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The Advanced Research Projects Agency—Health (ARPA-H): a new model for research in child health

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The Advanced Research Projects Agency—Health (ARPA-H) is being formed and will be a new vehicle for biomedical research under the National Institutes of Health. ARPA-H is intended to "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".[1] As Congress and the present White House Administration work to establish ARPA-H, this agency must ensure that its structure supports innovation focused on child and adolescent health and health across the lifespan. As highlighted by articles in this issue of *Pediatric Research*, research early in the life course critically affects population health outcomes and these articles suggest potential moonshot projects for ARPA-H.

ARPA-H has been modeled on the Defense Advanced Research Projects Agency (DARPA), a flexible and nimble strategy that has led to Department of Defense breakthrough advances for over 60 years. Undeterred by failure, this approach involves program managers from academic institutions or industry who are given independence and resources toward clear goals supporting innovative research, applied research, and advanced technology development. Examples of DARPA-like projects at National Institutes of Health (NIH) include the Human Genome Project, the Accelerating COVID-19 Therapeutic Interventions and Vaccines (ACTIV) program, and the COVID-19 Rapid Acceleration of Diagnostics (RADx) program. These programs accelerated progress through collaborations among academic researchers, industry, non-profit organizations, and government.

Leaders at the NIH and the Office of Science and Technology Policy have written about the limitations of the current science lifecycle.[2] NIH supports incremental, hypothesis-driven research while business translation requires a timely return on investment to attract investors. They note that promising ideas may never be pursued or mature because "(1) the risk is too high; (2) the cost is too large; (3) the time frame is too long; (4) the focus is too applied for academia; (5) there is a need for complex coordination among multiple parties; (6) the near-term market opportunity is too small to justify commercial investment given the expected market size challenges in adoption by the health care system; or (7) the scope is so broad that no company can realize the full economic benefit, resulting in underinvestment relative." These challenges are especially true for prevention and research early in the life course which have longer time frames for return on investment.

The ARPA-H authorizing legislation does not focus the agency's work on any specific diseases or conditions or areas of research, but instead it empowers the agency's director and leadership team to make those decisions. The history of funding for pediatric research indicates that without strong advocacy, it is likely that pediatric-focused research will again be left behind. When the Clinical and Science Translation Awards (CTSA) Program was developed in 2006, pediatric focused co-principal investigators were not permitted. While this has been remedied, CTSA funding continues to be heavily skewed towards adult medicine. Four years into the *All of Us* Precision Medicine Initiative, no pediatric participants have been enrolled. Although children comprise 20% of the US population, only 12–14% of NIH funding is directly or indirectly related to their health needs.[3,4] Of the 71 designated national cancer centers, only 1 is located at a free-standing children's hospital. Such disparities are inequitable and represent short-sighted policy since no area of research has a greater return on investment.

By funding transformative "moonshots," ARPA-H can change the landscape of health in this country and address some of the most difficult to solve problems in society from novel approaches to cure genetic diseases to eliminating health disparities. From a diagnostics perspective, ARPA-H could bridge the gap between various -omics approaches to characterizing and predicting disease and the development of precision diagnostics and therapeutics. In this issue of *Pediatric Research*, Beheshti and colleagues show that a variety of host, viral, and bacterial factors in saliva are predictive of future wheezing episodes.[5] Could an integrated platform be developed for both prediction and phenotypic characterization of wheezing phenotypes and could it be adapted for other respiratory diseases? Developing such a platform and the methods needed for its widespread implementation is the type of high-risk, high-reward project better suited for ARPA-H than traditional NIH funding mechanisms. Also, in this issue, Holgerson and colleagues characterize the oral, fecal, and breast milk microbiome in the first 5 years of life.[6] Is there any correlation of these factors with maternal and infant mortality? Are these factors modifiable? Socioeconomic and racial disparities in maternal and infant mortality are deeply engrained in society, and "moonshot" approaches to addressing this recalcitrant problem are needed.

ARPA-H could broadly improve the overall wellbeing of children in ways that targeted approaches cannot. In this issue, Lucchini and colleagues document how the pandemic adversely impacted children's sleep habits.[7] Sleep is a key element of well-being that can be influenced by a host of other important factors, such as mental health, relationships with technology, and socioeconomic factors. Could an integrated system be devised that could provide an assessment of all these different domains of child and adolescent well-being, identify high-risk individuals, and develop individualized strategies that would stem the mental health crisis in our children?

In addition to the research articles presented in this current issue, there are other critical areas of high-risk, high-reward research worthy of exploration. Cell-based therapies and gene-editing technology have the potential to transform the lives of children with some relatively common (i.e., Type 1 diabetes, sickle cell

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disease and cystic fibrosis) and uncommon (i.e., Tay–Sachs disease and severe combined immunodeficiency syndrome) diseases. The development of common platforms to deliver DNA- or RNA-based therapies or stem cells could be developed and modified in a disease or patient-specific manner. Instead of focusing on a disease, could we focus on an approach applicable to a family of diseases? Like for coronavirus disease 2019 (COVID-19) boosters, could nucleotide modifications be approved by the Food and Drug Administration without submitting an entirely new application? Could we develop high throughput in utero or newborn screening with digital genomics? Or a microneedle patch platform to deliver all childhood immunizations avoiding current cold chain obstacles? Finally, with children at the forefront of demographic change with increasing diversity, developing platforms to reduce health disparities in maternal and infant mortality by identifying individuals and communities at high risk and intervening is a worthy moonshot.

As ARPA-H becomes established, child and adolescent health researchers should be aware of this new approach and funding opportunity (see https://www.nih.gov/arpa-h). Growing research demonstrates that many conditions have their origins early in the life course with the opportunity for ARPA-H to prevent or change the trajectory of disease. ARPA-H should address inclusion of children in all research projects and assess the impact of research on health and disease across the lifespan and intergenerationally. ARPA-H should focus on prevention as well as cures, leveraging burgeoning technology developments. Finally, ARPA-H should focus on health equity starting early in the life course and examine the multiple ways that health disparities negatively impact children's development and predisposition to acute and chronic diseases.

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COMPETING INTERESTS

The authors declare no competing interests.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

No human subjects' consent was required for this commentary.

ADDITIONAL INFORMATION

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