization	Activity Code	Title
RFA-OD-17-006	NIH	U54	Tobacco Centers of Regulatory Science for Research Relevant to the Family Smoking Prevention and Tobacco Control Act (U54)
RFA-OD-17-007	NIH	R01	Tobacco Regulatory Science (R01)
RFA-OD-17-008	NIH	R03	Tobacco Regulatory Science Small Grant Program for New Investigators (R03)
RFA-OD-17-009	NIH	R21	Tobacco Regulatory Science (R21)
RFA-OD-17-012	NIH	R03	Tobacco Regulatory Science Small Grant Program for New Investigators (R03)
RFA-OD-17-013	NIH	R01	Tobacco Regulatory Science (R01)
RFA-OD-17-014	NIH	R21	Tobacco Regulatory Science (R21)

Table 3: 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
ICOs	NIH Institutes, Centers, and Offices
NCATS	National Center for Advancing Translational Sciences
NCCIH	National Center for Complementary and Integrative Health
NCI	National Cancer Institute
NEI	National Eye Institute
NHLBI	National Heart, Lung, and Blood Institute
NHGRI	National Human Genome Research Institute
NIA	National Institute on Aging
NIAAA	National Institute on Alcohol Abuse and Alcoholism
NIAID	National Institute of Allergy and Infectious Diseases
NIAMS	National Institute of Arthritis and Musculoskeletal and Skin Diseases
NIBIB	National Institute of Biomedical Imaging and Bioengineering
NICHD	<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
OAR	Office of AIDS Research, DPCPSI, OD
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, DPCPSI, OD
ODS	Office of Dietary Supplements, ODP, DPSCPSI, OD
ORIP	Office of Research Infrastructure Programs, DPCPSI, OD