DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

Report to Congress:

The Fiscal Year 2014 Pediatric Research Initiative

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PEDIATRIC RESEARCH AT THE NATIONAL INSTITUTES OF HEALTH

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

Pediatric research continues to be an NIH priority. The NIH's strong basic research portfolio provides the foundation for pediatric research in a variety of scientific areas, including neurodevelopment, cardiology, cancer, and behavioral and social sciences. In fiscal year (FY) 2014, the NIH funded research grants and projects directed specifically at pediatric research for a total of $3,485,980,777. The *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) funds the largest portion of pediatric research among the 27 NIH Institutes and Centers (ICs), taking a leadership role in many pediatric research efforts that involve trans-NIH collaborations. However, the NICHD alone accounts for only 20 percent of the total NIH support for pediatric research. This reflects the breadth of the research portfolio at the NIH dedicated to improving the health of children everywhere.

THE PEDIATRIC RESEARCH INITIATIVE

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

> "… annually report to Congress and the public on the extent of the total funds obligated to conduct or support pediatric research across the National Institutes of Health, including the specific support and research awards allocated through the Initiative."
> —Section 409D(c)(3), Public Health Service Act

In response to this request, the NIH has prepared the following report for FY 2014.

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

> (1) "to increase support for pediatric biomedical research within the National Institutes of Health to realize the expanding opportunities for advancement in scientific investigations and care for children;
> (2) to enhance collaborative efforts among the Institutes to conduct and support multidisciplinary research in the areas that the Director deems most promising; and
> (3) in coordination with the Food and Drug Administration, to increase the development of adequate pediatric clinical trials and pediatric use information to promote the safer and more effective use of prescription drugs in the pediatric population.
> —Section 409D(b), Public Health Service Act"

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

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

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

SELECTED SCIENTIFIC RESEARCH ADVANCES IN PEDIATRICS

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

Early Development

*Increased Burden of DNA Structural Variation Found in Patients with Congenital Heart Disease***:** New findings from the NHLBI Pediatric Cardiac Genomics Consortium, an international multicenter collaborative research effort, continue to add to our understanding of the causes of congenital heart disease, the most common type of birth defect. The researchers found an increased burden of spontaneous structural DNA variation, called copy number variants (CNVs), in patients with congenital heart disease compared to normal controls. CNVs were identified using whole exome sequencing and dense state-of-the-art single nucleotide polymorphism arrays. (LINK)

*Understanding Coronary Vasculature Development in the Neonatal Heart***:** There has been a long-standing knowledge gap of the most fundamental aspects of coronary vessel development. NHLBI-funded investigators revealed, using genetic mouse models, three distinct waves of cardiac microvasculature development distinguished by the cardiac layer of origin (endocardium versus epicardium), mechanism (de novo versus angiogenesis), and timing (fetal versus neonatal). Surprisingly, they discovered that even in neonatal mice, the coronary microvasculature continues to form de novo from cells of the innermost lining of the heart, the endocardium. This new insight adds to the body of basic knowledge critical for the development of improved therapeutic strategies for coronary vessel disease and heart failure. (LINK)

Health Care Costs for Conditions Affecting Infants with Very Low Birth Weight: Very low birth weight (VLBW) infants make up only 1.5% of births in the US, but account for 30% of newborn health care

costs. NINR-supported researchers determined the economic impact of several potentially preventable morbidities on hospital direct costs during neonatal intensive care unit (NICU) hospitalization of VLBW infants. These costs ranged from $10,055 for late-onset sepsis to $31,565 for bronchopulmonary dysplasia, and each additional morbidity added a $16,543 increase in direct costs. These findings can inform future studies evaluating the potential cost savings of interventions to prevent these morbidities. (LINK)

Prenatal Polybrominated Diphenyl Ether Exposures and Neurodevelopment in U.S. Children through 5 Years of Age: The HOME Study: NIEHS-funded research suggests children who are exposed to polybrominated diphenyl ether (PBDE) flame retardants while in the womb may suffer neurodevelopmental effects including decreased IQ and increased hyperactivity. (LINK)

"Mississippi Baby (Toddler)" Achieves Sustained HIV Remission for 46 Months: NIAID-supported investigators described a toddler who achieved sustained remission of HIV infection with undetectable HIV-1 plasma RNA through 46 months of age after receiving antiretroviral therapy (ART) 30 hours after birth and continuing therapy through 18 months of age. This child, popularly known as the "Mississippi Baby (Toddler)," eventually experienced viral rebound at 46 months of age after remaining off ART for 27 months and had to resume taking ART (LINK). However, such a prolonged period off ART is unprecedented in children and serves as the basis for ongoing NIAID HIV activities focused on very early ART and sustained HIV remission (LINK). These activities include the IMPAACT P1115 study: Very Early Intensive Treatment of HIV-Infected Infants to Achieve HIV Remission: A Phase I/II Proof of Concept Study (NCT02140255). Now open to enrollment at domestic and international sites, this study will evaluate triple drug ART initiated in the first 48 hours of life and assess its ability to lead to rapid and sustained control of viral replication in HIV-infected children on ART and to achieve sustained HIV remission by maintaining viral suppression off ART for at least 48 weeks. (LINK)

Rare Pediatric Diseases

Gene Linked to Rare Inflammatory Disease in Children: NIAMS intramural scientists are finding treatments for children who have rare diseases, while learning how the body maintains a delicate balance between protective and destructive responses. They identified a gene that underlies a very rare but devastating autoinflammatory condition, which the researchers named STING-associated vasculopathy with onset in infancy (SAVI). Several existing drugs have shown therapeutic potential in laboratory studies, and one is currently being studied in children with the disease. Because some of SAVI's characteristics appear in other diseases such as lupus, the work could lead to novel insights and new treatments that reach far beyond a single rare disease. (LINK)

NIDCD Scientists Seek to Understand Enlarged Vestibular Aqueduct (EVA) and Childhood Hearing Loss: NIDCD's intramural investigators developed an important new mouse model of a rare childhood hearing disorder called enlarged vestibular aqueduct, or EVA. EVA is the most commonly observed inner ear malformation in children with hearing loss. The new mouse model closely mimics the human condition, including erratic fluctuations in hearing ability and demonstrating that one ear is often more affected than the other. Using this new model, scientists hope to finally learn how and why EVA causes this bewildering form of hearing loss in children, and to develop new treatments.

*Steroids After Surgery Do Not Help Infants With Rare Liver Disease***:** Biliary atresia – a rare liver disease – is the most common cause of end-stage liver disease in children. At diagnosis, the primary treatment is a hepatoportoenterostomy, which entails surgical excision of the biliary remnant and creation of bile drainage via a jejunal Roux-en-Y anastomosis to the porta hepatis. Hepatoportoenterostomy results in successful bile drainage in only about half of patients with biliary atresia treated in the United States.

Controversy exists as to whether use of steroids after hepatoportoenterostomy improves clinical outcome. Infants with biliary atresia did not benefit from corticosteroid treatment after bile duct surgery and could face more harm. (LINK)

PASLI Disease Identified: Genetic mutations were identified as the cause of four immunological diseases in pediatric patients seen at the NIH:

- NIAID researchers and collaborators identified a novel primary immune deficiency (PID) disease they have named PASLI disease (for **p**110 delta **a**ctivating mutation causing **s**enescent T cells, **l**ymphadenopathy, and **i**mmunodeficiency). PASLI disease has been confirmed in 14 patients seen at the NIAID PID Clinic. The patients have experienced recurring infections since childhood, and some have developed Epstein-Barr virus (EBV)-associated lymphoma. Based on the cellular pathway affected by the mutation, the researchers identified rapamycin, already FDA-approved for the prevention of transplant rejection, as a potential treatment and are studying additional therapies. (LINK)
- *CTLA-4 Deficiency:* NIAID IRP researchers and collaborators have described a new genetic disorder caused by CTLA-4 haploinsufficiency, a partial deficiency in a receptor called CTLA-4 that serves as a brake for immune cells. Patients from four unrelated families with CTLA-4 haploinsufficiency who were seen at the NIAID PID Clinic experienced severe symptoms first developed in early childhood, including abnormal activity of T cells and disruption of organs by infiltrating immune cells. Organ lesions in affected patients, which may be mistaken for infection or cancer, are caused instead by dysregulated immune cells lacking an adequate amount of CTLA-4. The researchers found that the CTLA-4 receptor has novel roles in immune cells other than T cells, particularly antibody-producing B cells. (LINK)
- *CDG-IIb*: NIH IRP physicians and researchers have identified genetic defects in MOGS, the gene encoding the enzyme mannosyl-oligosaccharide glucosidase, cause the rare congenital disorder of glycosylation type IIb (CDG-IIb), also known as MOGS-CDG. This was discovered in two pediatric patients evaluated through both the NIH Undiagnosed Disease Program and the NIAID PID Clinic. The two siblings with CDG-IIb presented with multiple neurologic complications and a paradoxical immunologic phenotype. (LINK)
- *STING-associated vasculopathy with onset in infancy (SAVI)*: NIH IRP researchers (including NIAMS, CC, NIAID) discovered the cause of a novel autoinflammatory disease. Physicians evaluated six patients who presented in early infancy with systemic inflammation and lesions of fingers, toes, nose, cheeks, and ears that progressed to acral necrosis in most of the patients and did not respond to therapy. Researchers found their disease was caused by autosomal dominant mutations in TMEM173, the gene encoding the stimulator of interferon genes (STING). (LINK)

Recognizing Somatic Mutations in Neurodevelopmental Disorders: Somatic mutations are genetic variations that arise in the body's cells after conception, and the timing of the mutation during development or growth determines how widespread the mutation becomes in the body's various tissues. Somatic mutations are known to contribute to cancers and certain other diseases, and recent studies have shown a role for somatic mutations in neurodevelopmental disorders. However, the best ways to detect somatic mutations in neurodevelopmental disorders have been unclear, and their prevalence in these disorders remains unknown. Researchers supported by NINDS applied targeted, deep sequencing methods to blood samples from patients with congenital brain malformations and found that, in cases where a causal mutation was found, 30% had somatic mutations. The targeted sequencing method identified mutations missed by other methods, such as whole-exome and whole-genome sequencing, suggesting the need for complementary approaches in future research. (LINK)

Link Between Newborn Perinatal Complication and Accelerated Aging: NIA supports research on causes of and potential interventions to reverse long-term consequences of prenatal and early-life adversity.

Findings from the NIA-funded Dunedin Multidisciplinary Health and Development Study, which follows over 1000 individuals from birth into midlife, reveal that perinatal complications are related to shorter leukocyte telomere length in midlife. This finding provides support for early-life developmental programming by linking newborns' perinatal complications to accelerated aging at midlife.

Genetic disorder causes strokes and vascular inflammation in children: A collaboration between researchers from NHGRI, NHLBI, NIAID, NIAMS, NCI, NIDDK and the NIH Clinical Center led to the discovery of the genomic basis of a rare inflammatory disease in children, now called deficiency of ADA2 (DADA2). Through next-generation whole exome sequencing, NHGRI researchers identified variants in the CERC1 gene causing a debilitating syndrome of sporadic fevers, skin rashes and recurring strokes starting in early childhood. The researchers found that harmful variants in the CERC1 gene impede production of an enzyme called adenosine deaminase 2 (ADA2), which is a protein vital to the integrity of healthy blood vessel walls. NHLBI researchers established the link between ADA2 deficiency and white blood cell dysfunction. Faulty monocyte/macrophages attack the patients' own blood vessels, resulting in a vicious circle of vessel damage and inflammation that leads to stroke and other blood vessel-related problems. This discovery coincided with findings by an Israeli research group that identified an overlapping set of variants in the same gene in patients with a similar type of blood vessel inflammation. Finding the molecular basis of DADA2 paves the way toward targeted drugs that inhibit specific inflammatory proteins rather than treating patients with high doses of steroids. The researchers are also testing ways to replace ADA2 in the bloodstream. (LINK)

Prevention Research

Exercise might help make Children's Brains more Efficient: Scientists are still learning about how exercise actually affects the brain. Researchers measured the fitness levels of 24 children (9 and 10-years old) and also assessed them on tests of intelligence, attention, and brain activity. Through magnetic resonance imaging (MRI), scientists observed that the "white matter" in the aerobically fit children was different than in kids who were not as fit. The white matter seemed to be bundled more tightly in children who were more fit, potentially leading to better and faster brain performance. The findings underscore the importance of physical activity, not just for physical health but for brain health as well. (LINK)

Distracted Driving and Risk of Road Crashes among New and Experienced Drivers: Distracted driving is a major cause of motor vehicle crashes for drivers of all ages, but especially for teenagers who are new drivers. Researchers conducted two studies on the relationship between performing secondary activities, including cell-phone use, and the risk of crashes and near-crashes. Cameras and data-recording sensors were installed in the vehicles of both newly licensed teenagers and experienced adult drivers to assess their behaviors while driving and during a crash or near-crash.

The results showed that both teen and adult drivers performed secondary activities while driving about 10% of the time. Experienced adults were more than twice as likely to crash or near-crash when dialing a cell phone, but did not have an increased risk while performing other secondary activities. New teenage drivers were eight times more likely to crash or near-crash when dialing a cell phone, and also had a significant increased risk when performing other secondary activities such as reaching for a phone or other object, texting, or eating. New teenage drivers performed secondary activities more frequently over time, but experienced adult drivers did not significantly increase their secondary activities over time. Talking on the cell phone did not increase the risk of a crash among either the adults or the new teenage drivers. However, because talking on a cell phone is preceded by reaching for the phone and answering or dialing, restricting electronic device use may help prevent accidents, particularly among new teenage drivers. (LINK)

Newborn Infants Whose Mother Received Vitamin C during Pregnancy Protected from Smoking Effects on Lung Function: The impact of smoking during pregnancy can affect how the baby's lung develops and functions, affecting lung health for a lifetime. Smoking cessation is the best way to optimize the baby's health, but for many women nicotine addiction makes it difficult to quit. This NIH-funded study showed that newborn lung function was improved and wheezing over the first year of life was decreased for those babies exposed to Vitamin C during fetal life. The study randomized 179 pregnant women to 500 mg/day Vitamin C versus placebo starting in the second trimester if they were unable to quit smoking despite efforts at cessation. (LINK)

Assessing the Impact of Adolescent Alcohol Exposure on the Developing Brain: Adolescence is a period of significant brain maturation and also the time when many individuals initiate and escalate alcohol consumption. Previous studies have shown an association between excessive drinking during adolescence and deficits in brain structure and function; however, it is not clear whether the deficits predated the onset of alcohol use or occurred as a consequence of it. In 2012, NIAAA launched the National Consortium on Alcohol and Neurodevelopment in Adolescence (NCANDA), an ongoing multi-site longitudinal study to address alcohol's effects on normal brain development. The five NCANDA sites are collectively enrolling 800 adolescents ages 12 to 21, and using advanced brain imaging as well as psychological and behavioral research tools to evaluate brain structure and function, beginning before the participants start to drink. NCANDA's overall objectives are to elucidate the short- and long-term effects of alcohol exposure on the developing brain and to identify the brain characteristics that may predict alcohol use disorder. In a 2014 study supported through NCANDA, researchers used high resolution magnetic resonance imaging to assess the brain structure of 40 healthy adolescents, ages 12-17, half of whom initiated heavy drinking during a three year follow up. The researchers found that youth who transitioned from no or minimal substance use to heavy drinking had structural abnormalities prior to the initiation of alcohol use. These abnormalities included smaller brain volumes in specific regions of the frontal cortex, an area important for executive functioning. They also showed that youth who transitioned to heavy drinking had significant reductions in brain volumes after alcohol use was initiated, compared to non-drinking youth. These reductions occurred in regions important for sensory integration, feedback processing, motor control, habit learning, visual object recognition, and language comprehension. Whereas both heavy drinking and non-drinking groups showed reductions in brain volumes as a result of normal developmental pruning, those who transitioned to heavy drinking during the study showed accelerated reductions in brain volumes.

*Binge Drinking during Adolescence Reduces White Matter in Specific Regions of Rat Brains with Effects that Persist into Adulthood***:** Previous studies have demonstrated that binge drinking is associated with reduced white matter integrity in the corpus callosum of both the adolescent and alcohol-dependent adult brains. In a recent study, researchers used rodent models of adolescent binge drinking and adult alcohol dependence to gain insight into how alcohol affects white matter integrity in the frontal cortex of the brain. They found that adolescent binge drinking reduced the size of anterior branches of the corpus callosum and this neuropathology correlated with higher relapse to drinking in adulthood. The researchers also demonstrated that adolescent binge drinking was associated with damaged myelin, the insulating sheath that forms around the nerve cells that comprise white matter, in the medial prefrontal cortex in adulthood, as well as reduced density of myelin in the medial prefrontal cortex in adolescence. Heavier drinking in adolescence also predicted worse performance on a working memory task in adulthood. These results suggest that adolescent binge drinking may affect white matter integrity in the medial prefrontal cortex through reduction of myelin and these changes may contribute to deficits in executive function in adulthood. (LINK)

Blood Lead Concentrations and Children's Behavioral and Emotional Problems: A Cohort Study: Recent work funded by NIEHS has identified an association between lead exposure in children and an increased

risk of behavioral and emotional problems (LINK). This work provides additional evidence that there is no safe level of lead because the average blood lead level in children was below 10 ug/dL. (LINK)

Neurodevelopmental Disorders and Prenatal Residential Proximity to Agricultural Pesticides: The CHARGE Study: The Childhood Autism Risks from Genetics and Environment (CHARGE) study, funded by NIEHS, has identified an association between residential proximity to agricultural pesticides and autism spectrum disorder or developmental delays (LINK). The results are alarming because pyrethroids, which were associated with autism spectrum disorder, are supposed to be a safe alternative to organophosphates. (LINK)

Correlating Specific Aspects of Attention Deficit/Hyperactivity Disorder (ADHD) with Cannabis Use Disorders (CUD): ADHD is characterized by the triad of inattention, hyperactivity, and impulsivity and frequently co-occurs with cannabis use disorders. This study showed that each element comprising ADHD was associated with different risks and health consequences associated with cannabis use: 1) increased hyperactivity and impulsivity in childhood was associated with earlier cannabis initiation, but no other cannabis-related outcome while 2) current and childhood inattention were independently associated with more severe cannabis outcomes in young adulthood including higher levels of current use, dependence (current inattention only), craving, and use-related problems. Identification of specific aspects of ADHD that increase risk for the initiation, development and maintenance of CUD may permit more targeted treatments for both disorders at various stages of their expression. (LINK)

High Adolescent Self-Control Correlates with Reduced Cannabis Use and Depressive Mood into Young Adulthood: Several studies have shown that cannabis use often co-occurs with depression. This study showed that low levels of self-control during adolescence correlated with the co-occurrence of high levels of cannabis use and depressive mood from adolescence into young adulthood. Conversely, high self-control is associated with low marijuana use and low levels of depression over time. Thus, while poor self-control in adolescence constitutes a significant risk for maladjustment over time, high self-control is protective against marijuana use and depressive mood into young adulthood. (LINK)

Air Pollution Associated with Autism: NIEHS-funded researchers found that traffic-related air pollution and particulate matter could be associated with autism. The researchers used data from the Childhood Autism Risks from Genetics and the Environment study in California and modeled levels of traffic-related air pollution exposures using address information and Environmental Protection Agency (EPA) Air Quality System data. They found that exposure to traffic-related air pollution, nitrogen dioxide, and particulate matter less than 2.5 µm and 10 µm (PM2.5 and PM10) during pregnancy and the first year of life was associated with autism in children. (LINK)

Advancing Diagnosis and Treatment for Pediatric Diseases and Conditions

Disability Rates Growing Among U.S. Children: Researchers reviewed 2001-2011 data from the National Health Interview Survey, a continuing nationwide survey designed to collect information on the demographic characteristics, disability status, and health care use in the U.S. population. The number of children with a disability increased by over 15 percent between 2001–2002 and 2010–2011, with nearly 6 million children having a disability in 2010–2011. Children living in poverty experienced the highest rates of disability. However, children living in the highest-income households experienced the largest increase (28.4%) in disability rates over this 10-year period. The percentage of disability cases related to any physical health condition declined 11.8% during the decade, whereas cases related to any neurodevelopmental or mental health condition increased by 20.9%. (LINK)

Predicting Progression to Psychosis from a Clinical High-Risk State: The North American Longitudinal

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

Predictors of Successful Development of Speech and Language in Non-Verbal Children with Autism: NIDCD-funded researchers conducted a study to identify developmental, behavioral, and parental predictors of successful early speech and language in children with non-verbal autism spectrum disorders (ASD). Identification of reliable predictive factors helps determine appropriate early treatment target and inform intervention strategies for non-verbal children with autism. This project also provided a Minority Investigator Supplement to support an African-American graduate student currently completing his PhD and supports his effort to become an independent scientific investigator in the field of autism. This study also directly addresses one of the priority areas of the Interagency Autism Coordinating Committee's Strategic Plan. (LINK)

Improving Communication in Children with Autism: Many children with ASD have difficulty communicating. A frequently used treatment in many schools and clinics is applied behavior analysis (ABA) involving over 40 hours of instruction per week and can require many trials to learn a single word. An alternate intervention, pivotal response treatment (PRT), is derived from ABA, but is play-based and child-initiated. In a comparative effectiveness study, NIDCD-supported scientists compared these two approaches. The PRT intervention was found to improve verbal and pragmatic social communication in three months with only two hours of instruction per week. These results address evidence-based practices facing service delivery challenges; in addition, the findings identify intervention strategies which give children with ASD better communicative and social competency and improved outcomes. (LINK)

Predicting Functional Outcomes in Children Following Traumatic Brain Injury: Children with moderate to severe traumatic brain injury (TBI) often face hospitalization and extensive rehabilitation. Accurately predicting the outcomes for these children is helpful to those who need to plan for and coordinate follow-up care. The severity of the initial injury is one factor to consider, but measures of functional recovery soon after injury can also be helpful. In adults, two measures are often used: (1) the time from initial injury to when an individual can follow simple commands (TFC); and (2) the length of post-trauma amnesia (PTA). Researchers used these two measures in children ages three to 18 years old with moderate to severe TBI. One year after the children were discharged from inpatient rehabilitation, the researchers followed up with them to assess their self-care, cognitive function, and other abilities. The scientists found that the two-predictor combination (TFC and PTA) performed no better than TFC alone. Because TFC can be determined earlier in rehabilitation, the researchers considered it the more useful of the two predictors. (LINK)

Hospitalizations for Mental Health Problems in Children are Common and Costly: To assess the frequency and cost of mental health hospitalizations among children, scientists analyzed nationally-representative data on hospital discharges in 2009 for patients from 3 to 20 years of age. Nearly 10% of hospitalizations for children from 3 to 20 years of age nationwide were for a primary mental health diagnosis. Older children, boys, white children, and children with health insurance were more likely to be

admitted to the hospital for a mental health diagnosis. Mental health-related admissions were less common for free-standing children's hospitals compared with other institutions. Approximately 20% of children and adolescents in the U.S. have the diagnostic criteria for a mental health disorder. The inpatient and outpatient costs of treating these children are estimated to be $247 billion annually. The most frequent and expensive primary mental health diagnoses in the U.S. were depression (44.1% of all mental health admissions; $1.33 billion), bipolar disorder (18.1%; $702 million), and psychosis (12.1%; $540 million). (LINK)

Subtypes of Irritable Bowel Syndrome: Few studies of children with irritable bowel syndrome (IBS) have examined the range and distribution of IBS subtypes. Yet, in the adult IBS population, medical treatment and management of symptoms is increasingly targeted to IBS subtype, underscoring the importance of accurately differentiating patients. In an NINR-funded study, researchers found that children with irritable bowel syndrome (IBS) exhibit a different distribution of subtypes of IBS than typically found in adults with IBS. Study findings may have implications for better diagnosis and treatment of IBS in children (LINK).

Medication Did Not significantly Affect Growth for Young Children with Sickle Cell Anemia: Sickle cell anemia is a genetic condition in which a person does not have enough healthy blood cells to carry needed oxygen throughout their body. Hydroxyurea is a medication that is often used to treat patients with sickle cell anemia. Although hydroxyurea can be helpful for patients and can improve growth, scientists were not clear about how the medication affects growth in very young children, and there has been concern that the drug could have a negative effect on growth in infants and toddlers. Researchers conducted a 2-year clinical trial to assess hydroxyurea treatment in very young children with sickle cell anemia. The 193 children in the study ranged in age from 9 months to 18 months old. Scientists administered the medicine to half of the children and then monitored them periodically. At the end of 2 years they found that there were no significant differences in height, weight, or BMI for the kids who received the hydroxyurea medicine and the kids who did not. Children who received the medicine had a slightly smaller head circumference, though still within normal growth measurements. The study provides some data that treatment with hydroxyurea may not be harmful for the growth of young children. (LINK)

Genetic Testing for Disorders of Sex Development: A rare set of genetic conditions known as differences or disorders of sex development (DSD) often make it difficult to determine at birth if a newborn is a boy or a girl, because of the atypical appearance of the infant's genitalia. (In certain DSD the atypical development of the reproductive system is entirely internal, and so the differences may not be apparent until later.) The inability to know immediately whether a newborn baby is a boy or girl, and possible implications of that uncertainty for a child's future, are exceptionally stressful for families. The current array of DSD diagnostic procedures may not yield immediate answers. Genetic anomalies have been identified for only a minority of DSD and current genetic testing, typically one gene at a time, is time-consuming and also very expensive. A pilot trial, however, of a new, comprehensive genetic test suggests that it could produce more timely and affordable results. Using next-generation gene sequencing, this single test can detect all known genetic anomalies associated with DSD and provide multiple types of information about such anomalies. The test could be expanded if additional DSD-associated genes are identified. This new test could be the first diagnostic step for DSD in newborns, and the results can help parents better understand the cause and outcomes of their child's condition. (LINK)

Atenolol versus Losartan in Children and Young Adults with Marfan Syndrome: This randomized trial, conducted under the auspices of the NHLBI's Pediatric Heart Network, compared two medications, in patients with Marfan syndrome aged 6 months to 25 years. Aortic-root dissection, which is a risk when the aortic root enlarges, is the leading cause of death in Marfan syndrome. Patients with a dilated aortic root were treated with losartan versus atenolol over three years. Although the rate of change in the aortic

root did not differ between treatment groups, the severity of aortic-root enlargement decreased over time in both groups, particularly in young subjects, suggesting that starting therapy at an earlier age and stage of the disease might be warranted. Both drugs were found to be well-tolerated and safe, resulting in more treatment options for patients with Marfan syndrome. (LINK)

Severe Combined Immunodeficiency (SCID):

- An NIH-supported study suggests that early diagnosis of SCID leads to higher survival rates. Data from more than 3 million newborns confirmed that reliable identification of this inherited condition early in life leads to prompt treatment and high survival rates. (LINK)
- Results from an NIAID-funded study indicate that early hematopoetic stem cell transplantation is critical to achieve good outcomes for SCID infants. Data from 240 SCID infants at 25 transplant centers across North America showed that infants who received transplants before the age of 3.5 months were most likely to survive, regardless of the type of stem cell donor used. (LINK)
- NIAID-funded researchers found that gene therapy can restore the immune systems of children with X-linked SCID (SCID-X1), which primarily affects boys. Previous efforts to treat SCID-X1 with gene therapy were initially successful, but approximately one-quarter of the children developed leukemia two to five years after treatment. Results from the study suggest that the new vector is equally effective at restoring immunity and may be safer than previous approaches. (LINK)

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

Rapid Detection of Monogenic Causes of Childhood-onset Steroid-resistant Nephrotic Syndrome: Steroid-resistant nephrotic syndrome (SRNS) is frequently caused by genetic mutations. Researchers developed a genotyping approach that allows rapid (<3 weeks) mutation analysis of 21 genes that cause SRNS—perhaps obviating a course of high-dose steroids that would be ineffective. (LINK) A single gene cause has been detected in 29.5 percent of SRNS cases. (LINK)

Bionic Pancreas Outperforms Insulin Pump in Adults and Youth: People with Type 1 Diabetes who used a bionic pancreas instead of manually monitoring glucose using fingerstick tests and delivering insulin using a pump were more likely to have blood glucose levels consistently within the normal range, with fewer dangerous lows or highs. (LINK and LINK)

Silent Cerebral Infarcts Multicenter Clinical Trial (SIT study): Sickle cell anemia is a genetic disorder in which red blood cells become abnormally shaped and sticky, causing them to block blood flow resulting in pain, organ damage, and strokes. In the US, sickle cell disease is most common among African Americans, and about one third of children with the disease experience silent strokes (or strokes with no acute symptoms) that are due to blocked cerebral blood vessels and that are associated with long-term cognitive problems, poor academic performance, and increased risk for stroke recurrence. Until now, evidence for effective approaches to identify and treat children with these subclinical strokes has been

lacking. The SIT study, a randomized controlled clinical trial, demonstrated that monthly blood transfusions safely and effectively reduced the recurrence of silent strokes in children with sickle cell disease. (LINK)

De Novo Genetic Mutations in Epileptic Encephalopathies: Genetic studies are often too small to yield statistically significant evidence for the contribution of individually rare mutations to complex diseases such as childhood onset epileptic encephalopathies. To address this challenge, epilepsy researchers supported by NINDS pooled their patient data samples with those from two other international cohorts and were able to both confirm a causal role for a previously implicated gene and demonstrate that *de novo* mutations occur significantly more often in epileptic encephalopathy patients than in the general population. By analyzing the functions of affected genes, the researchers also found that a majority of *de novo* mutations affect proteins that regulate synaptic transmission, or the communication between neurons, suggesting an important role for such pathways in severe childhood epilepsies. This study's findings have already led to efforts to customize treatment for individual patients based on the genetic mutations identified. (LINK)

New Innovations in Measurement of Fetal Drug Exposures: The use of antiretrovirals during pregnancy is one of the greatest medical advances of our time. In Western countries, it has reduced the rate of mother-to-child HIV transmission during delivery to less than 2 percent. Nonetheless, some children born to mothers who took these medications have developmental abnormalities. NIDA-funded researchers are validating an important new tool for assessing fetal drug exposures to assist with the NIH-funded Pediatric HIV/AIDS Cohort Study (PHACS) (LINK). An assay has been developed to accurately measure 99.2 percent of antiretrovirals from infants through the meconium which is expelled in the first stool after birth. This innovation is an important tool to address prenatal exposure since a drug must have passed through the fetus to be present in meconium. These studies should enable physicians to identify and provide early interventions to children whose fetal exposure to antiretrovirals has put them at risk for developmental delays.

Hydroxyurea Treatment for Toddlers with Sickle Cell Reduces Hospitalizations and Medical Care Costs: NHLBI-funded researchers found that administrating hydroxyurea therapy to infants and toddlers with sickle cell anemia reduced hospitalization and cut medical costs. Hydroxyurea has been approved for adults and adolescents with sickle cell disease, and the BABY HUG trial, which involved 193 children ages 9 to18 months old when they enrolled, supported expanded use of the drug to patients across all ages. Continued concern over rising health care costs prompted the BABY HUG researchers to retrospectively assess hydroxyurea's impact on treatment cost. They calculated the estimated annual cost reduction to be 21 percent. This saving is estimated to grow as patients age and their symptoms increase in severity and frequency. The Pediatric Hydroxyurea Phase 3 Clinical Trial (BABYHUG) trial was funded by the NHLBI and the NICHD through the Best Pharmaceuticals for Children Act. (LINK)

Combination Therapy Improves Cystic Fibrosis Lung Function: Cystic fibrosis (CF) is an inherited disease of the secretory glands, including the glands that make mucus and sweat. The disease is caused by mutations in the CFTR gene that result in production of a defective CFTR protein. NHLBI-funded investigators tested the effect of two drugs in adult patients, each addressing a different problem: lumacaftor, an investigational CFTR corrector that increases incorporation of CFTR into the cell surface, and ivacaftor, a CFTR potentiator that enhances chloride ion transport by CFTR. Compared to placebo, the combination of lumacaftor and ivacaftor improved forced expiratory volume (FEV1) (the amount of air a person can blow out in one second following a full breath) for CF patients who are homozygous for the most common CFTR mutation. The combination also resulted in greater restoration of CFTR function. This finding suggests that the combination of lumacaftor and ivacaftor may be a new treatment for improving lung function in CF patients who are homozygous for the most common mutation,

suggesting this approach could be effective in treating CF. (LINK)

*Trial Results Show High Remission Rate in Leukemia following Immune Cell Therapy***:** Children and young adults with chemotherapy-resistant B-cell acute lymphoblastic leukemia (ALL) experienced high remission rates following treatment with an experimental immunotherapy. This finding, from an early-phase clinical trial, is important because children and young adults with chemotherapy-resistant leukemia who do not achieve remission have very poor outcomes. In 2014, it is estimated that there will be over 6,000 cases of this type of cancer diagnosed in the United States, with more than half occurring in children and young adults (from age 1 to age 30). Results from this ongoing clinical trial, in NCI's Center for Cancer Research, demonstrated that the immunotherapy treatment had anti-leukemia effects in patients and that the treatment was feasible and safe. The results of the findings appeared October 13, 2014, in *Lancet*. (LINK to abstract; LINK to NCI News Note).

Pediatric Cancer Genomics – recent findings:

- *Genetic Analysis of Patients with Treatment-Naive high-grade Astrocytomas*, a rare and incurable group of pediatric brain tumors, identified recurrent mutations specific to tumor location within the brain. Some of these mutations are potentially susceptible to blocking by existing drugs, and others are potential targets for drug development. (LINK)
- *Genetic Analysis of Inflammatory Myofibroblastic Tumor:* Genetic Analysis of Inflammatory Myofibroblastic Tumor,a rare form of childhood soft tissue sarcoma, identified gene fusions that result in a therapeutically targetable kinase protein in 85% of the 37 tumor samples examined, suggesting that routine molecular profiling of these cancers could inform treatment for individual patients. (LINK)
- *Genomic Analysis of Rhabdomyosarcomas*: The NCI has conducted comprehensive genomic analysis of rhabdomyosarcomas and identified minimal mutation rates in the alveolar histology, but substantial numbers of targetable mutations in non-alveolar subtypes (LINK to Cancer Discovery abstract; LINK to NCI Press Release).
- *TARGET (Childhood Cancer Therapeutically Applicable Research to Generate Effective Treatment) Initiative – The Genetic Landscape of High-Risk Neuroblastoma:* The study reported a low median frequency of exonic somatic mutations (0.60 mutations per megabase) and few genes overall that are recurrently mutated across the coding regions of these pediatric tumors. These results suggest that developing better treatment strategies for neuroblastoma patients will be challenging with a minimal number of targetable oncogenic drivers. Researchers are now focusing on how neuroblastoma tumors evolve in response to medicine and other factors, since neuroblastoma tumor cells often change rapidly over time. Given the few recurrent genetic mutations, this is likely due to factors including rare germline mutations, copy number variations, and epigenetic modifications during tumor evolution. (LINK)
- *TARGET Initiative – Targetable Kinase-Activating Lesions in Ph-Like Acute Lymphoblastic Leukemia*: The TARGET ALL team and other collaborators reported that Ph-like ALL is characterized by a range of genomic alterations that activate a limited number of signaling pathways, all of which may be amenable to inhibition with approved tyrosine kinase inhibitors. Based on these findings, trials identifying Ph-like ALL are in development to determine whether adding tyrosine kinase inhibitors to current therapy will improve the survival of patients with this type of leukemia. (LINK)
- *Genome-Wide Association Study of Osteosarcoma:* NCI researchers are leading genome-wide association studies to identify susceptibility loci for osteosarcoma, which is the most common primary malignant bone tumor in children and young adults, typically arising during the pubertal growth spurt. In 2014, the researchers identified two novel loci: a locus in the *GRM4* gene at 6p21.3, which is a plausible candidate gene, and a locus in the gene desert at 2p25.2. Closer examination of these regions is underway to inform functional studies,

which would uncover the biological mechanisms underlying susceptibility to osteosarcoma. (LINK)

NCI-Supported Researchers' Leadership in Neuroblastoma: Prior to a groundbreaking discovery by scientists supported by the NCI, the majority of children diagnosed with advanced-stage neuroblastoma had a high risk of treatment failure and little hope of surviving. Less than 40 percent of children with this disease lived five years after diagnosis. Now an immunotherapy 20 years in the making, originally called Chimeric Monoclonal Antibody 14.18 (ch14.18, and now dinutuximab) is providing new hope for children with this rare cancer. NCI manufactured ch14.18 and supported a Children's Oncology Group (COG) phase 3 trial that showed ch14.18 given with cytokines improved survival when used as maintenance therapy. Randomization to the phase 3 trial was stopped in 2009 because of the efficacy of the dinutuximab regimen. NCI then manufactured and provided dinutuximab to clinicians treating children with high-risk neuroblastoma under a COG-led expanded-access clinical trial (between 2009 and 2014, approximately 700 children received NCI-manufactured dinutuximab through this program). In 2010, NCI entered into a Cooperative Research and Development Agreement with Maryland-based United Therapeutics Corp., under which the company assumed responsibility for manufacturing dinutuximab and moving it through the steps required for regulatory approval. The FDA approved dinutuximab as part of first-line therapy for children with high-risk neuroblastoma on March 10, 2015. The FDA approval was based on the findings from the NCI-sponsored COG phase 3 clinical trial noted above, and it is the first approval of a therapy specifically for patients with the high-risk form of neuroblastoma. As part of the dinutuximab approval, United Therapeutics will conduct additional studies to gather more information about the product's safety, efficacy, and optimal use.

Childhood Forearm Fractures Due to Mild Trauma Linked to Bone Deficits: Even though previous research has not found a connection between forearm fractures in pediatric patients and bone health as measured by conventional DXA, advanced imaging tools have revealed differences in the bone strength and quality of children who break bones following a mild trauma (such as a fall during a minor playground scuffle) and those who experience a more forceful impact (such as falling off a bicycle). Compared with the children without fracture, the children in the mild trauma fracture group showed compromised bone strength and bone quality. In contrast, those children whose fractures occurred during a more forceful trauma did not show any significant differences in bone quality compared with their uninjured peers. These results suggest that children who break a bone after a mild trauma are at increased risk of future fractures and could benefit from dietary changes and physical activities to help them build stronger bones. (LINK)

Benefits of Bracing in Adolescents with Idiopathic Scoliosis: Adolescent idiopathic scoliosis (AIS) is a curvature of the spine with no clear underlying cause. In mild cases, monitoring over time by a physician may be all that is needed. However, in more severe cases — especially when the child is still growing — the use of a brace, or even surgery, may be recommended. NIAMS-supported researchers from the Bracing in Adolescent Idiopathic Scoliosis Trial (BrAIST) compared the risk of curve progression in adolescents with AIS who wore a brace with those who did not. The trial was stopped early after finding that bracing significantly reduced the risk of curve progression and the need for surgery, and that more hours of brace wear was associated with higher success rates. (LINK)

Global Pediatric Health

Antigen May Serve as Protection to Malaria: NIAID intramural scientists, in association with NIAID extramural grantees, identified PfSEA-1, an antigen that can hinder the ability of malaria parasites to multiply and may protect against severe malaria infection. The researchers measured PfSEA-1 antibody

levels in 453 Tanzanian children and discovered that no cases of severe malaria occurred during periods when the children had detectable antibodies. Further, the scientists found that in a sample of 138 males ages 12-35 living in a malaria-endemic area of Kenya, individuals with detectable antibodies to PfSEA-1 had 50 percent lower parasite densities compared to individuals with no detectable antibodies. These findings support investigation of PfSEA-1 as a potential vaccine candidate. (LINK)

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

HIV Tracking System improves Retention in Kenya: Early diagnosis and treatment is critical for the survival of HIV infected babies. Without proper treatment, more than half of HIV infected babies will die before they are 2 years old. If babies are treated before they reach 12 weeks of age, their chances of survival increase dramatically. The challenge around the globe, especially in countries with low resources, has been keeping track of the babies that need treatment and then following up adequately so that they receive appropriate treatment at the right time. Researchers tested the effectiveness of a computer system used in Kenya that was designed to help keep track of patients. The HIV Infant Tracking System (HITSystem) used text messages and computer alerts to notify mothers and medical providers when medical test results were ready and prompt them when medical action was needed. Results showed the HITSystem led to an increase in treatment of HIV-positive babies as well as a faster turnaround time of results, which led to more timely treatment. Technologies such as this have the potential to save the lives of many children around the world. (LINK)

New Rotavirus Vaccine for Use in India: The NIAID partnered with the government of India, Bharat Biotech, the Program for Appropriate Technology in Health, and others to develop ROTAVAC®, the first rotavirus vaccine developed entirely in India. Results from a phase III clinical trial showed ROTAVAC® to be safe and effective. Bharat Biotech plans to file for registration of the vaccine in India. If approved, ROTAVAC® will provide a safe, effective, and affordable option for protecting infants and children in India against severe rotavirus-induced gastroenteritis. (LINK)

Child Growth in Ethiopia, India, Peru and Vietnam: Under-nutrition contributes to more than one-third of the 7.7 million deaths annually among children under age 5 years, mostly in the developing world. As many as 171 million young children have stunted growth, putting them at risk for death, poor health, inadequate motor development, cognitive disability, and inability to participate in schooling. While some research has suggested that stunted development may be irreversible after 1 or 2 years of age, this paper

finds evidence that increased growth is possible through age 5. These findings call attention to the need for additional research on the factors that influence child growth from infancy through childhood. Researchers analyzed data on over 7,200 children in Ethiopia, India, Peru, and Vietnam to help identify potential age ranges and other factors associated with growth recovery in children. Compared with other countries, a higher percentage of children in Ethiopia had stunted growth as infants, but Ethiopian children also had the highest growth rate between ages 1-5. Results across the 4 countries indicated that height and weight at age 1 was the strongest predictor of later height and weight and most factors associated with increased growth had the strongest impact before the child reached age 5. Although infancy is a crucial period for establishing a child's growth, the researchers find evidence that some children are able to recover from a difficult start between the ages of 1-5. Growth recovery was associated with parents' level of schooling, household consumption, and the presence of a hospital in rural areas. (LINK)

Global Cost of Lead Exposure: Although children's blood lead levels have declined worldwide following the removal of lead in gasoline, significant exposure remains, particularly in low- and middle-income countries. NIEHS-supported researchers estimated a total cost of $977 billion (range of $728.6 billion to $1162.5 billion) in low- and middle-income countries in economic costs attributable to lead exposure, amounting to approximately 1.2 percent of the world's gross domestic product (GDP). (LINK)

Parasite Burden and Severity of Malaria in Tanzanian Children: NIAID IRP researchers and NIAID extramural grantees with additional support from the Bill and Melinda Gates Foundation reported the outcome of a study of *Plasmodium falciparum* infection and disease in 882 Tanzanian children followed from birth for an average of 2 years and for as long as 4 years. They found direct evidence that reoccurrence of severe malaria is unlikely but that the first occurrence of severe malaria commonly occurs after one or more previous infections, including high-density infections, rather than during the first infection. However, they found that immunity to severe malaria was not related to improved control of parasite density. The evidence suggests that naturally acquired immunity targets a conserved feature of the various severe-malaria syndromes, such as parasite virulence or host inflammation. An understanding of the natural history of *P. falciparum* infection and disease can guide mechanistic studies of the pathogenesis of and immunity to severe malaria, which in turn can lead to the development of new therapeutics. (LINK)

SELECTED NEW AND EXPANDED RESEARCH EFFORTS FOR FY 2014 IN PEDIATRICS

Selected New Pediatric Research Efforts for FY 2014

NIH ICs launched a range of new research programs and efforts related to pediatrics in FY 2014. Selected highlights of new initiatives are given below. Several programs are focused on understanding risk factors for complex conditions in children. However, the majority of the programs are concerned with developing and delivering evidence-based treatments.

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

Discovering New Therapeutic Uses for Existing Molecules Initiative: In 2014, NCATS released a

funding opportunity announcement to explore new therapeutic uses for pediatric indications. Through this initiative, NCATS facilitates partnerships between pharmaceutical companies that have investigational drugs previously tested in adults and academic researchers with new therapeutic use ideas for pediatric indications. (LINK)

Rare Diseases Clinical Research Consortium (RDCRC) on ASD/ID Genetic Syndromes: The RDCRC on ASD/ID Genetic Syndromes is an NCATS initiative. NINDS, with co-funding from NIMH, NICHD, and NCATS, supports a new Rare Diseases Clinical Research Consortium (RDCRC) to study natural history, imaging biomarker discovery, and shared pathophysiology in three rare genetic disorders associated with high prevalence of autism spectrum disorder (ASD) and intellectual disability (ID): tuberous sclerosis complex (TSC), Phelan McDermid Syndrome (Shank3 mutations), and PTEN mutation patients. Research suggests that hundreds of individually rare genetic mutations may contribute to ASD and ID, but that many of the affected genes converge on common biological pathways. By focusing on three well-established causes of ASD/ID and understanding their shared mechanisms, research by this consortium may yield insights broadly relevant to other causes of ASD/ID and to potential treatments. (LINK)

New Fragile X Center Focuses on Genetic Modifiers of Disease: NINDS, with co-funding from NICHD, supports a new research center as part of the NICHD-led Centers for Collaborative Research in Fragile X (LINK). The new center aims to identify and characterize genes that modify the clinical characteristics manifested in individuals with mutations in the FMR1 gene that cause Fragile X syndrome and related disorders. In particular, center projects will use cutting-edge technologies to look for genetic modifiers of Fragile X syndrome-associated epilepsy, Fragile X-associated primary ovarian insufficiency (FXPOI), and Fragile X-associated tremor/ataxia syndrome (FXTAS). This research will advance understanding about the mechanisms underlying FMR1-associated disorders and the variability of symptoms and severity seen in affected individuals.

Excellence in Hemoglobinopathies: Hemoglobinopathies, which include sickle cell disease and the thalassemias, are the most common clinically significant diseases caused by a single gene mutation in the world. The primary objective of this new program is to accelerate high-impact multidisciplinary basic and translational research in hemoglobinopathies and to facilitate maximal collaborations among basic and translational scientists and clinical hematologists to develop innovative therapies for sickle cell disease and its complications.

Pediatric Brain Tumor Consortium: NCI approved release of a funding opportunity announcement to support continuation of the research activities of the Pediatric Brain Tumor Consortium (PBTC) for an additional 5-year funding period. The new award began in April, 2014.

Pediatric Oncology Trials:

- NCI Pediatric Oncology Branch trials that were activated in FY2014 included:
    - NCT00628498: Defibrotide for Patients with Hepatic Veno-Occlusive Disease (VOD): A Treatment IND Study
    - SARC025: Phase I Study of a Combination of the PARP Inhibitor, Niraparib and Temozolomide in Patients with Previously Treated, Incurable Ewing Sarcoma
    - SARC023: A Phase I/II Trial of Ganetespib in Combination with the mTOR Inhibitor Sirolimus for Patients with Unresectable or Metastatic Malignant Peripheral Nerve Sheath Tumors
    - NCT02153957: A Randomized Controlled Trial Evaluating an Enhanced Physical Activity Intervention to Improve Cognitive Late Effects in Children Treated with Cranial Radiation for Brain Tumors

- NCT02153931: Effects of an Internet Support Group for Parents of a Child with Neurofibromatosis Type 1
- NCT02108028: An Exploratory Study of Voicing My CHOiCES as a Tool for Advanced Care Planning in Young Adults with Metastatic, Recurrent, or Progressive Cancer

- Children's Oncology Group clinical trials that were activated in FY2014 included:
  - AALL1231: A Phase III Randomized Trial Investigating Bortezomib on a Modified Augmented BFM (ABFM) Backbone in Newly Diagnosed T-Lymphoblastic Leukemia (T-ALL) and T-Lymphoblastic Lymphoma (T-LLy)
  - ANBL1232: Utilizing Response- and Biology-Based Risk Factors to Guide Therapy in Patients with Non-High-Risk Neuroblastoma
  - ARST1321: Pazopanib Neoadjuvant Trial in Non-Rhabdomyosarcoma Soft Tissue Sarcomas (PAZNTIS): A Phase II/III Randomized Trial of Preoperative Chemoradiation or Preoperative Radiation Plus or Minus Pazopanib
  - ARET12P1: A Multi-Institutional Feasibility Study of Intra-Arterial Chemotherapy Given in the Ophthalmic Artery of Children with Retinoblastoma
  - ACNS1221: A Phase II Study for the Treatment of Non-Metastatic Nodular Desmoplastic Medulloblastoma in Children Less Than 4 Years of Age
  - ANHL12P1: A Randomized Phase II Trial of Brentuximab Vedotin or Crizotinib in Combination with Chemotherapy for Newly Diagnosed Patients with Anaplastic Large Cell Lymphoma (ALCL)

- Children's Oncology Group Phase I Consortium clinical trials that were activated in FY2014 included:
  - ADVL1315: A Phase I Study of the VEGF Receptor Tyrosine Kinase Inhibitor Axitinib in Children with Recurrent or Refractory Solid Tumors
  - ADVL1314: A Phase I Study of Eribulin Mesylate a Novel Microtubule Targeting Chemotherapeutic Agent in Children with Refractory or Recurrent Solid Tumors (Excluding CNS), Including Lymphomas
  - ADVL1411: A Phase I/II Study of BMN 673, an Oral Poly(ADP-Ribose) Polymerase Inhibitor, Plus Temozolomide in Children with Refractory or Recurrent Malignancies
  - ADVL1312: A Phase I/II Study of AZD1775 in Combination with Oral Irinotecan in Children, Adolescents, and Young Adults with Relapsed or Refractory Solid Tumors

- Pediatric Brain Tumor Consortium clinical trials that were activated in FY2014 included:
  - PBTC-042: Phase I Study of CDK 4-6 Inhibitor PD-0332991 in Children with Recurrent, Progressive or Refractory Central Nervous System Tumors
  - PBTC-039: Phase II Study of Peginterferon Alfa-2b (PEGIntron) for Pediatric Patients with Unresectable or Recurrent Craniopharyngioma
  - PBTC-037 A Phase I Study of Intratumoral/Peritumoral Herpes Simplex Virus-1 Mutant HSV1716 in Patients with Refractory or Recurrent High Grade Gliomas (HGG)

- The New Approaches to Neuroblastoma Therapy (NANT) Consortium clinical trials that were activated in FY2014 included:
  - NANT 2011- 01: Randomized Phase II Pick the Winner Study of 131I-MIBG, 131I-MIBG With Vincristine and Irinotecan, or 131I-MIBG With VOrinostat for Resistant/Relapsed Neuroblastoma

- N2012-01: Phase I Study of Difluoromethylornithine (DFMO) and Celecoxib With Cyclophosphamide/Topotecan for Patients With Relapsed or Refractory Neuroblastoma

Pediatric Suicide Prevention in Emergency Departments: (RFA-MH-14-070). In August 2014, NIMH awarded a cooperative grant (U01MH104311) to support the Emergency Department Screen for Teens at Risk for Suicide (ED-STARS) study. The researchers will develop and prospectively validate an instrument to screen for suicide risk, as well as refine algorithms capable of predicting which youth are most likely at risk for attempting suicide in the future. The capacity to classify youth as high, moderate, or low risk would be of tremendous benefit to emergency department clinicians, as it will enable efficient triaging of limited resources and identification of modifiable risk factors to target in treatment. The study will take place in 13 hospital emergency departments affiliated with the Pediatric Emergency Care Applied Research Network, and the Whiteriver PHS Indian Hospital. These emergency departments serve geographically and socio-demographically diverse groups of youth, including American Indian youth. More than 8,000 youth will be enrolled over the three-year project period.

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

Advanced Clinical Trials to test Artificial Pancreas Device Systems in Type 1 Diabetes: A program led by NIDDK will support advanced clinical trials designed to test the clinical safety and efficacy of artificial pancreas (AP) device systems in type 1 diabetes, to improving glycemic control and reducing acute and chronic complications of the disease. These trials should generate data able to satisfy safety and efficacy requirements by regulatory agencies regarding the clinical testing of AP device systems. RFA-DK-14-024

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

Limited Competition for the Continuation of the SEARCH for Diabetes in Youth Cohort Study (UC4): NIDDK plans to continue the SEARCH for Diabetes in Youth Study. The overarching goal of SEARCH is to provide population-based data on the incidence and prevalence of diabetes and its complications in U.S. youth. RFA-DK-14-508

Improving Diabetes Management in Young Children with Type 1 Diabetes (DP3): NIDDK will support research to develop, refine, and pilot test innovative strategies to improve diabetes management in young children with type 1 diabetes (5 years old and under). This program is designed to produce a well-developed and well-characterized intervention that has been demonstrated to be safe, feasible to

implement, acceptable in the target population, and, if promising, ready to be tested in a larger efficacy trial. RFA-DK-14-022

Understanding Factors in Infancy and Early Childhood (Birth to 24 months) That Influence Obesity Development (R01): This program is designed 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 children's families and/or caregivers. PAR-14-323

Healthy Behaviors in Children and Adolescents: A funding announcement, led by NINR and OBSSR, is soliciting applications for developing sustainable healthy behaviors in children and adolescents. The FOA is designed to support innovative research to identify mechanisms of influence and/or promote positive sustainable health behavior in children and youth. Topics to be addressed include: effective, sustainable processes for influencing young people to make healthy behavior choices; identification of the appropriate stage of influence for learning sustainable lifelong health behaviors; the role of technology and new media in promoting healthy behavior; identification of factors that support healthy behavior development in vulnerable populations, identification of barriers to healthy behaviors; and, identification of mechanisms and mediators that are common to the development of a range of habitual health behaviors (PA-14-177, PA-14-176).

Palliative Care: NINR's Palliative Care: Conversations Matter® campaign is designed to raise awareness of pediatric palliative care and to facilitate conversations about palliative care between health care providers, children living with a serious illness, and their families. The campaign includes video vignettes that offer advice to health care providers on how to initiate conversations about pediatric palliative care with families. It also includes customizable patient education sheets to help guide health care providers through conversations with patients and their families and to identify local resources and services. Campaign materials can be downloaded from NINR's website and are also available upon request (LINK).

*Continuation of the Hepatitis B Research Network Clinical Centers***:** The Network, including seven pediatric study sites, will promote translational research on hepatitis B focusing upon elucidating the pathogenesis and natural history and developing means of treatment and control. RFA-DK-14-506

Clinical Partnership to Conduct International Clinical Trial in Hydrocephalus: Investigators at the Children's Hospital of Boston/Harvard have partnered with CURE Children's Hospital of Uganda to investigate the optimal course of surgical treatment for post-infectious hydrocephalus in infants, likely the dominant cause of hydrocephalus in children worldwide. Funded by FIC, this is the first randomized control trial comparing the effectiveness of ETV/CPC (endoscopic third ventriculostomy and choroid plexus cauterization), a minimally invasive technique that reduces post-surgical infections, complications, and the need for follow-up care, to standard shunt placement of a device to drain the excess fluid in the brain of Ugandan infants. The CT images of brain, cerebrospinal volumes, and the neurocognitive outcomes of patients who have had shunt placement will be compared to patients who have undergone ETV/CPC at six and twelve months. The same volumetric parameters will be tested pre-operatively for their utility as a diagnostic tool for post-treatment outcomes. In the process of conducting this trial, the investigators hope to build research capacity at the Ugandan Hospital to enable its evolution into an independent hydrocephalus research and clinical trial site.

Selected Expanded Pediatric Research Efforts for FY 2014

In addition to launching new research programs, NIH ICs built on successful programs to expand research

efforts related to pediatrics. Selected highlights of expanded research efforts are given below. As with the new programs, the majority of these expanded initiatives are concerned with developing and delivering evidence-based treatments.

Sudden Death in the Young (SDY) Registry: NINDS and NHLBI have partnered with the CDC to build on their Sudden Unexpected Infant Death (SUID) Case Registry to create a registry of Sudden Death in the Young (SDY), including both sudden unexplained death in epilepsy (SUDEP) and sudden cardiac death (SCD) in individuals up to age 19 in 10 states through 2018. By collecting comprehensive data, including biospecimens in a subset of cases, the registry will help define the scope of SUDEP in young people with epilepsy, develop standards for evaluating SUDEP cases, and establish a resource for research on SUDEP causes and risk factors. The Data Coordinating Center was awarded in 2013, and in September 2014, grants were awarded to 10 states for their participation in the registry (LINK [announcement] and LINK [press release]).

Leveraging a Recovery Act Resource to Accelerate Research on Neurodevelopment: (RFA-MH-15-400). In 2009, NIMH funded two large grants to characterize and collect data on cognitive function, emotion processing, stress reactivity, and other domains that are vulnerable to neurodevelopmental aberration from a large, representative cohort of already genotyped youth, and to build a resource of data and biomaterials for future studies. The Philadelphia Neurodevelopmental Cohort (PNC), the result of this collaborative effort, has collected data on approximately 10,000 youth (ages 8-21), and including comprehensive neuroimaging on over 1,000 youth. In FY 2015, NIMH is funding efforts to develop techniques that use PNC data, either alone or in conjunction with other existing data, to advance our understanding of the multi-directional influences among genetics, brain maturation, neurocognitive function, and psychiatric symptoms across development. The initiative will stimulate broad use of the data resource, accelerate research on neurodevelopment and trajectories of risk for mental illness, advance methods for data integration, enhance diversity of analytic approaches, foster collaborations, and support early stage investigators.

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

Children's Environmental Health Centers: NIEHS is continuing and expanding the extremely successful Centers for Children's Environmental Health and Disease Prevention Research, originally created in 1998 and jointly funded by NIEHS and the Environmental Protection Agency (EPA). The guiding principle for this program is to safeguard and promote the healthy growth and development of children, protect them from potential environmental threats and improve the environments where they live, learn and play using a sustainable and holistic approach. The program includes community-based projects, applied and basic science research approaches, as well as community outreach and translation components to facilitate multi-directional communication with appropriate groups. EPA/NIEHS Children's Centers use multidisciplinary approaches to look at the consequences of exposures to environmental chemicals on the health of children and adolescents. By combining research and community-engagement, the Children's Centers provide the foundation for a broad base of research on children's environmental health. They have developed a national network of researchers, health care professionals, advocacy and parents groups to address a range of harmful environmental exposures and other factors that may affect children's health outcomes. A holistic approach includes factors that may impact a child's health and well-being including

a child's developmental stage, physiology, and activities and behaviors, and environmental agents, chemical and non-chemical stressors, economic, and societal (both family and community) factors as well. (LINK)

Neuroprotection for Preterm Infants: Extremely Low Gestational Age Neonate (ELGANs) born prior to 28 weeks of gestation are at high risk for death or moderate to severe neurodevelopmental impairment. The Preterm Epo Neuroprotection Trial (PENUT Trial) seeks to determine whether neonatal treatment with recombinant erythropoietin (Epo) will decrease early mortality and neurodevelopmental disability in ELGANs, as measured at two years of age. Epo is a widely available and affordable drug with promising neuroprotective properties, and it has been used safely in neonates to stimulate red blood cell production. The trial was first funded in FY2013, and supplemental funding from NINDS and NIDDK in FY2014 has allowed the addition of a new study aim to determine the incidence of acute kidney injury in ELGANs and whether Epo treatment affects kidney injury and development. (LINK)

FaceBase: In FY 2014, NIDCR funded a second round of cooperative agreement awards for its FaceBase consortium, bringing 10 new research projects into the group. Initiated in FY 2009, FaceBase is designed to bring together investigators from across the spectrum of craniofacial development and dysmorphology research. This will help facilitate interactions and collaborations between craniofacial researchers with very different areas of expertise and integrate the data from these projects. The integrated data will be made available to the entire research community. The new projects include using both human and model organism data to reveal the epigenetic code controlling craniofacial gene expression during embryonic development, identifying novel genes involved in human craniofacial dysmorphologies, studies about how craniofacial sutures form to better understand how this process can go awry in craniosynostosis, and development of interfaces for analyzing human genotypic data while protecting the privacy of research participants. All of these research projects are tied together through a central data management and coordination hub whose responsibilities include data annotation and curation.

Funding Opportunities in FY 2014 for Pediatric Research

In FY 2014, the NIH issued 120 Funding Opportunity Announcements (FOAs) that specifically called for applications related to pediatric research. These FOAs are listed in Table 3 of the Appendix to this report. Much of the NIH's pediatric research portfolio comes from investigator-initiated research, and a large number of funded grants are associated with funding opportunities that do not have a pediatric focus. However, the FOAs listed in Table 3 provide information about the range of areas that NIH ICs have taken steps to address in pediatric research. In FY 2014, the NIH issued FOAs in pediatric health disparities, diabetes, violence, underage drinking, asthma, nutrition, pediatric drug formulations, and autism, among other areas.

SELECTED MAJOR ONGOING NIH PROGRAMS IN PEDIATRIC RESEARCH

The NIH supports a large number of ongoing programs in pediatric research. In FY 2014, around 100 NIH-supported center or network programs supported pediatric research, and many other additional programs support pediatric research outside of center/network grant mechanisms. Many, but not all, pediatric research programs were focused exclusively on child health. For example, the NICHD's Collaborative Pediatric Critical Care Research Network links pediatric intensive care units at hospitals across the country to conduct clinical studies to improve research practice in pediatric critical care. The center/network programs supporting pediatric research at the NIH include some that are targeted to a specific disease or condition—the Autism Centers of Excellence, for example—and others, like the pediatric component of the Clinical and Translational Science Awards, that are not specific to any one condition. This report highlights selected key ongoing NIH programs supporting the pediatric research

community.

Early Development

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

Mob: The Norwegian Mother & Child Cohort (Mob) is a prospective study of approximately 100,000 pregnant women enrolled at about week 18 of pregnancy with the goal of studying in utero and early life influences on childhood health through young adulthood. Women were followed through pregnancy with questionnaires and collection of biologic samples. A father's questionnaire and blood sample were also collected during pregnancy. Health outcomes include a broad range of rare and common health outcomes in children. In this pregnancy cohort, offspring are followed through childhood. The cohort is primarily funded by the Norwegian government, with additional support from NIEHS and others. NIEHS has funded the administration of the seven year questionnaire which includes outcome and exposure questions relevant to asthma and allergies (among other health conditions). Other NIEHS projects are looking at risk factors for cerebral palsy, neurodevelopmental outcomes, and childhood obesity. *IFED:* The Infant Feeding and Early Development (IFED) is a prospective birth cohort (with a few women sampled in the 3rd trimester of pregnancy). The study enrolled 283 newborns in the Philadelphia, PA area who were exclusively fed cow milk formula (n = 111), soy formula (n = 102) or breast milk (n = 70). Since soy is a rich source of plant based estrogen-like compounds, this study was conducted with the aims of i) characterizing early estrogen dependent development in the infant, and ii) studying the effects exclusive soy feeding (i.e., high dose exposure to a suspected endocrine disruptor) on estrogen-dependent outcomes. Specific health outcomes include sex hormone metabolism and breast and internal and external genital development in infancy. (LINK)

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

Studies of Epilepsy Medications during Pregnancy: Epilepsy is one of the most common neurological disorders affecting women of childbearing age, and poor pregnancy outcomes are more common in women with epilepsy and their children. The Maternal Outcomes and Neurodevelopmental Effects of

Antiepileptic Drugs study, supported by the NINDS and the NICHD, follows over 300 women with epilepsy recruited during pregnancy to determine the effects of common epilepsy drugs (alone or in combination) on long-term neurodevelopment in children, as well as on maternal outcomes. Results from the initial funding period of this project—associating valproate exposure with adverse cognitive and other outcomes in children—are already informing clinical practice for managing epilepsy in women of childbearing age to optimize outcomes for both mother and child (U01NS038455).

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

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

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

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

(LINK)

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

Global Network for Women's and Children's Health Research: The Global Network, funded by the NICHD, supports and conducts clinical trials in resource-limited countries by pairing foreign and U.S. investigators, with the goal of evaluating low-cost, sustainable interventions to improve maternal and child health and simultaneously building local research capacity and infrastructure. Today, the Global Network focuses on community-based common protocols, conducted at three or more sites, which address major maternal and newborn health challenges, with the goal of evaluating low-cost, sustainable interventions to improve maternal and child health. This unique position allows scientists to identify gaps between science and practice and disseminate the research findings to inform local and national health policy. Each study examines either a novel evidence-based treatment or an innovative use of a proven treatment to improve the health, well-being, and survival of pregnant women and infants. (LINK)

Advancing Diagnosis and Treatment for Pediatric Diseases and Conditions

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

- Pediatric Brain Tumor Consortium (PBTC), a multidisciplinary cooperative research organization devoted to the identification of superior treatment strategies for children with primary brain tumors (recently approved for an additional 5-year funding period, starting April 2014, LINK);
- Childhood Cancer Survivor Study (CCSS) addresses the long-term effects of cancer and cancer therapy in approximately than 35,000 survivors of childhood cancer diagnosed between 1970 and 1999 and approximately 8,000 siblings of survivors (LINK);
- Pediatric Preclinical Testing Program (PPTP), which identifies new, more effective agents for treating childhood cancers and has tested more than 50 agents in the past five years with several PPTP-tested agents moving into clinical testing (LINK);
- Pediatric Oncology Branch (POB) in NCI's Center for Cancer Research, which conducts high-risk high-impact basic, translational and clinical studies (LINK);
- Children's Oncology Group (COG), part of the NCI National Clinical Trials Network, that develops and coordinates pediatric cancer clinical trials that are available at over 200 member institutions, including cancer centers throughout the United States and Canada (LINK). A component of the COG is the COG Phase 1 Consortium, which conducts Phase 1 and pilot studies to support the introduction of new anticancer agents into the pediatric setting (LINK);
- TARGET Initiative: TARGET is a public-private partnership harnessing genomics

technology to identify molecular targets to diagnose and treat childhood cancers more precisely, effectively, and safely than ever before. To date, the initiative has led to two clinical trials for new drugs against childhood tumors and identified numerous new mutations and chromosomal abnormalities associated with pediatric tumors. TARGET, part of the NCI Center for Cancer Genomics (CCG), is also collaborating with CCG's Cancer Genome Characterization Initiative as it leads genomic studies of various pediatric cancers that do not respond well to treatment: medulloblastoma, high-risk Acute Myeloid Leukemia, Burkitt Lymphoma, two types of rare kidney tumors, and gastrointestinal stromal tumor (GIST);

- Clinical Studies of Familial Cancer Syndromes: NCI leads a comprehensive program of clinical studies on rare familial cancer syndromes, several of which involve children with gene mutations that convey a very high risk of cancer at younger-than-expected ages. The Inherited Bone Marrow Failure Syndrome Cohort Study, the Li-Fraumeni Syndrome Study, and the new Pleuropulmonary Blastoma Study regularly collect information from enrolled families and assess various clinical and environmental factors and outcomes over time. NCI researchers leading these studies aim to improve the clinical understanding and management of disease, develop optimal protocols for early cancer detection and treatment, and provide a network of support to individuals and families experiencing these rare conditions. This research is aided by new genomic technologies, and has led to important genetic discoveries that affect cancer risk in families and the general population.

Pediatric Heart, Lung, and Blood Diseases:

- The Bench to Bassinet program is a pediatric cardiovascular translational research program supported by NHLBI.(LINK)
    - The Cardiovascular Development Consortium generates and disseminates comprehensive data about the molecular networks and pathways that regulate cardiovascular development using model organism systems and high-throughput technologies.
    - The Pediatric Cardiac Genomics Consortium (PCGC) identifies genetic causes of congenital heart disease (CHD) and works to relate genetic variants to clinical outcomes. The PCGC has recruited over 9000 subjects with CHD and their relatives.
    - The Pediatric Heart Network (PHN) conducts clinical research on CHD and other cardiovascular disorders. The PHN has nine main clinical sites, a data coordinating center and many auxiliary sites. (LINK) The PHN has enrolled approximately 3700 patients into observational studies.
- The Therapeutic Hypothermia after Pediatric Cardiac Arrest trials is designed to determine whether whole body cooling, in children aged 48 hours to 18 years who have had a cardiac arrest, will result in better survival and less brain injury. Trial results have shown the benefits of cooling in adults after myocardial infarction and babies with birth asphyxia. However, this is the first trial to compare body cooling (hypothermia) to normal body temperature (normothermia) in a pediatric population. Recruitment and follow-up of 295 children into the out-of-hospital arrest trial has concluded with results expected imminently. The in-hospital arrest trial continues to recruit and is expected to complete follow-up of more than 500 children in 2017.
- Transfusion of Prematures (TOP) Study: Though data are limited, it has been estimated that very low birth weight infants (<1500 g) in the U.S receive more than 250,000 total red cell transfusions/year. Despite the widespread use of transfusion in this population, there is no consensus regarding the optimal hemoglobin level at which such infants should be transfused. (Over transfusion could potentially endanger the neonate by impairing microvascular blood flow and tissue perfusion.) The NHLBI-funded Transfusion of Prematures (TOP) study is a definitive randomized clinical trial designed to resolve this issue. This trial, being performed by the NICHD Neonatal Research Network, is enrolling 1,824 extremely low birth weight

(ELBW) infants who will be randomized to receive red blood cells using either a high hemoglobin (liberal) or lower hemoglobin (restrictive) threshold. The trial will compare the two groups for the incidence death or significant neurodevelopmental impairment in survivors at 18-22 months of corrected age.

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

Mental Health and Mental Illnesses:

- Technologies have come a long way in mapping the trajectory of mental illnesses. The BrainSpan Atlas of the Developing Brain – a partnership among the Allen Institute for Brain Science, Yale University, the University of Southern California, and NIMH – has created a comprehensive three-dimensional brain blueprint. The Atlas details not only the anatomy of the brain's underlying structures, but also exactly where and when particular genes are turned on and off during mid-pregnancy – a time during fetal brain development when slight variations can have significant long-term consequences, including heightened risk for autism or schizophrenia. Knowledge of the location and time when a particular gene is turned on can help us understand how genes are disrupted in mental illnesses, providing important clues to future treatment targets and early interventions. Atlas resources are freely available to the public on the Allen Brain Atlas data portal. See: PMID: 24695229; PMID: 24267886; PMID: 23911319
- *Attention Deficit-Hyperactivity Disorder (ADHD) Heterogeneity, Mechanisms, and Risk Profile:* The diversity of biological and behavioral factors at play in the current diagnostic framework for ADHD has long hampered traditional symptom-based classification methods. NIMH-funded researchers are addressing this problem through a longitudinal research project using dimensions of temperament and a graphical analytical measure called community detection to identify subgroups within a sample of over 430 children with and without ADHD (R37MH059105, R01MH086654). The researchers have identified three novel subtypes of ADHD using this approach. Importantly, these novel subtypes were correlated with peripheral physiological measures, central nervous system measures, and clinical outcomes assessed a year later. Such biologically based subtyping methods can better predict clinical course than symptom-based classifications, are stable over time, and are more informative regarding neurobiological mechanisms of pathology. This approach is consistent with the NIMH Research Domain Criteria (RDoC) project and demonstrates how RDoC may inform clinical practices for diagnosing and treating mental illness in the future. Related research efforts will incorporate genetic variation in the subtypes (R01MH099064). (LINK).

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

Traumatic Brain Injury: Traumatic brain injury (TBI) is a leading cause of death and disability in

children and young adults. The NINDS has begun a five-year observational study that will enroll 1,000 children at about 40 treatment centers. Scientists will compare the effectiveness of six major critical care guidelines for which evidence is lacking and for which practices vary across centers. Findings from this study could improve clinical care for children with severe TBI and provide the foundation for more effective clinical trials of interventions. (LINK)

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

- NIAID's Vaccine and Treatment Evaluation Units (VTEUs) work to develop new and improved vaccines and therapies against infectious diseases and have conducted hundreds of clinical trials, many of which have contributed to vaccine licensure. Currently, the VTEUs are conducting several studies involving pediatric subjects, including a Phase II study designed to assess the safety, reactogenicity, and immunogenicity of a H3N2v influenza vaccine candidate (NCT02100436), and a Phase II study to determine the safety and efficacy of mupirocin in eradicating colonization with *Staphylococcus aureus* and preventing the occurrence of invasive and other clinically significant *Staphylococcus aureus* infections among critically ill infants in the intensive care unit (NCT01827358).
- Researchers at the NIAID Vaccine Research Center are working to develop a vaccine against respiratory syncytial virus (RSV), a leading cause of illness and hospitalization among very young children worldwide. Building on their previous report describing the atomic structure of a metastable viral surface protein, NIAID scientists used the structural information to design stabilizing mutations and produce a vaccine antigen that elicited high levels of RSV-specific neutralizing antibodies when tested in animals. Early-stage human clinical trials of the candidate vaccine are planned in the next several years.

Food Allergies: NIAID supports several major food allergy clinical trials, including trials involving pediatric populations, through the Consortium for Food Allergy Research (CoFAR; co-sponsor: NIDDK), the Asthma and Allergic Diseases Cooperative Research Centers (AADCRCs; co-sponsor: NIH ORWH), and the Immune Tolerance Network (ITN).

Asthma: The NIAID supports the Inner-City Asthma Consortium to develop clinical trials that evaluate the safety and efficacy of immune-based therapies to reduce asthma severity and prevent disease among children living in inner-city environments. A longitudinal, prospective study of a birth cohort of 606 inner-city children (the Urban Environment and Childhood Asthma study) is examining the immunologic causes of recurrent wheezing and asthma. Another clinical trial compared short-term (4 to 5 months) use of Anti Immunoglobulin E (Anti-IgE) monoclonal antibody therapy versus short-term boost of inhaled steroids to protect against asthma fall seasonal exacerbations. The trial was completed in 2014 and results will be published in 2015 [Prose Study]. The Asthma Phenotype in the Inner City (APIC) study, a year-long longitudinal study of over 700 children and adolescents with asthma, has collected information on response to treatment and clinical and immunology markers to identify different types of asthma. Results will be available in 2015. (LINK)

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

middle ear and studies that seek to develop vaccines against OM. (LINK)

Substance Abuse: The NIDA and the NIAAA continue to fund multiple programs addressing substance abuse specifically among adolescents. For example, NIAAA is developing a research-based, user-friendly decision tool and guide to help colleges and universities select appropriate strategies to meet their alcohol intervention goals. This tool and guide, the NIAAA College Alcohol Interventions Matrix (CollegeAIM), will allow users to search for strategies according to intervention level (e.g., individual, group, campus-wide, community) and evaluate factors such as effectiveness, cost, and ease of implementation. The NIAAA CollegeAIM will be released in 2015. An interactive online version of the decision tool is envisioned. NIDA continues to fund research utilizing brief combined treatments among drug- and alcohol-involved middle and high-school adolescents using cognitive therapies and interview techniques with motivational cues along with additional caregiver sessions to significantly reduce symptoms of substance use disorders.

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

Obesity in Pregnancy and Childhood: The Hyperglycemia and Adverse Pregnancy Outcome Follow-Up Study (HAPO-FUS), cosponsored by the NIDDK and the NICHD, is determining whether maternal glucose levels during pregnancy are associated with later obesity or adverse metabolic or cardiovascular status in offspring of mothers with well-characterized pregnancies, in addition to looking at maternal outcomes. Because maternal obesity and excessive weight gain during pregnancy are linked to adverse health consequences in mothers and offspring, the NIDDK, with other IC partners, started the Lifestyle Interventions for Expectant Moms (LIFE-Moms), a set of studies of lifestyle interventions in overweight and obese pregnant women designed to control gestational weight gain and improve metabolic outcomes for the women and their offspring. The NIDDK continues to support a multicenter observational study in teens, called the Teen Longitudinal Assessment of Bariatric Surgery (Teen-LABS), to collect data on the longer-term risks and benefits of bariatric surgery in obese adolescents. In addition to investigating surgical outcomes, another broader goal of Teen-LABS is to understand better the etiology, pathophysiology, and behavioral aspects of severe obesity in youth and how this condition affects human beings over time. U01DK094830

Childhood Diabetes: The NIDDK study, The Environmental Determinants of Diabetes in the Young (TEDDY), is working to determine the infectious agents, dietary factors, or other environmental conditions that trigger type 1 diabetes in genetically susceptible individuals, which could inform future efforts to prevent type 1 diabetes. This long-term study is following more than 8,000 genetically susceptible children from birth until age 15. Children enrolled in the study are developing autoimmunity and type 1 diabetes at the predicted rates. Pilot studies to address questions related to the etiology and pathogenesis of islet immunity and type 1 diabetes are under way in the following areas: diet,

microbiome, and virome; genes and gene expression; and metabolome. The Treatment Options for type 2 Diabetes in Adolescents and Youth (TODAY) study was a randomized, controlled, comparative effectiveness trial with three treatment arms (metformin alone, metformin with lifestyle intervention, or metformin with rosiglitazone). NIDDK will continue to follow the TODAY cohort to track the progression of type 2 diabetes and related comorbidities and complications as the participants transition to young adulthood. This research is critical for preventing a potential public health crisis since the TODAY data suggest that individuals who develop type 2 diabetes during adolescence may be at risk for developing vascular complications, including cardiovascular disease, in the prime of their lives. (LINK).
HIV/AIDS: The NICHD, the NIAID, and other ICs support and conduct domestic and international research related to HIV infection and its complications in infants, children, and adolescents. For example, the NICHD and other ICs support the Adolescent Medicine Trials Network for HIV/AIDS Interventions (ATN), the only national, multicenter research network devoted to the health and well-being of HIV-infected and at-risk adolescents and young adults. As the HIV epidemic has evolved in the United States and globally, the NIH has ensured that research reflects these changes and addresses important research opportunities and gaps as they arise. The NICHD and the NIAID address research gaps related to many HIV-associated co-infections—such as tuberculosis, hepatitis, and malaria—in children and pregnant women. The NIAID and the NICHD support studies, including the Promoting Maternal and Infant Survival Everywhere (PROMISE) study, to determine the optimal antiretroviral regimen for reducing mother-to-child HIV transmission during pregnancy, labor and delivery, and breastfeeding (NCT01061151). The International Maternal Pediatric Adolescent AIDS Clinical Trial Network (IMPAACT) includes both a domestic research agenda and an international research agenda. The domestic research agenda includes a focus on evaluating the pharmacokinetics, safety, optimal dosing, and long-term complications of new antiretroviral (ARV) therapies for HIV/AIDS in pediatric and adolescent populations. The international research agenda includes a focus on the prevention of mother-to-child HIV transmissions and reduction of maternal and infant HIV/AIDS morbidity and mortality through studies such as PROMISE. The findings from the PROMISE study support the recommendation by the World Health Organization to provide a three-drug regimen to all pregnant women with HIV infection. (LINK); (LINK)

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

Down Syndrome Registry: The CDC estimates that there are about 250,000 people living with Down syndrome in the United States. The NIH Down Syndrome Working Group has partnered with public and private organizations to create a centralized, secure national resource, DS-Connect™, for storing and sharing health information about Down syndrome. The registry allows people with Down syndrome and their family members, researchers, and parent and support groups to share information and health history in a safe, confidential, online database. Users can create and edit their customizable online profiles, share their profiles with Down syndrome investigators and biorepositories, and view information about medical research and Down syndrome-related events. DS-Connect™ also provides access to general information about Down syndrome, as well as aggregate, de-identified data based on user responses to survey questions. People with Down syndrome and their families create password-protected profiles after

providing online informed consent to participate in the registry. If registered users give permission to be contacted about a research study, the registry coordinator may invite eligible users to contact the clinician or researcher directly to sign up for the study or trial. The registry complies with all regulations and laws governing privacy, personally identifiable information, and health data and has been created on a Federal Information Security Management Act (FISMA) moderate platform to ensure that the health and demographic information is protected. Originally launched in September 2013, a professional portal to support investigators who request access to the de-identified data in the registry was launched in October 2014. (LINK)

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

Collaborative Pediatric Critical Care Research Network (CPCCRN): The technology, therapeutic agents, and strategies for treatment and life support in childhood critical illness and injury have evolved rapidly during the past 2 decades. Children with illnesses and injuries who were once thought to be beyond the reach of modern medicine now survive in large numbers in multidisciplinary pediatric intensive care units (PICUs). Although mortality in U.S. PICUs has fallen precipitously, survivors of childhood critical illness and injury remain at risk for morbidity and disability. Pediatric critical care practice has evolved rapidly, but most of this development has occurred without the benefit of descriptive studies that might enable translational understanding of the pathophysiology of life-threatening illnesses and injuries in childhood. Focused on critically ill infants and children, the NICHD's CPCCRN aims to reduce morbidity and mortality from pediatric critical illness and injury by enhancing knowledge of the scientific bases of pediatric critical care practice. The CPCCRN conducts a wide range of research activities, reaching across traditional disciplinary lines and transcending customary thinking and organizational structures to achieve innovative research in the care of critically ill and injured children. (LINK)

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

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

investigations of allergic diseases, pediatric-onset mastocytosis, and the immunology and pathogenesis of severe malaria in children. (LINK)

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

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

Children with Cleft Palate: Individuals with cleft lip and/or palate (CLP) have multiple special needs including speech and language problems, facial differences, atypical dental development, malocclusion, learning disabilities, chronic ear infections, and associated psychosocial sequelae. The goal of one NIDCR-supported study is to improve the understanding of quality of life (QoL) and related issues among youth with CLP who are between 8 and 18 years old and who are undergoing secondary corrective surgery. This study may provide insight into how effective cleft habilitation is at improving oral health-related QoL and overall QoL, and it may identify subgroups where targeted interventions are most needed. Another NIDCR study explores provider and family communication as they decide on treatment options for children with CLP. R01DE018729

Rare Diseases Clinical Research Network (RDCRN): Led by the National Center for Advancing Translational Sciences (NCATS) and cofunded by eight other ICs, the Rare Diseases Clinical Research Network conducts collaborative clinical research in rare diseases, including longitudinal studies of individuals with rare diseases, clinical studies, and/or clinical trials. The RDCRN is comprised of 22 distinctive Rare Diseases Clinical Research Consortia (RDCRC) and a central Data Management and Coordinating Center that are working in concert to improve availability of rare disease information, treatment, clinical studies, and general awareness for both patients and the medical community. The RDCRN also aims to provide up-to-date information for patients and to assist in connecting patients with advocacy groups, expert doctors, and clinical research opportunities. Many of the rare diseases studied under this network occur primarily or frequently in children, including primary immune deficiency diseases, urea cycle disorders, mitochondrial diseases, lysosomal diseases, and Angelman, Rett, and Prader-Willi syndromes. (LINK)

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

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

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 (LINK).

Childhood Arthritis and Rheumatology Research Alliance (CARRA) Registry: CARRA, formed in 2001, is an organization of pediatric rheumatologists committed to advancing the health and quality of life of children with rheumatic diseases and arthritis who have joined together to answer critical research questions to elucidate the causes of rheumatic diseases in children, determine the best treatments, and track long-term outcomes. The CARRAnet registry was established with support from the American Recovery and Reinvestment Act as part of CARRA to create a unified, scalable informatics infrastructure and to engage families, patients, and communities in addressing critical clinical research questions. The NIAMS supports a number of clinical trials that leverage the CARRA infrastructure. For example, the Atherosclerosis Prevention in Pediatric Lupus Erythematosus (APPLE) study, which tested the use of statins to prevent atherosclerosis in pediatric lupus patients, was conducted within CARRA.

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

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

particular focus on enhancing involvement of underrepresented groups in scientific careers. (LINK); (LINK)

Cross-Cutting Areas of Pediatric Research

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

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

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

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

The RPDP program is designed to establish predictive nonclinical models, including animal studies; cell-, tissue-, and organ-based systems; computational and systems modeling; and integration of signals and information from multiple systems to evaluate response- and age-specific toxicity, particularly neurologic

and behavioral effects. The program performs nonclinical and clinical research to understand mechanisms of age- and developmentally related changes in metabolism and response to medicinal products, and it develops outcome and assessment measures that are age-appropriate to determine response or toxicity. The FDA is working closely with the NIH to maximize the success of this important program. (LINK); (LINK)

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

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 FY2014, fifteen Institutes admitted 3,322 pediatric patients to the Clinical Center to 248 protocols that included children who were seen in 12,172 pediatric out-patient visits on 9,893 out-patient days and 689 inpatient admissions for 6,515 pediatric in-patient days**.** In comparison to FY2013, this was a 19% increase in inpatient admissions and a 19% increase in inpatient days. Inpatient admissions were the highest in four years and pediatric inpatient days were the highest ever recorded at the Clinical Center. The proportion of Clinical Center activity that involved children increased from 10% to 12% of all Clinical Center inpatient activity and increased from 11% to 12 % of all Clinical Center outpatient visits.

Natural history studies, often in patients with rare diseases, make up about half of the pediatric clinical research conducted at the Clinical Center. Understanding the basis for rare diseases often leads to new approaches to common problems. Most of the other clinical research studies are the early Phase 1 and 2 trials that are the first studies of new treatments and therapies, with 1,611 clinical research studies, 35 percent in children.

A comprehensive pediatric program is part of the state-of-the-art Clinical Research Center that opened April 2, 2005 at the NIH. The Clinical Research Center has one unified pediatric multi-Institute unit with 22 beds and 14 day hospital stations, one 6-bed pediatric behavioral health inpatient unit plus room for 2 day patients, and a multi-Institute pediatric outpatient clinic with 21 patient care rooms. The size of the pediatric area was determined based on protocol activity, and trends toward implementing new protocols in an ambulatory setting.

To accommodate the growing number of pediatric intramural research subjects, the Children's Inn at the NIH completed its first expansion in FY2004. Now almost doubled in size, the family-centered residence can care for 65 families every night. In FY2014, 1501 families stayed 13,347 nights at The Inn and The Woodmont House, a transitional home which was opened in FY2011 to accommodate up to 7 families requiring longer stays. This represents a 2.7% increase in nights accommodated. Since its opening in 1990, over 12,000 families have stayed at The Inn and The Woodmont House. Children and families have come from all 50 states and 84 countries.

Clinical and Translational Science Awards: The NCATS Clinical and Translational Science Award (CTSA) program offers academic homes for translational sciences and supporting research resources needed by local and national research communities to improve the quality and efficiency of all phases of translational research, including clinical trials. CTSA centers also support the training of clinical and

translational scientists and the development of all disciplines needed for a robust workforce for translational research. The CTSA program includes a special provision to support pediatric research, allowing a pediatric principal investigator to be appointed within a single CTSA with a separate budget and infrastructure for child health clinical research. Eight CTSA centers are headed by principal investigators who are also pediatricians, and 51 centers included children's hospitals conducting pediatric research as partners in their CTSA applications. 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). (LINK)

Research Training, Career Development, and Loan Repayment

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

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

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

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

Pediatric Critical Care and Trauma Scientist Development Program: The NICHD Pediatric Critical Care and Trauma Scientist Development Program is a national faculty training program that develops successful pediatric critical care and pediatric trauma physician scientists. The goal of the program is to increase the number of highly trained, successfully funded, and sustainable pediatric critical care and pediatric trauma physician scientists who will conduct research to enhance the scientific understanding,

clinical management, and long-term outcome of critical illness and trauma in children. (LINK)

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

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

APPENDIX

Table 1: All NIH Pediatric Research, FY 2014

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

	Fiscal Year 2014
FIC	$5,921,856
NCATS	$42,118,945
NCCAM	$4,351,234
NCI	$322,311,359
NEI	$60,219,641
NHGRI	$60,551,468
NHLBI	$335,058,727
NIA	$17,413,204
NIAAA	$114,148,846
NIAID	$283,141,623
NIAMS	$61,096,730
NIBIB	$9,231,068
NICHD	$682,846,759
NIDA	$164,028,222
NIDCD	$72,290,576
NIDCR	$84,173,364
NIDDK	$199,048,481
NIEHS	$115,454,441
NIGMS	$70,268,465
NIMH	$368,497,916
NIMHD	$35,520,981
NINDS	$188,240,435
NINR	$24,391,618
NLM	$966,862
OD	$99,437,448
Common Fund	$24,438,378
Type 1 Diabetes	$40,812,130
NIH Total	$3,485,980,777

Table 2: Pediatric Research Initiative, FY 2014

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

	Fiscal Year 2014
FIC	$45,000
NCATS	$3,143,001
NCCAM	$24,750
NCI	$86,480,105
NEI	$123,997
NHGRI	$97,300
NHLBI	$12,273,578
NIA	$12,526,281
NIAAA	$7,522,093
NIAID	$29,565,544
NIAMS	$2,850,384
NIBIB	$200,000
NICHD	$29,475,514
NIDA	$25,661,181
NIDCD	$16,033
NIDCR	$25,446,382
NIDDK	$24,469,441
NIEHS	$16,116,002
NIMH	$33,504,807
NINDS	$5,313,183
NLM	$813,893
OD	$3,279,738
Common Fund	$2,927,628
Type 1 Diabetes	$21,506,110
NIH Total	$343,381,945

Table 3: NIH Funding Opportunity Announcements That Solicited Applications for Pediatric Research, FY 2014

Announcement Number	Issuing Organization	Activity Code	Title
PAR-14-332	FIC	R01	Global Brain and Nervous System Disorders Research Across the Lifespan (R01)
PAR-14-331	FIC	R21	Global Brain and Nervous System Disorders Research Across the Lifespan (R21)
PAR-14-028	FIC	R21	Mobile Health: Technology and Outcomes in Low and Middle Income Countries (R21)
PAR-14-294	NCCAM	R01	Arts-Based Approaches in Palliative Care for Symptom Management (R01)
RFA-CA-13-502	NCI	UM1	Limited Competition: Pediatric Brain Tumor Consortium (UM1)
RFA-CA-14-018	NCI	U01	Pediatric Preclinical Testing Consortium: Research Programs (U01)
PA-14-277	NHGRI	R03	Ethical, Legal, and Social Implications (ELSI) of Genomic Research Small Research Grant Program (R03)
PA-14-276	NHGRI	R01	Ethical, Legal, and Social Implications (ELSI) of Genomic Research Regular Research Program (R01)
PA-14-278	NHGRI	R21	Ethical, Legal, and Social Implications (ELSI) of Genomic Research Exploratory/Developmental Research Program (R21)
RFA-HL-14-026	NHLBI	R43/R44	Development of a Microfluidic Platform for Blood Testing in Neonatal and Pediatric Patients SBIR (R43/R44)
RFA-HL-14-023	NHLBI	R01	Clinical Research in the Prevention, Diagnosis, and Treatment of HIV-Related Heart, Lung, and Blood (HLB) Diseases in Adults and Children (R01)
RFA-HL-14-024	NHLBI	R01	Basic Research in the Pathogenesis of HIV-Related Heart, Lung, and Blood (HLB) Diseases in Adults and Children (R01)
RFA-HL-14-029	NHLBI	R21	Basic Research in the Pathogenesis of HIV-Related Heart, Lung, and Blood (HLB) Diseases in Adults and Children (R21)
PAR-14-022	NIA	R03	Juvenile Protective Factors and Their Effects on Aging (R03)
PAR-14-338	NIAAA	R01	Secondary Analyses of Existing Alcohol Epidemiology Data (R01)
PA-14-337	NIAAA	R03	Secondary Analyses of Existing Alcohol Epidemiology Data (R03)
PA-14-336	NIAAA	R21	Secondary Analyses of Existing Alcohol Epidemiology Data (R21)
PAR-14-268	NIAAA	U01	International Research Collaboration on Alcohol and Alcoholism (U01)

Announcement Number	Issuing Organization	Activity Code	Title
PA-14-190	NIAAA	R01	Epidemiology and Prevention in Alcohol Research (R01)
PA-14-189	NIAAA	R03	Epidemiology and Prevention in Alcohol Research (R03)
PA-14-188	NIAAA	R21	Epidemiology and Prevention in Alcohol Research (R21)
PAR-14-255	NIAID	R01	Multidisciplinary Studies of HIV and Viral Hepatitis Co-Infection (R01)
PAR-14-254	NIAID	R21	Multidisciplinary Studies of HIV and Viral Hepatitis Co-Infection (R21)
PAR-14-248	NIAID	R21	Basic Research on HIV Persistence (R21)
PAR-14-247	NIAID	R01	Basic Research on HIV Persistence (R01)
PAR-13-390	NIBIB	R03	Indo-US Collaborative Program on Affordable Medical Devices (R03)
PA-14-349	NICHD	R21	Studies in Neonatal and Pediatric Resuscitation (R21)
PA-14-351	NICHD	R03	Studies in Neonatal and Pediatric Resuscitation (R03)
PA-14-350	NICHD	R01	Studies in Neonatal and Pediatric Resuscitation (R01)
PAR-14-324	NICHD	R24	NICHD Consortium for Research on Pediatric Trauma and Injury Prevention (R24)
PAR-14-272	NICHD	R01	Medically Assisted Reproduction: Investigation of Mechanisms Underlying the Adverse Outcomes and Development of New and Improved Methods to Overcome the Adverse Outcomes (R01)
PAR-14-273	NICHD	R21	Medically Assisted Reproduction: Investigation of Mechanisms Underlying the Adverse Outcomes and Development of New and Improved Methods to Overcome the Adverse Outcomes (R21)
PA-14-312	NICHD	R01	Patient Safety in the Context of Perinatal, Neonatal, and Pediatric Care (R01)
PA-14-311	NICHD	R21	Patient Safety in the Context of Perinatal, Neonatal, and Pediatric Care (R21)
PA-14-313	NICHD	R03	Patient Safety in the Context of Perinatal, Neonatal, and Pediatric Care (R03)
PAR-14-269	NICHD	R21	Innovative Therapies and Tools for Screenable Disorders in Newborns (R21)
PAR-14-270	NICHD	R01	Innovative Therapies and Tools for Screenable Disorders in Newborns (R01)
PAR-14-271	NICHD	R03	Innovative Therapies and Tools for Screenable Disorders in Newborns (R03)
PAR-14-274	NICHD	R01	Pharmacogenetics, Pharmacoepigenetics and Personalized Medicine in Children (R01)
PAR-14-264	NICHD	R01	Global "Omics" Approaches Targeting Adverse Pregnancy and Neonatal Outcomes Utilizing Existing Cohorts (R01)

Announcement Number	Issuing Organization	Activity Code	Title
PA-14-056	NICHD	R01	Genetic Susceptibility & Variability of Human Structural Birth Defects (R01)
PAR-13-389	NICHD	R01	Discovery of Molecular Targets for Pregnancy-Related/Induced Diseases and Development of Therapeutics to Prevent/Treat These Diseases (R01)
PA-14-164	NIDA	R03	Effects of Cannabis Use and Cannabinoids on the Developing Brain (R03)
PA-14-163	NIDA	R01	Effects of Cannabis Use and Cannabinoids on the Developing Brain (R01)
PA-14-162	NIDA	R21	Effects of Cannabis Use and Cannabinoids on the Developing Brain (R21)
PA-14-061	NIDA	R01	Substance Use and Abuse, Risky Decision Making and HIV/AIDS (R01)
PA-14-062	NIDA	R21	Substance Use and Abuse, Risky Decision Making and HIV/AIDS (R21)
PA-14-063	NIDA	R03	Substance Use and Abuse, Risky Decision Making and HIV/AIDS (R03)
PA-14-037	NIDA	R03	Women & Sex/Gender Differences in Drug and Alcohol Abuse/Dependence (R03)
PA-14-036	NIDA	R21	Women & Sex/Gender Differences in Drug and Alcohol Abuse/Dependence (R21)
PA-14-038	NIDA	R01	Women & Sex/Gender Differences in Drug and Alcohol Abuse/Dependence (R01)
PA-14-026	NIDA	R01	Basic Mechanisms of Brain Development for Substance Use and Dependence (R01)
PAS-14-020	NIDA	R01	Public Health Impact of the Changing Policy/Legal Environment for Marijuana (R01)
PAR-14-104	NIDA	R03	Synthetic Psychoactive Drugs and Strategic Approaches to Counteract Their Deleterious Effects (R03)
PAR-14-105	NIDA	R21	Synthetic Psychoactive Drugs and Strategic Approaches to Counteract Their Deleterious Effects (R21)
PAR-14-106	NIDA	R01	Synthetic Psychoactive Drugs and Strategic Approaches to Counteract Their Deleterious Effects (R01)
PA-14-084	NIDA	R01	Neuroimmune Signaling in Substance Use Disorders (R01)
PA-14-083	NIDA	R21	Neuroimmune Signaling and Function in Substance Use Disorders (R21)
RFA-DE-15-006	NIDCR	UH2/UH3	Multidisciplinary and Collaborative Research Consortium to Reduce Oral Health Disparities in Children: A Multilevel Approach (UH2/UH3)
RFA-DE-15-007	NIDCR	U01	Multidisciplinary and Collaborative Research Consortium to Reduce Oral Health Disparities in Children: Data Coordinating Center (U01)

Announcement Number	Issuing Organization	Activity Code	Title
PAR-14-143	NIDCR	R01	Establishing Behavioral and Social Measures for Causal Pathway Research in Dental, Oral and Craniofacial Health (R01)
PAR-14-144	NIDCR	R21	Establishing Behavioral and Social Measures for Causal Pathway Research in Dental, Oral and Craniofacial Health (R21)
PAR-13-379	NIDCR	R01	Establishing Outcome Measures for Clinical Studies of Oral and Craniofacial Diseases and Conditions (R01)
PAR-13-380	NIDCR	R21	Establishing Outcome Measures for Clinical Studies of Oral and Craniofacial Diseases and Conditions (R21)
RFA-DK-14-021	NIDDK	UC4	Consortium on Beta-cell Death and Survival (HIRN-CBDS) (UC4)
RFA-DK-14-017	NIDDK	DP3	Type 1 Diabetes Complications IMPACT Award (DP3)
PAR-14-323	NIDDK	R01	Understanding Factors in Infancy and Early Childhood (Birth to 24 months) That Influence Obesity Development (R01)
RFA-DK-14-024	NIDDK	UC4	Advanced Clinical Trials to test Artificial Pancreas Device Systems in Type 1 Diabetes (UC4)
RFA-DK-14-022	NIDDK	DP3	Improving Diabetes Management in Young Children with Type 1 Diabetes (DP3)
PA-14-059	NIDDK	R41, R42	Small Business Technology Transfer Research (STTR) to Develop New Diagnostic, Monitoring and Therapeutics Technologies for the Complications of Type 1 Diabetes (T1D) [STTR (R41/R42)]
PA-14-058	NIDDK	R43, R44	Small Business Innovation Research (SBIR) to Develop New Diagnostic, Monitoring and Therapeutics Technologies for the Complications of Type 1 Diabetes (T1D) (SBIR (R43/R44)

Announcement Number	Issuing Organization	Activity Code	Title
RFA-DK-14-502	NIDDK	U01	Limited Competition: Continuation of the Treatment Options for Type 2 Diabetes in Adolescents and Youth (TODAY) Study (U01)
RFA-DK-14-508	NIDDK	UC4	Limited Competition for the Continuation of the SEARCH for Diabetes in Youth Cohort Study (UC4)
RFA-DK-14-507	NIDDK	UC4	Limited Competition: Data Coordinating Center for Type 1 Diabetes TrialNet (UC4)
RFA-DK-14-016	NIDDK	U01	Type 1 Diabetes TrialNet Clinical Centers (U01)
RFA-DK-14-505	NIDDK	UC4	Limited Competition: Data Coordinating Center for The Environmental Determinants of Diabetes in the Young (TEDDY) Study (UC4)
PAR-14-258	NIDDK	DP3	Research Using Subjects From Selected Type 1 Diabetes Clinical Studies (Living Biobank) (DP3)
PAR-14-064	NIDDK	DP3	Research Using Subjects From Selected Type 1 Diabetes Clinical Studies (Living Biobank) (DP3)
PAR-14-257	NIDDK	DP3	Research Using Biosamples from Selected Type 1 Diabetes Clinical Studies (DP3)
PAR-14-065	NIDDK	DP3	Research Using Biosamples from Selected Type 1 Diabetes Clinical Studies (DP3)
RFA-DK-14-014	NIDDK	DP3	Diabetes Impact Award-Closed Loop Technologies: Clinical, Physiological and Behavioral Approaches to Improve Type 1 Diabetes Outcomes (DP3)
RFA-DK-13-028	NIDDK	R43/R44	Small Business Innovation Research to Develop New Therapeutics and Monitoring Technologies for Type 1 Diabetes (T1D): Towards an Artificial Pancreas (SBIR) (R43/R44)
RFA-DK-14-015	NIDDK	DP3	Diabetes Impact Award-Closed Loop Technologies: Development and Integration of Novel Components for an Automated Artificial Pancreas System (DP3)
PAR-14-202	NIEHS	R21	Environmental Contributors to Autism Spectrum Disorders (R21)
PAR-14-203	NIEHS	R01	Environmental Contributors to Autism Spectrum Disorders (R01)

Announcement Number	Issuing Organization	Activity Code	Title
RFA_ES-12-001	NIEHS	P50	Children's Environmental Health and Disease Research Centers (P50)
PAR-13-374	NIGMS	R01	Modeling Social Behavior (R01)
PA-14-127	NIMH	R01	Targeted Basic Behavioral and Social Science and Intervention Development for HIV Prevention and Care (R01)
PA-14-128	NIMH	R21	Targeted Basic Behavioral and Social Science and Intervention Development for HIV Prevention and Care (R21)
PA-14-134	NIMH	R21	Advancing Structural Level Interventions Through Enhanced Understanding of Social Determinants in HIV Prevention and Care (R21)
PA-14-133	NIMH	R01	Advancing Structural Level Interventions Through Enhanced Understanding of Social Determinants in HIV Prevention and Care (R01)
PA-14-131	NIMH	R01	Improving Delivery of HIV Prevention and Treatment through Implementation Science and Translational Research (R01)
PAR-14-283	NIMH	R21	High Throughput Screening (HTS) to Discover Chemical Probes (R21)
PAR-14-284	NIMH	R01	High Throughput Screening (HTS) to Discover Chemical Probes (R01)
PAR-14-279	NIMH	R01	Discovery of in vivo Chemical Probes (R01)
RFA-MH-15-340	NIMH	R01	Confirmatory Efficacy Clinical Trials of Non-Pharmacological Interventions for Mental Disorders (R01)
PA-14-196	NIMH	R41/R42	Complex Technologies and Therapeutics Development for Mental Health Research and Practice (R41/R42)
PA-14-197	NIMH	R43/R44	Complex Technologies and Therapeutics Development for Mental Health Research and Practice (R43/R44)
PAR-14-107	NIMH	U01	First in Human and Early Stage Clinical Trials of Novel Investigational Drugs for Psychiatric Disorders (U01)
RFA-MH-15-300	NIMH	R21/R33	Exploratory Clinical Trials of Novel Interventions for Mental Disorders (R21/R33)
RFA-MH-15-310	NIMH	R33	Exploratory Clinical Trials of Novel Interventions for Mental Disorders (R33)
PAR-14-120	NIMH	P50	Silvio O. Conte Centers for Basic or Translational Mental Health Research (P50)
RFA-MH-14-050	NIMH	R01	Dimensional Approaches to Research Classification in Psychiatric Disorders (R01)
PA-14-068	NINDS	R01	Neurobiology of Migraine (R01)
PA-14-069	NINDS	R21	Neurobiology of Migraine (R21)
PA-14-345	NINR	R15	Self-Management for Health in Chronic Conditions (R15)

Announcement Number	Issuing Organization	Activity Code	Title
PA-14-343	NINR	R21	Self-Management for Health in Chronic Conditions (R21)
PA-14-344	NINR	R01	Self-Management for Health in Chronic Conditions (R01)
PA-14-316	NINR	R01	Obesity and Asthma: Awareness and Self-Management (R01)
PA-14-176	NINR	R21	Healthy Habits: Timing for Developing Sustainable Healthy Behaviors in Children and Adolescents (R21)
PA-14-177	NINR	R01	Healthy Habits: Timing for Developing Sustainable Healthy Behaviors in Children and Adolescents (R01)
PA-14-033	NINR	R01	Reducing Health Disparities Among Minority and Underserved Children (R01)
PA-14-034	NINR	R21	Reducing Health Disparities Among Minority and Underserved Children (R21)
PA-14-030	NINR	R21	Chronic Illness Self-Management in Children and Adolescents (R21)
PA-14-029	NINR	R01	Chronic Illness Self-Management in Children and Adolescents (R01)
PAR-14-315	ODP	R01	Testing Interventions for Health-Enhancing Physical Activity (R01)
PAR-14-321	ODP	R21/R33	Developing Interventions for Health-Enhancing Physical Activity (R21/R33)
PAR-14-326	ORIP	R41/R42	Serious STEM Games for Pre-College and Informal Science Education Audiences (STTR) (R41/R42)
PAR-14-325	ORIP	R43/R44	Serious STEM Games for Pre-College and Informal Science Education Audiences (SBIR) (R43/R44)

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

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