

Ensuring ARPA-H Enables a Focus on Child and Adolescent Health & Lifespan Research

SUPPORTED BY: Academic Pediatric Association, American Academy of Allergy, Asthma, and Immunology; American Academy of Pediatrics, American College of Allergy, Asthma and Immunology; American Pediatric Society, Association of Medical School Department Chairs, Coalition for Pediatric Medical Research; Council of Pediatrics Subspecialties; North American Society for Pediatric Gastroenterology, Hepatology & Nutrition; Pediatric Endocrine Society; Pediatric Policy Council, Society for Adolescent Health and Medicine; Society for Developmental and Behavioral Pediatrics; Society for Pediatric Dermatology, Society for Pediatric Research

Overview

As Congress and the Biden Administration work to establish the Advanced Research Projects Agency – Health (ARPA-H), this agency must ensure that its structure supports research focused on child and adolescent health and health across the lifespan. Legislators have been crafting ARPA-H so it will not be focused on or limited to specific diseases or conditions and will be undeterred by the possibility of failure. ARPA-H could prevent or change the trajectory of multiple diseases if it focuses on research early in the lifespan, as research demonstrates that many conditions have their origins early in the life course. Understanding the trajectories of diseases in childhood requires intentional focus across the life course.

This white paper:

- 1 Explores the structural challenges to child and adolescent health research
- 2 Describes the benefits of child and adolescent health lifespan research
- 3 Identifies opportunities for studies early in the life course
- 4 Offers recommendations for policymakers and the new agency to consider

ARPA-H Goals and Intent

The overarching goals for establishing ARPA-H are to create an entity that will “foster the development of new, breakthrough capabilities, technologies, systems and platforms to accelerate innovations in health and medicine that are not being met by federal programs or private citizens” and to “promote high-risk, high-reward innovation for the development and translation of transformative health technologies.” (*ARPA-H Act*: H.R. 5585). The authorizing legislation does not focus the agency’s work on any specific diseases or conditions or areas of research, but instead empowers the agency’s director and leadership team to make those decisions.

Limited Inclusion of Children and Adolescents in Large Research Programs

Previous federal research programs have excluded or severely limited inclusion of children and adolescents, and they have neglected to explore developmental origins of health and disease. Examples of past challenges include:

- **Clinical and Science Translation Awards (CTSA) Program:** The CTSA program originally did not allow for a pediatric-focused co-principal investigator (PI) or for a children’s hospital application. Subsequent legislation changed this; however, funding and resources have historically been oriented toward adult-focused research activities even when awards have a pediatric Co-PI.
- **All of Us Precision Medicine Initiative:** More than four years after the start of nationwide enrollment, the program has yet to move forward in recruiting children into the program. This is a significant limitation to the overall program and its ability to advance precision medicine.
- **National Cancer Institute Designated Centers:** Of the 71 NCI designated cancer centers, there is only one free-standing pediatric facility, and most centers focus on adults.
- **Cancer Moonshot Shortcomings:** While revised Cancer Moonshot program guidance has supported some pediatric-focused grants, the Moonshot has traditionally not adequately included children’s hospitals and pediatric cancer research as a central research priority (ex: the February 2022 White House fact sheet did not mention children or pediatrics).
- **Slower Advancement of Medical Care for Children:** Advancements in medical care are slower in children than in adults. For example, while acute respiratory distress syndrome was first described in adults in 1967, a definition of pediatric acute respiratory distress syndrome was not adopted until 2015. Because of limited research related to drug safety and effectiveness in children, off-label medication use is common in pediatrics, especially in neonates and younger age groups. Clinical trials and approval of COVID-19 mRNA vaccines in children substantially lagged that of adults.
- **Underinvestment:** The overall percentage of NIH funding that goes to children is not proportionate to the population. In 2021, only 12-14% of NIH dollars were allocated towards projects that were wholly or in part focused on developmental or pediatric conditions. Underscoring this misalignment of funding priorities, children comprise 20% of the U.S. population and 50% of the world-wide population.
- **NIH Award Challenges:** Only institutions of higher education are eligible for some NIH awards, creating challenges for freestanding children’s hospitals in applying. Conversely, some NIH awards are limited to one application per institution resulting in limited opportunity for pediatrics since most institutions are adult-oriented.

In summary, pediatric research interests have faced barriers to inclusion in research initiatives which represents a missed opportunity to improve health across the life course. Failing to recognize this history – and plan accordingly in ARPA-H’s implementation – could lead to similar impediments within ARPA-H.

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Importance of Including Child/Adolescent Health Research

Research demonstrates that many adult-onset health issues are rooted in childhood and adolescence. Research focused on improving early health, education, and well-being of children and adolescents has a life-long positive impact. Nevertheless, absent an adequate commitment to pediatric research, disease prevention or early interventions are limited. Chronic mental and physical health conditions engrained in childhood and adolescence have long-term economic ramifications due to the impact on educational achievements, emotional and physical health, and cost of medical care. As we know, the economic future of the U.S. lies in the health and education of children.

The child and adolescent population is increasingly diverse (in 2020, 50% of children were people of color), and health disparities begin in childhood. Similar to other “natural disasters,” the COVID-19 pandemic uncovered severe health disparities by race/ethnicity and socioeconomic status in rates of infection, hospitalization, and death. Addressing health equity must start early in the life course.

Rare diseases are overrepresented in the pediatric population and as they age, impact their productivity as adults. Unfortunately, market disincentives make it harder for research to focus on rare diseases.

Importantly, infants and children are not small adults. Body size, physiology and metabolism differ greatly and change throughout the lifespan. Currently, infants and children who survive catastrophic medical conditions bear the lifelong sequelae of therapy and interventions; examples include delayed cognitive/cardiovascular effects of therapy for childhood cancer and organ damage from chronic diseases (i.e. juvenile diabetes or sickle cell anemia). Therapeutic and technological discoveries in children must include innovative interventions to eliminate disease and improve their entire lifespan.

There are numerous examples of pediatric research positively impacting adult health, including:

- Surfactant replacement therapy for prematurely born infants has permitted the routine survival of infants born at less than 32 weeks gestation and improved life-long lung health.
- Tuberculosis screening strategies developed in children have been applied in adults.
- Clinical trials in children using CAR-T cells to treat leukemia provided safety data and proof of efficacy that justified the development of CAR-T cells to treat adult malignancies.
- Childhood and adolescent vaccines preventing morbidity and mortality in adulthood.

Potential Child and Adolescent Focused Projects for APRA-H to Consider:

Technology-focused investments

- Development of high throughput in utero or newborn screening with digital genomics.
- Development of a microneedle patch platform to deliver all childhood immunizations.
- Development of novel, non-invasive screening tools for diseases such as focused breath metabolome analysis for rapid diagnosis of pulmonary disorders.
- Regenerative and cell-based therapy approaches to curing Type I diabetes mellitus, sickle cell disease, and other diseases using stem cells and gene editing.
- Rapid development of technology platforms for molecular treatments, including gene editing, gene therapy and cellular therapies informed by increasing understanding of the molecular aspects to human disease.
- Development of artificial intelligence programs in pediatrics to reduce biases, enhance equity, and predict poor outcomes (e.g. predict the trajectory of anxiety, depression, and suicide).
- Use of virtual and semi-automated approaches to screen for and address mental health disorders, suicide risk, obesity, addiction, and substance abuse.
- Assess the impact of social media on child health and develop strategies to promote healthy social connections and coaching strategies with technology.

Health Outcomes/Disparities

- Platforms to reduce health disparities in maternal morbidity and mortality and infant mortality by identifying individuals and communities at highest risk and developing and integrating strategies toward health equity.
- Platforms to develop and test innovative *in utero* treatments to cure congenital diseases and correct deformities before birth.
- Platforms to address developmental origins of health and health inequity, and precision medicine approaches starting early in the life course (including premature births) with a focus on social, environmental, and biologic influences on *in utero* and child health and their trajectory into adulthood.
- Examination of the microbiome, epigenome, exposome, and metabolome on maternal and fetal health and its impact on health throughout the lifespan.
- Comprehensive evaluation and treatment programs targeted to mitigate the effects of opioid exposure during pregnancy.
- Multi-omics approaches to identifying the mechanisms of progression from acute to chronic multiorgan failure in children.
- Development of effective and scalable intersectoral, multilevel prevention strategies for mental and substance use disorders and chronic physical illness in childhood and adolescence.

Recommendations

With these potential projects in mind, we recommend that ARPA-H includes the important perspective and unique benefits of pediatric research and treatments:

- ARPA-H must address inclusion of children and adolescents in all research projects and assess the impact of research on health and disease across the lifespan.
- ARPA-H should prioritize a subset of spending to include child and adolescent health research and focus on prevention as well as cures, leveraging burgeoning technology developments.
- ARPA-H should focus on health equity starting early in the life course and examine the multiple ways that health disparities negatively impact child and adolescent development and predisposition to acute and chronic diseases.