September 22, 2017

The Child Enrollment Scientific Vision Working Group
National Institutes of Health
9000 Rockville Pike
Bethesda, Maryland 20892

RE: Request for Information: Pediatric research that All of Us may be uniquely positioned to enable NOT-PM-17-004

Submitted electronically through: https://grants.nih.gov/grants/rfi/rfi.cfm?ID=65

Dear Sir or Madam,

The American Society of Hematology (ASH) appreciates the opportunity to respond to the Request for Information (RFI) on Pediatric research that All of Us may be uniquely positioned to enable (NOT-PM-17-004), issued September 1, 2017 by the National Institutes of Health (NIH).

ASH represents over 17,000 clinicians and scientists worldwide, who are committed to the study of blood and blood-related diseases. These disorders encompass malignant hematologic disorders, such as leukemia, lymphoma, and multiple myeloma, as well as non-malignant conditions, such as sickle cell anemia, thalassemia, bone marrow failure, venous thromboembolism, and hemophilia. ASH membership is comprised of basic, translational, and clinical scientists, as well as physicians, who are working in diverse settings, including universities, hospitals, and private practices. In the last few decades, hematologists have pioneered the use of various technologies including gene therapy, recombinant protein expression, immunotherapy, and stem cell transplantation. Hematologists have applied these techniques to define novel treatments that have had a dramatic impact on patient survival, and as such, the Society’s members have a vested interest in research that spans the pediatric to adult continuum.

ASH commends the NIH for considering the enrollment of children as part of the All of Us initiative as this ensures that the research participants are representative of the United States, given that roughly 25% of the population is under age 18\(^1\) and 1 out of 76 Americans are born with a blood disorder.\(^2\) Including the pediatric population as part of the All of Us initiative will provide an additional evidence base for therapeutic development and improved clinical decision-making for this important patient population.

Below are ASH’s recommendations for precision medicine research questions that could be addressed through the inclusion of children in the All of Us program:
1. **Improving genomic profiling and annotation of genomic variants in the pediatric population:** Recent advances in sequencing technology and data analysis have provided valuable new insights into the genetic basis of various hematologic diseases. Given that childhood diseases are frequently inherited and often originate during embryogenesis, profiling children will be vital in helping to elucidate underlining disease-causing mechanisms. These mechanisms could have important implications for future pediatric research and clinical care, especially in areas such as the development of molecular diagnostics, targeted therapies and drug discovery.

While personalized medicine shows great promise, significant gaps remain in understanding the impact that genetic variations in children have on predisposition to disease (e.g., myeloid neoplasms, platelet disorders) and their therapeutic response. Given that pharmacogenomics will play a pivotal role in therapeutic decision making, it is essential that pediatric research studies identify genomic variants that will respond to therapies. Furthermore, such studies could enhance drug efficacy, reduce adverse events among the pediatric population and ultimately improve patient outcomes.

As genomic profiling continues to drive significant research progress across the field of hematology, it is essential that the pediatric population benefit from this technology to identify predictors of disease risk and the development of novel drug targets.

2. **Elucidating the impact of epigenetic modifications on disease progression within the pediatric population:** As advances are made in the field of epigenetics, it is becoming increasingly clear that epigenetic modifications occurring during childhood could impact disease risk in adult life, thereby providing a completely new ensemble of therapeutic targets for treating hematologic disorders. In addition, these modifications have enormous implications for understanding the molecular underpinnings of the normal development of the nascent hematopoietic system in the embryo, as well as hematologic disorders – both benign (e.g., hemophilia) and malignant (e.g., acute lymphocytic leukemia). Pediatric study designs should include research focused on epigenetics, proteomics, metabolomics, complement activation, and regulatory RNAs as such studies would help explain variability in disease phenotype (e.g., bleeding and clotting), and identify valuable therapeutic targets that may lead to potentially transformative diagnostic tools and/or treatment regimens. Such studies will also further the understanding of hemoglobin biosynthesis and its role in the onset of diseases such as sickle cell disease, thalassemia, and other anemias.

3. **Evaluating promising biomarker candidates for prevention and treatment of disease in the pediatric population:** The rare nature and genetic variability of most hematologic diseases creates a need for the identification of unique biomarkers of disease risks and disease severity. For example, in sickle cell disease the identification of proteomic biomarkers, such as serum amyloid, have been associated with an increased risk of vasoocclusive crisis, a predictor of disease severity and mortality in patients. Conducting comparative studies among the healthy and asymptomatic carrier (i.e., sickle cell trait)
American Society of Hematology’s Response to NIH on its request for information on Pediatric Research that All of Us may be uniquely positioned to enable.

pediatric populations may provide critical insights into the pathophysiology of various hematologic diseases such as sickle cell disease and could identify additional biomarkers that may serve as promising diagnostic and/or therapeutic targets.

4. **Including pain assessment studies as part of pediatric trial design**: Given the impact of pain on a patient’s quality of life and that the fact that pain is frequently experienced by patients with malignant and non-malignant hematologic disorders such as leukemias and sickle cell disease, respectively, pediatric study designs should include methods to assess pain and predictors of pain medication response. Additionally, there is a limited evidence base for pain assessment among racial and ethnic minorities, especially in the pediatric subpopulations of these groups. Further research could elucidate the specific impact of pain on children and their responses to interventions.

5. **Designing appropriate data infrastructure for clinical use**: An All of Us program tailored to the pediatric population should include content-rich portals that contain biomonitoring, environmental and genomic data from participants in this pilot. This portal could allow for the assessment of interactions impacting childhood development, such as environmental exposures (i.e., allergen exposure, tobacco smoke) and genetics. Through collaborative efforts with the Centers for Disease Control and Prevention, such databases should facilitate access to raw genomic and public health data that can be used for interrogating and sharing results without compromising patient privacy. This publicly accessible platform should be:

1. sufficiently comprehensive to identify all relevant variant information;
2. allow for robust bioinformatic analysis with rapid return of results; and
3. foster reliable interpretation of the data.

ASH would like to thank the NIH for the opportunity to comment on this RFI. Observational research studies such as the All of Us program will help provide insight on a wide range of scientific questions, and offer a wealth of information that will be useful to the scientific and medical community continues as it pursues the development of effective tools and resources for the practice of precision medicine.

ASH looks forward to working with the NIH on this important initiative, provide further information, and be a resource for the agency. Please contact the ASH Scientific Affairs Manager, Alice Kuaban, MS (akuaban@hematology.org) or the ASH Manager of Sickle Cell Disease Policy and Programs, LaTasha Lee, PhD, MPH (llee@hematology.org) for any additional information.

Sincerely,

Kenneth C. Anderson, MD
President
American Society of Hematology’s Response to NIH on its request for information on Pediatric Research that All of Us may be uniquely positioned to enable.

References: