Opportunities Enabled Through the Enrollment of Children in the *All of Us* Research Program

The Child Enrollment Scientific Vision Working Group Report to the *All of Us* Research Program Advisory Panel

December 15, 2017

Roster

Tina Cheng, M.D., M.P.H. (co-chair)
Johns Hopkins University School of Medicine (*All of Us* Research Program Advisory Panel member)

Marie Lynn Miranda, Ph.D. (co-chair)
Rice University (*All of Us* Research Program Advisory Panel member)

Deanna Barch, Ph.D.
Washington University in St. Louis

Carol Blaisdell, M.D.
Environmental Influences on Child Health Outcomes (ECHO), National Institutes of Health

Clifford Bogue, M.D.
Yale New Haven Children's Hospital

Rebecca Fry, Ph.D.
University of North Carolina

Holly Garriock, Ph.D.
All of Us Research Program, National Institutes of Health

Christine Cole Johnson, Ph.D., M.P.H.
Henry Ford Health System, Trans-American Consortium for the Health Care Systems Research Network (TACH)

Valerie Maholmes, Ph.D.
Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD), National Institutes of Health

Andreas Theodorou, M.D.
University of Arizona, Banner Health

David A. Williams, M.D.
Boston Children's Hospital

TABLE OF CONTENTS

REPORT OF CHILD ENROLLMENT SCIENTIFIC VISION WORKING GROUP TO THE *ALL OF US* RESEARCH PROGRAM ADVISORY PANEL

Executive Summary

Two of the core values of the *All of Us* Research Program are to reflect the rich diversity of the United States and to allow everyone who wants to participate in the program the opportunity to do so. The inclusion of children in the cohort is consistent with both of these core values and adds significant scientific validity and utility to the research resource. The importance of including individuals from all life stages in the *All of Us* Research Program was first recommended at the inception of the program. The Advisory Committee to the NIH Director Precision Medicine Initiative (ACD PMI) Working Group delivered a report, *The Precision Medicine Initiative Cohort Program — Building a Research Foundation for 21st Century Medicine*. This report, which serves as the blueprint for the *All of Us* Research Program, recommended that NIH "develop specific approaches to address the needs of [children] so that they may be included and retained in the cohort" (p. 79).[1]

The Child Enrollment Scientific Vision Working Group (CESVWG), a working group of the *All of Us* Research Program Advisory Panel, was formed to develop a thoughtful and appropriate approach to the inclusion of pediatric populations in the *All of Us* Research Program. Specifically, the group's charge was to "…describe the critical research *All of Us* may be uniquely positioned to enable through the enrollment of children from diverse backgrounds into the cohort."[2] The charge also included outlining the "…associated research outcomes that are achievable in the short-, medium-, and long-term."

The group's primary deliverable is this report, which identifies research questions and outcomes that the *All of Us* Research Program could enable through child enrollment.

The CESVWG met six times via videoconference and once in person between July and October 2017. The group also engaged with stakeholders and members of the public through a Request for Information (RFI). The RFI focused on identifying research questions that can be addressed by the inclusion of pediatric populations in the program, the research resources that the inclusion of children could potentially generate, and gaps in current pediatric study designs that might be appropriate for *All of Us* to address through the enrollment of children.

The CESVWG identified four major themes that illuminate what *All of Us* can do for pediatrics research and what pediatric populations and a life-course perspective can do for *All of Us*. Those themes include consideration of multiple influences on health status, primary prevention and resilience, family context and life course, and intergenerational perspectives.

In addition to these themes, the CESVWG reviewed the scientific opportunities outlined in the ACD PMI Working Group report. The CESVWG explored these opportunities from a pediatric perspective, developed new questions, and identified gaps in the existing scientific research that *All of Us* could fill.

This report will inform the subsequent work of an additional consortium working group, which will examine the practical considerations of child enrollment and data collection involving children for each scientific opportunity, including the pros and cons of enabling these opportunities. Among the issues the group may consider are different recruitment and follow-up strategies; active vs. passive enrollment; the time point of entry of enrollment (e.g., what life stage will be enrolled in the program, ranging from preconception through adolescence); the types of questions, measures, and samples that are comparable to the rest of the cohort and that will be specific to children; and the sample sizes required to address the themes and scientific opportunity areas described here.

Purpose and Activities of the Child Enrollment Scientific Vision Working Group

Purpose

The Child Enrollment Scientific Vision Working Group (CESVWG) is a working group of the *All of Us* Research Program Advisory Panel. On July 6, 2017, *All of Us* Research Program director Eric Dishman charged the working group with supporting the program's efforts to develop an approach for including pediatric populations. The charge included describing "…what critical research *All of Us* may be uniquely positioned to enable through the enrollment of children from diverse backgrounds into the cohort…" and outlining "…the associated research outcomes that are achievable in the short-, medium-, and long-term."[3] The work of the CESVWG will inform the subsequent work of an additional consortium working group, which will examine the practical considerations of child enrollment and data collection involving children for each research outcome, including the pros and cons of enabling these scientific opportunities.

Activities

This report results from the expertise of CESVWG members, consultations with leaders of existing long-term research cohorts, responses to a Request for Information (RFI), and contributions and feedback from NIH scientific and programmatic leaders.

The CESVWG met six times via videoconference and once in person between July and October 2017. On September 1, 2017, *All of Us* published an RFI titled "Pediatric research that *All of Us* may be uniquely positioned to enable" (NOT-PM-17-004). The RFI sought community input on (1) the most significant short-, medium-, and long-term precision medicine research questions that could be addressed by including pediatric populations in the *All of Us* Research Program; (2) key gaps in current pediatric study designs that might be appropriate for *All of Us* to address through pediatric enrollment; and (3) research resources that pediatric inclusion in the *All of Us* Research Program could generate. The web-based mechanism for responding to the RFI remained open September 2–22, 2017. There was a total of 73 respondents, including members of the public and relevant stakeholder groups. The CESVWG considered these suggestions in developing this report.

Goals of the *All of Us* Research Program

Precision medicine is an approach to disease treatment and prevention that seeks to maximize effectiveness by taking into account individual variability in genes, environment, and lifestyle. Precision medicine seeks to redefine our understanding of disease onset and progression, treatment response, and health outcomes through careful measurement of molecular, environmental, and behavioral factors that contribute to health and disease. Such understanding may lead to more accurate and earlier diagnoses, more rational wellness and disease-prevention strategies, better treatment selection, and the development of novel therapies. Coincident with advancing the science of health and medicine is a changing culture of practice and research that

engages individuals not just as patients or research subjects but as active partners. For children, this also means active engagement of parents and families. *All of Us* believes the combination of a highly engaged population and rich biological, health, behavioral, and environmental data has the potential to usher in a new and more effective era of health and health care in the United States.

The mission of the *All of Us* Research Program is to accelerate health research and medical breakthroughs, enabling individualized prevention, treatment, and care for all. The overall objective of the program is to build a robust research resource to facilitate the exploration of biological, clinical, social, and environmental contributors to health and disease. The program will collect and curate health-related data and biospecimens from individuals who reflect the diversity of the United States; these data and biospecimens will then be made broadly available to the research community.

The program seeks to achieve this mission through relationships with one million or more participant partners and by delivering the largest, richest biomedical dataset ever, catalyzing a robust ecosystem of researchers and funders eager to use and support it. By combining health-related information from a large pool of diverse participants, the *All of Us* Research Program will reach the scale and scope necessary to enable research on a wide range of diseases and health topics.

Rationale for Inclusion of Children

The enrollment of children in the *All of Us* cohort has been an important goal of the program since its inception. The Advisory Committee to the NIH Director Precision Medicine Initiative (ACD PMI) Working Group, which developed the final report that informs the *All of Us* Research Program, strongly supported the inclusion of children in the cohort, recommending that NIH work thoughtfully and carefully to "…develop specific approaches to address the needs of [children] so that they may be included and retained in the cohort."[4]

While *All of Us* has always considered the inclusion of children central to the program's mission and goals, the program appreciates the necessity of addressing this vulnerable population separately to ensure that the rights, safety, and welfare of those enrolled are not compromised.[i] Federal legislators and public interest groups have long worked for the increased inclusion of children in research, and special regulatory protections exist to safeguard their participation in human research.

[i] This is in keeping with the ACD PMI Working Group recommendation that "NIH consider the safeguards necessary to ensure the appropriate enrollment, retention, and protection" of vulnerable populations like children. NIH PMI Working Group of the Advisory Committee to the Director. The Precision Medicine Initiative Cohort Program – Building a Research Foundation for 21st Century Medicine (2015), p. 27.

The inclusion of children in the *All of Us* cohort will enable researchers to address critical issues in children's health, as well as better understand the developmental origins of adult disease. The program also has the opportunity to enroll pregnant women, enabling the study of maternal health, related biospecimens, and prenatal exposures and their effects on diseases occurring from birth to adulthood. Additionally, *All of Us* has the potential to increase the number of clinical trials that involve children, allowing for better understanding of the effectiveness and safety of treatments in pediatric patients.

Children represent 24% of the U.S. population, according to the 2010 U.S. Census.[5] Excluding them would limit the scientific utility of the cohort related to early antecedents of disease. It would deprive this age group of opportunities to benefit from the *All of Us* Research Program, and it would limit the development of therapies for disease prevention and treatment.

Childhood and adulthood are distinct life stages with key differences known as the "5 D's."[6,7] This framework may be useful to *All of Us* in its considerations of research design and methods.

1) Development. In physical status and behavioral patterns, children are still developing and attaining basic competencies and skills. Exploring mechanisms and outcomes to ensure that children are on an optimal developmental trajectory is a critical area of pediatric research.

2) Dependence. Children depend on adults, and so the functioning of families is key. A broad understanding of the effects of child care, schools, families, and social influences provides a more complete picture of childhood.

3) Demographics. Children experience a disproportionate rate of poverty, compared to adults, and are more diverse in race/ethnicity. Their well-being requires a focus on educational and health disparities and support for the most disadvantaged.

4) Disease. Children and adults have different developmental challenges and illnesses, with different solutions. Children often have different, and sometimes unique, exposures to psychosocial and environmental hazards, requiring different (and often greater) protections.

5) Dollars. For children, the key financial resources are family income and wealth, family support and education spending, and Medicaid and the Children's Health Insurance Program (CHIP). Health factors related to health care access and the context of services and policy are unique for children.

Key Themes Regarding Inclusion of Pediatric Populations in the *All of Us* Research Program

The CESVWG identified four major themes that illuminate what *All of Us* can do for pediatrics research and what pediatric populations and a life-course perspective can do for *All of Us*. Those themes include consideration of multiple influences on health status, primary prevention and resilience, family context, and life-course and intergenerational perspectives.

Theme 1: Multiple Contributors to Health: Biology, Behavior, and Social and Physical Environments

Although experts agree that maternal and child health and well-being are determined by multiple forces, surprisingly little is known about the interactions of those forces. For example, elevated environmental toxic exposures often occur in communities already facing social stressors like deteriorating housing, inadequate access to health care, poor schools, high unemployment, high crime, and high poverty—all of which may compound the effects of toxic chemical exposures. This phenomenon is especially severe for low-income and minority families, and has significant health implications. In addition, despite an emerging consensus that numerous gene-environment interactions influence maternal and child health, we know little about how genetic, social, and environmental factors combine to protect against or promote adverse outcomes.

By enrolling children, ***All of Us*** **has the opportunity to help disentangle host, social, and environmental factors and their complex relationships that shape outcomes for children and, subsequently, adults.**

Theme 2: Positive Health: Primary Prevention and Resilience

Chronic diseases are leading causes of morbidity and mortality in the United States. Most research in this area has focused on the diagnosis and management of established chronic diseases rather than prevention. The inclusion of child participants and pregnant mothers benefits researchers by providing an opportunity to identify key periods in the life course when health trajectories bend toward disease. For example, identification of presymptomatic features of cardiovascular disease (like hypertension and hypercholesterolemia) has resulted in effective intervention strategies and contributed to a reduction of incident cases and mortality from myocardial infarction.

Child enrollment in *All of Us* provides a compelling opportunity to widen the lens on disease prevention and optimizing health. A necessary step in developing primary preventive interventions is defining disease onset and/or the preclinical stages of disease to identify critical windows. Identification of risk factors for chronic disease also permits risk stratification or "market segmentation" (where "market" is determined by combined social/medical phenotypes) for targeted primary prevention strategies and detection of resilience factors that protect at-risk individuals from developing disease. Lastly, the discovery of factors associated with positive or maximal health (greater than 90th percentile for age) enables strategies for health promotion that improve the quality of life and extend the lifespan of children, adolescents, and adults.

Impacts sustained during prenatal development and childhood may contribute to a cascade of health effects into adulthood. In fact, the effects of these exposures can ultimately shape health and well-being in individuals and intergenerationally. Thus, understanding how to prevent adverse environmental and social exposures is critically important to the health of our nation.

Trajectories of health begin with maternal health and at fertilization, with rapid growth and development of organs and tissues in utero, continuing through childhood and adolescence. At

some point in the life course of individuals who go on to develop chronic disease, the organs/tissues take on characteristics that are abnormal when compared to those of healthy individuals. Clinical and molecular advances now allow for data collection on multiple factors (e.g., genetic, immune, microbiome, nutrition, and environmental exposure) that can contribute to the trajectory of disease processes and/or aging-related changes and decline in function. For example, symptoms of wheezing and/or atopy in preschool-aged children indicate individuals at risk for chronic disease; however, only some of these individuals ultimately develop asthma. We do not understand which host resilience factors protect against disease development, nor have we identified the critical period(s) for intervention.

Data and specimen collection from child participants or pregnant mothers may enable testing of hypotheses of presymptomatic chronic disease, maximal health, or resilience factors associated with recovery from dysregulated biology/physiology.

Most importantly, children with disease deserve study as much as adults do.

Theme 3: Importance of the Family Context

The composition of families in the United States has evolved considerably from the traditional two-parent nuclear family of past generations. The U.S. Census Bureau reports that 65% of children under age 17 lived with two married parents in 2016, compared to 77% in 1980. In 2008, it was estimated that 2.5% of children in the United States joined their families through adoption (adoptions from foster care, private domestic adoptions, international adoptions, and stepparent adoptions).[8] Moreover, in 2016, 23% of children lived with only their mothers, 4% lived with only their fathers, and 4% lived with neither parent.[9] Children now grow up amid diverse living arrangements, including households headed by parents of the same sex. Information about the presence of other adults in the household, such as unmarried partners, grandparents, and other relatives, is important for understanding the short- and long-term effects of these living arrangements and the impact of the larger social context on children's physical and mental health.[10]

Just as families play an important role in promoting child health and well-being, chronic and serious illnesses have a profound effect not only on the ill child or family member, but on the entire family. Understanding family context and relationships among its members offers enhanced opportunities to document the extent to which these relationships foster health promotion and disease prevention. Research that captures this information will also provide better insight into the ways in which the family environment may contribute to fluctuations in the health and development of both children and adults.

Many existing parent-child studies focus on maternal influences; little attention is paid to paternal and other familial influences, both social and hereditary. By enrolling children linked to parents also enrolled in the research resource, *All of Us* has a unique opportunity to enable research exploring the family's role in promoting positive health and health behaviors, as well as its role in buffering negative effects of adversity. Long-term benefits of involving the family in these studies include opportunities to study attitudes about health; adoption of these attitudes by family members; and the effects of attitudes and behaviors on the health of children, parents, and other members in a family context regardless of biological relationship.

The clustering of disease within families may be due to genetic or environmental factors. Familial aggregation studies are a common first step in understanding the genetics of disease.[11] Pediatric populations allow study designs not possible in adult populations that can address gene, epigenetic (imprinting), and environmental factors. These could include sibling pairs, other relative pairs (e.g., cousins), parent-child trios, and grandparents.[12] *All of Us* could also enable consideration of gene-environment interactions and their impact on health, as well as the influence of social and physical environments on epigenetic change. **A family-based approach for enrolling children in *All of Us* would provide an opportunity to both understand and disentangle the complex relationships among genetics and social and physical environments and their effect on pediatric health.**

The three-generation continuum, emphasizing the importance of family and family dynamics in health and well-being outcomes and across generations, is illustrated in Figure 1.[13] Family studies can help researchers understand the health and genetics of an index child and their family members as well as their health and genetics as a parent for the next generation. **The potential of *All of Us* to enroll multiple individuals from the same family with known relationships may enable research to assess family functioning, family aggregation of disease, and transmission of health and disease to new families.**

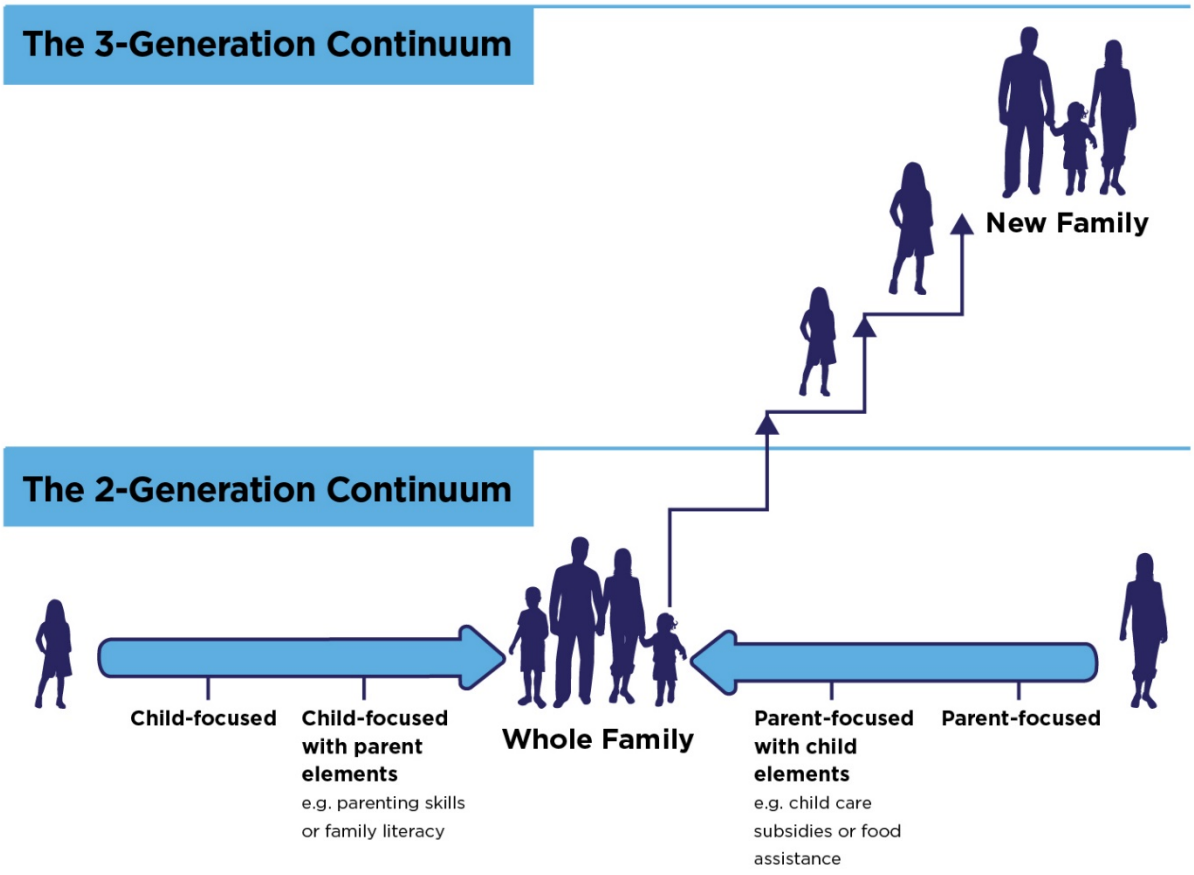

Figure 1. The three-generation continuum. Derivative work based on figure used with permission from Pediatrics, *Vol. 137, e20152467, copyright © 2016, The American Academy of Pediatrics. Permission granted 2017.*

Theme 4: Life-Course and Intergenerational Perspective

Development is a set of nonlinear physical, cognitive, social, and emotional processes. The preconception and prenatal periods represent some of the most critical windows of development. This is the time when maternal health, behaviors, and exposures create the fetal environment. It is the time in which a fertilized zygote grows from a single cell into a multicellular embryo, ultimately becoming a fetus. During this time, cell lineages are established and organs are formed that will remain from the prenatal period into adulthood. Adverse exposures (e.g., maternal stress, environmental contaminants) during this critical period can disrupt normal development and lead to detrimental health effects later in life. Conversely, a positive social and physical environment may put children on a positive health trajectory. Thus, early life exposures and outcomes—both positive and negative—can shape long-term health.

In the early 1990s, epidemiologist Dr. David Barker invented what would become known as the Barker Hypothesis. Barker suggested an inverse relationship between birth weight and coronary artery disease later in life.[14] The study was the first of its kind to investigate and reveal the

relationships between early life factors and health in adulthood. Since then, a study investigating the Dutch winter famine of 1944–1945 revealed that individuals exposed to famine conditions early in prenatal development showed altered DNA methylation six decades later compared to their unexposed same-sex siblings.[15]

Survivors of low birth weight and preterm birth are at significant risk for both short-term neonatal morbidity as well as long-term disabilities,[16] including respiratory distress syndrome,[17] variable heart rate,[18] cerebral ventriculomegaly,[19] cerebral palsy,[20] intellectual disability,[21] blindness,[22] deafness,[23] learning disabilities,[24,25] behavioral disabilities,[26] and motor impairment.[27] Of similar importance is the impact of lower birth weight on increased risk of diabetes, obesity, cardiovascular disease, and other health problems in adulthood.[28,29,30,31]

More recent studies show that early prenatal adverse exposures that alter germ-line epigenetics have the potential to affect not only the developing embryo but subsequent generations as well.[32] Some reports have shown that epigenetic regulators can be a driver of some cancers,[33] and some childhood leukemias have been traced to in utero genetic mutations. Exposures that occur for an individual have the potential to impact the health of multiple future generations (see **Figure 2**).

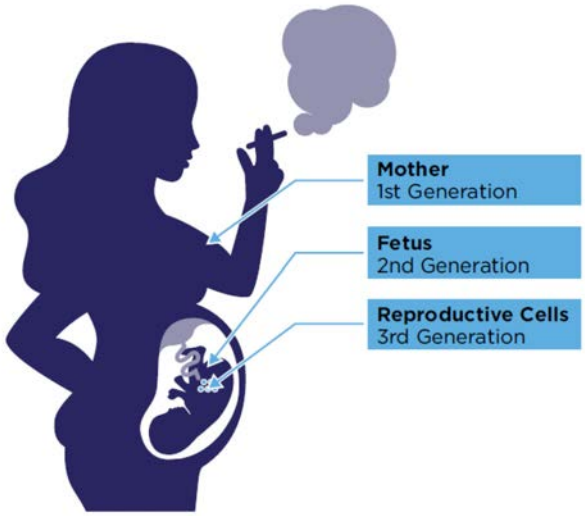

Figure 2. Multiple generation transmission of health effects from environmental exposures.

Taken together, the data highlight the importance of including preconception, prenatal, child, and adolescent populations in *All of Us* to enable the exploration of how exposures and experiences during these periods drive subsequent disease.

Early in life and through adolescence, the foundation for physical and emotional well-being is developed, and behaviors that shape adult health are being established. Children residing in the United States are exposed to high rates and many forms of social adversity threatening their health, including domestic and neighborhood violence, physical and sexual abuse, household substance abuse and mental health issues, parental separation or death, and severe economic hardship.[34] The CDC Kaiser Adverse Childhood Experiences (ACE) Study found a strong dose-response relationship between adverse childhood experiences and negative health and well-being outcomes—including cardiovascular disease, lung disease, depression, and poor work performance—later in life.[35] With the inclusion of children and adolescents, the *All of Us* Research Program has the opportunity to enable research on the biology of toxic stress and the mechanisms through which early experiences affect biology and physiology and have lasting effects on learning and health.

Life-course research enabled through the *All of Us* Research Program offers the opportunity to understand clues about early roots of disorders, developmental progression of wellness and disease, differential manifestation of disease across the lifespan, and methods to identify individuals at risk in early stages of disease/disorder.

Scientific Opportunities Enabled Through the Enrollment of Children

The charge of the CESVWG was to focus on "…what critical research *All of Us* may be uniquely positioned to enable through the enrollment of children from diverse backgrounds into the cohort." To accomplish this, the working group spent significant time reviewing the program's adult protocol and considering the ways in which a pediatric population could broaden the program's science. The group also worked to identify unique themes relevant to children.

The CESVWG utilized the scientific opportunities or objectives outlined by the ACD PMI Working Group report as a framework for accomplishing its charge. The CESVWG explored these opportunities from a pediatric perspective, developed new questions, and identified gaps in the existing scientific research that *All of Us* could fill.

This analysis will allow the Child Enrollment Working Group to focus on practical considerations of child enrollment and data collection involving children for each research outcome, including the pros and cons of enabling those scientific opportunities. This, in turn, will help determine which types of questions, measures, and samples are comparable to the rest of the cohort and which will be specific to children.

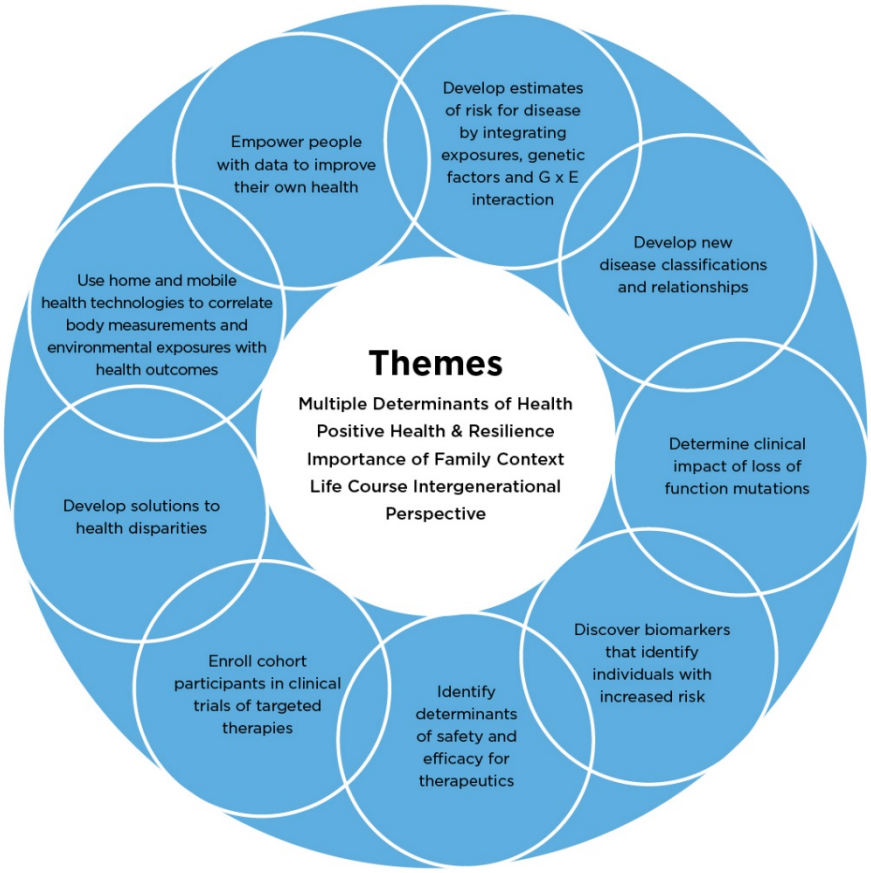

Figure 3. CESVWG's four themes and nine scientific opportunities.

1) Developing quantitative estimates of risk for a range of diseases by integrating environmental exposures, genetic and epigenetic factors, and gene-environment interactions

As with diseases and other conditions that affect adults, a wide variety of environmental and genetic risk factors have been found for both frequent and infrequent diseases and traits that arise in childhood, including those with onset as early as the neonatal and even fetal periods. Ideally, the genetic code that predisposes to disease and the epigenetic mechanisms that control gene expression would be available to the clinician and family prenatally or early in life, providing opportunities to intervene. However, the data relevant to understanding the relative impact of genetic and environmental factors and their interaction on early emerging diseases and traits come from relatively small samples that are, as yet, unable to support strong conclusions. Inferences strong enough to allow early intervention or prevention of environmental exposures would require much larger datasets. Including children in the *All of Us* cohort could help fill these major gaps in our knowledge and could help address a range of key questions, both about diseases that manifest in childhood and their early prevention and about the childhood antecedents of adult diseases.

The literature includes a number of important examples in which identifying gene-environment interactions have led to highly successful intervention strategies early in life. One example is a very rare condition called phenylketonuria (PKU), which is caused by a mutation in the phenylalanine hydroxylase (*PAH*) gene. This mutation alters the metabolism of phenylalanine (Phe), resulting in excess accumulation of Phe, which, in turn, leads to significant and irreversible intellectual deficits. Scientific advances have made it possible to identify PKU in newborns and to modify their diet to restrict the intake of Phe. This has helped reduce the occurrence of intellectual deficits.[36] Another example is the practice, now adopted by many states, of screening newborns for severe combined immunodeficiency (SCID), which allows curative intervention before highly morbid, and often fatal, first infections.

2) Developing new childhood disease classifications and relationships

As new and potentially paradigm-shifting data emerge from longitudinal cohort studies, opportunities arise for more valid and flexible classifications of childhood diseases and disorders. In addition, there is excellent opportunity to correlate genotype with phenotype, as there are significant knowledge gaps regarding what constitutes a pathogenic mutation in the context of different age groups. Including children in the *All of Us* cohort could help elucidate continuities and discontinuities between child and adult ailments and determine whether current classifications further or hamper our ability to accurately diagnose disease and design effective therapeutic interventions.

For example, there is a critically important need for reliable and valid criteria for identifying and assessing mental health symptoms and psychiatric disorders in very young children. The unique characteristics of children in this age group, including rapid changes in cognitive development and language acquisition, present challenges for applying existing diagnostic criteria. Researchers contend that current mental health classifications are imperfect in that they are based on clinical observations of overlapping clusters of specific behaviors and emotional states, and lack specificity and biological correlates.[37] An evidence-based diagnostic technique that would be based on a dimensional measurement of function and correlated across several units of analysis would be preferable and is best achieved using a large longitudinal dataset. Studies of psychiatric disorders in children are limited by relatively small high-risk samples drawn from social service or care settings, or from families with parents or siblings with these conditions.[38] **Including children in the *All of Us* cohort would allow for a broader, more diverse sample of children and would provide opportunities to empirically determine mechanisms causing these disorders and the boundaries between normative and clinically significant presentations.**

The large *All of Us* dataset could advance understanding of the relationships among multiple biological systems and behaviors. It would allow for the development of clinically and biologically meaningful disease classification that would enable better and more precise ways to identify and treat child and adolescent diseases and disorders in general, and in the very young in particular. Diseases and conditions common in adults may present in a substantially different manner in the pediatric population due to developmental differences. The extent to which adult criteria are applied to children must be decided on the basis of good conceptual frameworks and

empirical data about the continuity of disorders from childhood into adulthood. For example, mood disorders are diagnosed according to adult criteria—the consequence of which is that most surveys of depression find prevalence rates of zero in children under 8 years of age.[39]

The *All of Us* platform would allow for clinical research studies that would confirm empirically that diseases common in adults are not always typical in children. It could help explain why and how these differences exist, and give rise to new classifications or disease subtypes, which could lead to better and more tailored treatments. A rich set of complex data on pediatric conditions may help to locate unexpected connections between health, environment, and molecular physiology, providing opportunities to advance pediatric health and identify risks for disease development later in life.

Finally, for enrolled children who have developmental disabilities or acquire disabilities in childhood, research may identify important links between timing of onset of disability, favorable or unfavorable environmental conditions, and risk for development of secondary conditions.

3) Determining the clinical impact of loss-of-function mutations on children

While the ACD PMI Working Group focused on loss-of-function mutations in its scientific opportunities, the CESVWG focused more broadly on the advantages of pediatric genomic research. Advances in genomic sequencing technologies and techniques in recent years now enable an unparalleled ability to discover new genetic mutations that cause disease and/or alter disease progression in children. The use of genetic sequencing data presents productive opportunities to diagnose disease, identify new treatments for genetic diseases, understand the causes of disease progression and variation, and predict disease recurrence in families.

A current gap exists in genomic studies as they relate to children. This is particularly the case in the context of rare pediatric diseases. To date, success in understanding mutations tied to rare diseases in children has only been possible through the use of databases based on large adult cohorts, those that aggregate whole-genome or -exome sequencing (e.g., ExAC and gnomAD). *All of Us* is poised to create a dataset with genomic and phenotypic information that bridges childhood and adulthood.

The enrollment of children and their parents in *All of Us* is crucial to addressing four critical areas of researching genetic determinants of disease in both children and adults. First, children should be included in studies using whole-genome or -exome sequencing. This is particularly important in the context of children with de novo single gene mutations that cause severe disease and reduced fitness, resulting in underrepresentation in adult populations. Second, the ability to analyze participants' whole exomes and/or genomes along with their phenotype and follow them longitudinally over many years can greatly enhance our ability to correlate disease phenotype and progression with potential genetic contributors to that disease progression. Third, the ability to accurately annotate DNA variants is needed for better prognostic counseling and treatment. Currently, most genomic database annotation focuses on the most severely affected individuals. Finally, the ability to perform whole-genome or -exome sequencing on trios (two parents and a child) or entire families greatly enhances our ability to identify disease-causing genetic mutations.

One important example of the success of this approach is the NIH-funded Pediatric Cardiac Genomics Consortium. By performing whole-exome sequencing on thousands of children with congenital heart disease, along with their parents, the Consortium has identified many new genetic mutations and molecular pathways that cause structural heart disease. **The potential impact of discovering new genetic mutations that cause disease and/or alter disease progression is large and includes the use of genetic sequencing data to diagnose disease, to identify potential new or personalized treatments for genetic diseases, to understand the causes of disease progression and variation, and to predict the recurrence of disease in families.**

4) Discovering biomarkers to identify individuals at an increased risk of developing common diseases

The NIH Biomarkers Definitions Working Group defined a biomarker as "a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention."[40] Biomarkers can be indicators of exposure to environmental substances, predictors of response to therapeutics, or indicators of disease endpoints that can be measured within biological samples. Biomarkers included in the *All of Us* Research Program could be assessed temporally to define early-life biomarkers of current or later-life health, disease, or disease severity. **The identification of biomarkers in children that are apparent prior to actual disease development later in life will be critical for identifying modifiable developmental windows for risk susceptibility or disease resiliency.** Biomarkers may also be measured at a single time point in children to predict treatment response. Types of biomarkers include, but are not limited to, CpG methylation, gene expression, microRNA expression, protein expression, and metabolite levels.

The Extremely Low Gestational Age Newborns Study, for example, demonstrated that protein expression within the first few weeks of life was associated with neurodevelopment later in life.[41] Gene expression can be used as a biomarker of environmental toxic metal exposure in infants.[42]

A medium-term outcome is the identification of specific biomarkers and their validation as indicators of environmental exposures and/or health effects. The inclusion of biomarkers identified through *All of Us* in clinical trials could also shorten trials and allow attainment of endpoints with smaller numbers of pediatric clinical trial accruals.

A long-term outcome could be the identification of biological pathways that are disrupted and associated with disease, that can be targeted for disease prevention or specific therapeutics.

5) Identifying the determinants of safety and efficacy for commonly used therapeutics

Pharmacogenetics is an ever-growing field, and one that is as important in children as it is in adults. Unfortunately, less is known about the safety and effectiveness of drugs in children, and off-label use is more common. ***All of Us* could contribute to understanding the efficacy of**

therapeutics and individual variation in children. The efficacy of therapies given for rare (acute lymphoblastic leukemia, epilepsy) and common (attention deficit/hyperactivity disorder, atopic dermatitis) conditions in childhood have been shown to vary depending on a child's genetic variants.[43,44,45,46]

Asthma is the most common chronic disease in childhood. The most commonly used therapeutics in pediatric asthma are β-agonists, inhaled corticosteroids, and leukotriene antagonists. Although these drugs are effective for many patients, responses vary considerably. For example, refractory asthma is not responsive to inhaled corticosteroids. While only 5% to 10% of children with asthma fall into this category, they represent a population exposed to an ineffective medication with potential side effects. This lack of effective treatment is a tremendous cost burden on the health system. Similarly, genetically driven and common metabolic variations have been associated with differences in the plasma concentrations of leukotriene modifiers, which are administered orally.[47] But clinical trials on this subject have historically been limited; many that consider genetic variations and response to asthma medications are not validated, many rely on small samples, and most are limited to study populations of predominantly adults or European American children.[48] Furthermore, drugs or biomarkers that are useful in adults may not be effective in children. The biomarker periostin can predict morbidity in adults, but not children, with asthma.[49,50,51]

Additional longitudinal electronic health record and survey data would illuminate other important variables that influence responses to therapy. Similar family data from parents and siblings would help distinguish genetic versus environmental and social influences related to treatment success.[52,53]

The inclusion of a large number of children in the *All of Us* research platform could foster studies to identify children who would not benefit from various therapies or, even worse, be harmed by them.

6) Enrolling cohort participants in clinical trials of targeted pediatric therapies

It takes years and sometimes decades to develop and establish a clinical trial, enroll participants, and follow them successfully. Much time and expense is invested in identifying potential participants, screening them for eligibility, and recruiting them into a trial. These issues are even more acute in pediatrics. The FDA reported that, as of 2008, only 50% to 60% of the drugs prescribed for children had actually been studied in a pediatric population and that the remainder lack sufficient pediatric safety, dosing, or pharmacokinetic data.[54,55] Moreover, pediatric trials take longer than adult studies to institute and complete and are operationally more complicated. As a result, the majority of drugs are brought to market without pediatric data and labeling.[56] The younger the patient, the less evidence we have that a drug or device is or is not beneficial. A large standing and more efficient research infrastructure for pediatric clinical trials would obviate some of these barriers and result in better medical care for children**.**

7) Developing solutions for pediatric health disparities

Disparities in health and health care related to race/ethnicity and socioeconomic status remain persistent and pervasive. The causes of health disparities are multifactorial, likely accumulating across the life course and possibly transmitted across generations. Understanding the mechanisms and exposures leading to health disparities from preconception through adulthood will be crucial in resolving them. This requires consideration of the biopsychosocial context in which health develops, including physical and social environment, health behavior, and biology.

Establishing a cohort to explore the development of health and health care disparities will offer opportunities to understand mechanisms, ascertain periods of vulnerability, and guide prevention and early-intervention strategies. Enrollment of families would allow familial aggregation analysis—the clustering of certain traits, behaviors, or disorders within a given family, teasing out genetic or environmental similarities.

Medium-term outcomes might include disentangling the many causes of health disparities. For instance, despite improvement in the infant mortality rate in the United States in the past decade, the preterm birth rate is nearly 50% higher for black infants than for white infants.[57] In addition, there are nearly four times more deaths among black infants related to short gestation and low birth weight. **Though there are multifactorial reasons for this racial disparity, *All of Us* could improve our understanding of the causes of preterm birth and low birth weight, including the contributions of genetics, gene-environment influences, physical environment, social environment, and maternal behavior.**

Long-term outcomes from *All of Us* could elucidate the life-course effects of race, ethnicity, and socioeconomic status from preconception through adulthood, the mechanisms underlying these effects, and ways to ameliorate negative outcomes (e.g., obesity, cardiovascular risk, asthma/allergy).

As our society becomes increasingly diverse in race/ethnicity starting in childhood, and considering that children are disproportionately poor, ensuring a diverse sample across the life course will be critical to ensuring truly generalizable findings. This may require oversampling of certain racial/ethnic groups and the ability to enroll and collect data in multiple languages. While *All of Us* has the potential to elucidate mechanisms of wellness and disease and target interventions, research findings must be relevant, and interventions accessible, to different racial/ethnic and socioeconomic groups to achieve health equity.

8) Using home and mobile health (mHealth) technologies to correlate body measurements and environmental exposures with pediatric health outcomes

The development of more advanced, more comprehensive, smaller, and more comfortable wearable sensors and monitors can allow us to better study how external exposures shape health in adults, infants, and children. This may be especially useful for infants and children who cannot verbalize their condition and for whom measurement can be difficult. mHealth devices can track typical biometrics such as heart rate, temperature, blood pressure, glucose level, degree of movement, and even quality of sleep, as well as the nature of the ambient environment in terms of language and cognitive stimulation. GPS tracking from cell phones can capture travel history, and novel sensing adaptations can track noise pollution, air quality, and UV exposure.

The exposures that can significantly impact health or disease are not exclusively external in origin. The total exposome includes endogenously generated substances like hormones, metabolites, and microbiota.

These novel wearable devices represent an opportunity to understand how the total exposome interacts with hormonal and metabolic changes during growth and development to impact health outcomes. Because these data may be collected continuously and passively, mHealth technologies afford new opportunities for understanding the relationships between these measures and health outcomes throughout development, from fetal exposure to infancy and into adulthood.

Specific examples of state-of-the-art sensing technologies as applied to children include screening and intervention for children with autism spectrum disorder[58] and monitoring of body movements in neonates for seizures or abnormal movements like those seen in cerebral palsy and other neurodevelopmental impairments.[59] A variety of sensor types can be applied to athletic training and sports injury prevention.[60] The application of a host of sensors and smart wearable devices can be brought together to create a “smart system” that can be used to manage chronic illness in children.[61] The impact of such technology on short-term outcomes, like hospitalization rates, or long-term impact on survival has yet to be fully evaluated.

Sensor devices in infant socks, clipped on diapers, or embedded in baby clothing purport to monitor movement (or the lack of movement), temperature, and even heart rate and blood oxygenation. Though these products are commercially available, the FDA has not approved them as medical devices. **With great relevance to children, a population in which measurement can be difficult, the *All of Us* Research Program is ideally situated to assess the value of these monitors versus the potential risks they pose.**

9) Using data to empower children, adolescents, and parents to improve health

Self-management programs for adults with chronic disease are well known and have been in practice for some time. With a growing proportion of children with chronic health conditions, it is important to understand how children and adolescents can be empowered, with the support of their families and health care teams, to manage their own health. Recent advances in technology and mHealth create the opportunity to get more information to children and/or their parents with subsequent improved control of illness and, potentially, better outcomes.

As digital natives, children and adolescents are not only comfortable receiving electronic data but begin to do so at an early age. A recent Kaiser Family Foundation survey showed that 85% of children age 14–17 have cell phones, as do 69% of children age 11–14 and 31% of children age 8–10. Social media use and text messaging are common activities, as is accessing the Internet to gain information. This comfort with and attraction to technology may present an opportunity for young people to gain more autonomy in managing their health, especially children and adolescents with chronic disease. Diabetes,[62] asthma,[63] cystic fibrosis,[64] obesity,[65] pain,[66] and mental health are a few areas in which mobile and wireless technologies have allowed for better self-care in the pediatric population, though long-term impact on outcomes and the transition to adult care have yet to be fully studied.[67] The combination of mHealth technologies, children as digital natives, and enrollment of families in the *All of Us* Research Program provides the opportunity to improve health.

Health care disparities may potentially be addressed in children when they are empowered with information available through mobile technology. Access to in-person care remains problematic in many rural communities, while telemedicine services continue to expand.

Conclusion

The CESVWG identified four critical themes for *All of Us* to consider regarding the inclusion of children in the research program. The working group also evaluated the unique importance of the nine scientific opportunities from the ACD PMI Working Group as they pertain to children (see Figure 3 on page 12). These themes and opportunities should be considered by the next working group and the *All of Us* Research Program Advisory Panel as they discuss expansion of the cohort across the life course. **Attention to multiple contributors to health, prevention and resilience, family context, and a life-course and intergenerational perspective will strengthen pediatric health research and the overall impact of the science made possible through *All of Us*.**

The scientific opportunities identified by the CESVWG will benefit from the practical and logistical consideration of the subsequent working group. Among the issues that the subsequent group may consider are different recruitment and follow-up strategies (e.g., active versus passive recruitment); the time point of entry of child enrollment (e.g., what life stage will be enrolled in the program, ranging from preconception through adolescence); the types of questions, measures, and samples that are comparable to the rest of the cohort and that will be specific to children; and the sample sizes required to address the themes and opportunity areas described here.

References

1. NIH PMI Working Group of the Advisory Committee to the Director. The Precision Medicine Initiative Cohort Program – Building a Research Foundation for 21st Century Medicine (2015). https://www.nih.gov/sites/default/files/research-training/initiatives/pmi/pmi-working-group-report-20150917-2.pdf.
2. The Child Enrollment Scientific Vision Working Group of the *All of Us* Research Program Advisory Panel. https://allofus.nih.gov/about/who-we-are/child-enrollment-scientific-vision-working-group.
3. Ibid.
4. NIH PMI Working Group. The Precision Medicine Initiative Cohort Program – Building a Research Foundation for 21st Century Medicine. (2015).
5. U.S. Census Bureau (2010).
6. Stille C, Turchi RM, Antonelli R, Cabana MD, Cheng TL, Laraque D, et al. The family-centered medical home: specific considerations for child health research and policy. *Academic Pediatrics*. 2010; 10:211-7.
7. Forrest CB, Simpson L, Clancy C. Child health services research. Challenges and opportunities. *JAMA*. 1997; 277:1787-93.
8. Federal Interagency Forum on Child and Family Statistics. *America's Children: Key National Indicators of Well-Being, 2011*. Washington, DC: U.S. Government Printing Office. https://www.childstats.gov/pdf/ac2011/ac_11.pdf.
9. Federal Interagency Forum on Child and Family Statistics. *America's Children: Key National Indicators of Well-Being, 2017*. Washington, DC: U.S. Government Printing Office. 2017:228. https://www.childstats.gov/pdf/ac2017/ac_17.pdf
10. Ibid.
11. Matthews AG, Finkelstein DM, Betensky RA. Analysis of familial aggregation studies with complex ascertainment schemes. *Statistics in Medicine*. 2008; 27:5076-92.
12. Weinberg CR. Studying parents and grandparents to assess genetic contributions to early-onset disease. *American Journal of Human Genetics*. 2003; 72:438-47.
13. Cheng TL, Johnson SB, Goodman E. Breaking the intergenerational cycle of disadvantage: the three generation approach. *Pediatrics*. 2016; 137.
14. Hales CN, Barker DJ. Type 2 (non-insulin-dependent) diabetes mellitus: the thrifty phenotype hypothesis. *Diabetologia*. 1992; 35:595-601.
15. Heijmans BT, Tobi EW, Stein AD, Putter H, Blauw GJ, Susser ES, et al. Persistent epigenetic differences associated with prenatal exposure to famine in humans. *Proceedings of the National Academy of Sciences of the United States of America*. 2008; 105:17046-9.
16. Hack M, Klein NK, Taylor HG. Long-term developmental outcomes of low birth weight infants. *The Future of Children*. 1995; 5:176-96.
17. Lemons JA, Bauer CR, Oh W, Korones SB, Papile LA, Stoll BJ, et al. Very low birth weight outcomes of the National Institute of Child Health and Human Development neonatal research network, January 1995 through December 1996. NICHD Neonatal Research Network. *Pediatrics*. 2001; 107:E1.
18. Doussard-Roosevelt JA, Porges SW, Scanlon JW, Alemi B, Scanlon KB. Vagal regulation of heart rate in the prediction of developmental outcome for very low birth weight preterm infants. *Child Development*. 1997; 68:173-86.

19. Ment LR, Vohr B, Allan W, Westerveld M, Katz KH, Schneider KC, et al. The etiology and outcome of cerebral ventriculomegaly at term in very low birth weight preterm infants. *Pediatrics*. 1999; 104:243-8.
20. Kuban KC, Leviton A. Cerebral palsy. *The New England Journal of Medicine*. 1994; 330:188-95.
21. Lorenz JM, Wooliever DE, Jetton JR, Paneth N. A quantitative review of mortality and developmental disability in extremely premature newborns. *Archives of Pediatrics & Adolescent Medicine*. 1998; 152:425-35.
22. Crofts BJ, King R, Johnson A. The contribution of low birth weight to severe vision loss in a geographically defined population. *The British Journal of Ophthalmology*. 1998; 82:9-13.
23. Lorenz JM (1998).
24. Saigal S, Hoult LA, Streiner DL, Stoskopf BL, Rosenbaum PL. School difficulties at adolescence in a regional cohort of children who were extremely low birth weight. *Pediatrics*. 2000; 105:325-31.
25. Resnick MB, Gueorguieva RV, Carter RL, Ariet M, Sun Y, Roth J, et al. The impact of low birth weight, perinatal conditions, and sociodemographic factors on educational outcome in kindergarten. *Pediatrics*. 1999; 104:e74.
26. Ross G, Lipper EG, Auld PA. Social competence and behavior problems in premature children at school age. *Pediatrics*. 1990; 86:391-7.
27. Avchen RN, Scott KG, Mason CA. Birth weight and school-age disabilities: a population-based study. *American Journal of Epidemiology*. 2001; 154:895-901.
28. Osmond C, Barker DJ, Winter PD, Fall CH, Simmonds SJ. Early growth and death from cardiovascular disease in women. *BMJ: British Medical Journal* (Clinical research ed). 1993; 307:1519-24.
29. Barker DJ, Martyn CN, Osmond C, Hales CN, Fall CH. Growth in utero and serum cholesterol concentrations in adult life. *BMJ: British Medical Journal* (Clinical research ed). 1993; 307:1524-7.
30. Weiss JL, Malone FD, Emig D, Ball RH, Nyberg DA, Comstock CH, et al. Obesity, obstetric complications and cesarean delivery rate—a population-based screening study. *American Journal of Obstetrics and Gynecology*. 2004; 190:1091-7.
31. Braveman P, Barclay C. Health disparities beginning in childhood: a life-course perspective. *Pediatrics*. 2009; 124 Suppl 3:S163-75.
32. Xin F, Susiarjo M, Bartolomei MS. Multigenerational and transgenerational effects of endocrine disrupting chemicals: a role for altered epigenetic regulation? *Seminars in Cell & Developmental Biology*. 2015; 43:66-75.
33. Huether R, Dong L, Chen X, Wu G, Parker M, Wei L, et al. The landscape of somatic mutations in epigenetic regulators across 1,000 paediatric cancer genomes. *Nature Communications*. 2014; 5:3630.
34. Felitti VJ, Anda RF, Nordenberg D, Williamson DF, Spitz AM, Edwards V, et al. Relationship of childhood abuse and household dysfunction to many of the leading causes of death in adults. The Adverse Childhood Experiences (ACE) Study. American Journal of Preventive Medicine. 1998; 14:245-58.
35. Ibid.
36. Al Hafid N, Christodoulou J. Phenylketonuria: a review of current and future treatments. *Translational Pediatrics*. 2015; 4:304-17.

37. Egger HL, Emde RN. Developmentally sensitive diagnostic criteria for mental health disorders in early childhood: the diagnostic and statistical manual of mental disorders-IV, the research diagnostic criteria-preschool age, and the diagnostic classification of mental health and developmental disorders of infancy and early childhood-revised. *The American Psychologist*. 2011; 66:95-106.
38. Bufferd SJ, Dougherty LR, Carlson GA, Rose S, Klein DN. Psychiatric disorders in preschoolers: continuity from ages 3 to 6. *American Journal of Psychiatry*. 2012; 169:1157-64.
39. Scott S. Classification of psychiatric disorders in childhood and adolescence: building castles in the sand? *Advances in Psychiatric Treatment*. 2002; 8:205-13.
40. Strimbu K, Tavel JA. What are biomarkers? *Current Opinion in HIV and AIDS*. 2010; 5:463-6.
41. O'Shea TM, Joseph RM, Kuban KC, Allred EN, Ware J, Coster T, et al. Elevated blood levels of inflammation-related proteins are associated with an attention problem at age 24 mo in extremely preterm infants. *Pediatric Research*. 2014; 75:781-7.
42. Fry RC, Navasumrit P, Valiathan C, Svensson JP, Hogan BJ, Luo M, et al. Activation of inflammation/NF-kappaB signaling in infants born to arsenic-exposed mothers. *PLoS Genetics*. 2007; 3:e207.
43. Moriyama T, Yang YL, Nishii R, Ariffin H, Liu C, Lin TN, et al. Novel variants in NUDT15 and thiopurine intolerance in children with acute lymphoblastic leukemia from diverse ancestry. *Blood*. 2017; 130:1209-12.
44. Mei S, Feng W, Zhu L, Yu Y, Yang W, Gao B, et al. Genetic polymorphisms and valproic acid plasma concentration in children with epilepsy on valproic acid monotherapy. *Seizure*. 2017; 51:22-6.
45. Gomez-Sanchez CI, Carballo JJ, Riveiro-Alvarez R, Soto-Insuga V, Rodrigo M, Mahillo-Fernandez I, et al. Pharmacogenetics of methylphenidate in childhood attention-deficit/hyperactivity disorder: long-term effects. *Scientific Reports*. 2017; 7:10391.
46. Mathyer ME, Coughlin CC, de Guzman Strong C. Effect of counting genetic variants on precision treatment for pediatric atopic dermatitis: do count your chickens before they hatch. *JAMA Dermatology*. 2017; 153:269-70.
47. Mougey EB, Feng H, Castro M, Irvin CG, Lima JJ. Absorption of montelukast is transporter mediated: a common variant of OATP2B1 is associated with reduced plasma concentrations and poor response. *Pharmacogenetics and Genomics*. 2009; 19:129-38.
48. Weiss ST. New approaches to personalized medicine for asthma: where are we? *Journal of Allergy and Clinical Immunology*. 2012; 129:327-34.
49. Matsusaka M, Kabata H, Fukunaga K, Suzuki Y, Masaki K, Mochimaru T, et al. Phenotype of asthma related with high serum periostin levels. *Allergology International*. 2015; 64:175-80.
50. Inoue Y, Izuhara K, Ohta S, Ono J, Shimojo N. No increase in the serum periostin level is detected in elementary school-age children with allergic diseases. *Allergology International*. 2015; 64:289-90.
51. Konradsen JR, Skantz E, Nordlund B, Lidegran M, James A, Ono J, et al. Predicting asthma morbidity in children using proposed markers of Th2-type inflammation. *Pediatric Allergy and Immunology*. 2015; 26:772-9.
52. Galli SJ. Toward precision medicine and health: Opportunities and challenges in allergic diseases. *Journal of Allergy and Clinical Immunology*. 2016; 137:1289-300.

53. Doyle R. Drug development and biologics in asthma: a new era. *Annals of the American Thoracic Society*. 2016; 13 Suppl 1:S83-4.
54. Bogue C, DiMeglio LA, Maldonado S, Portman RJ, Smith PB, Sullivan JE, et al. Special article: 2014 Pediatric Clinical Trials Forum. *Pediatric Research*. 2016; 79:662-9.
55. Connor EM, Smoyer WE, Davis JM, Zajicek A, Ulrich L, Purucker M, et al. Meeting the demand for pediatric clinical trials. *Science Translational Medicine*. 2014; 6:227fs11.
56. Bogue, C. et al. (2016).
57. Riddell CA, Harper S, Kaufman JS. Trends in differences in U.S. mortality rates between black and white infants. *JAMA Pediatrics*. 2017; 171:911-3.
58. Billeci L, Tonacci A, Tartarisco G, Narzisi A, Di Palma S, Corda D, et al. An integrated approach for the monitoring of brain and autonomic response of children with autism spectrum disorders during treatment by wearable technologies. *Frontiers in Neuroscience*. 2016; 10:276.
59. Chen H, Xue M, Mei Z, Bambang Oetomo S, Chen W. A review of wearable sensor systems for monitoring body movements of neonates. *Sensors* (Basel, Switzerland). 2016; 16.
60. Li RT, Kling SR, Salata MJ, Cupp SA, Sheehan J, Voos JE. Wearable performance devices in sports medicine. *Sports Health*. 2016; 8:74-8.
61. Sendra S, Parra L, Lloret J, Tomás J. Smart system for children's chronic illness monitoring. *Information Fusion*. 2018; 40:76-86.
62. Giani E, Scaramuzza AE, Zuccotti GV. Impact of new technologies on diabetes care. *World Journal of Diabetes*. 2015; 6:999-1004.
63. Geryk LL, Roberts CA, Sage AJ, Coyne-Beasley T, Sleath BL, Carpenter DM. Parent and clinician preferences for an asthma app to promote adolescent self-management: a formative study. *JMIR Research Protocols*. 2016; 5:e229.
64. Calvo-Lerma J, Martinez-Jimenez CP, Lazaro-Ramos JP, Andres A, Crespo-Escobar P, Stav E, et al. Innovative approach for self-management and social welfare of children with cystic fibrosis in Europe: development, validation and implementation of an mHealth tool (MyCyFAPP). *BMJ Open*. 2017; 7:e014931.
65. Turner T, Spruijt-Metz D, Wen CK, Hingle MD. Prevention and treatment of pediatric obesity using mobile and wireless technologies: a systematic review. *Pediatric Obesity*. 2015; 10:403-9.
66. Stinson JN, Lalloo C, Harris L, Isaac L, Campbell F, Brown S, et al. *iCanCope with Pain*™: User-centred design of a web- and mobile-based self-management program for youth with chronic pain based on identified health care needs. *Pain Research & Management*. 2014; 19:257-65.
67. Grist R, Porter J, Stallard P. Mental health mobile apps for preadolescents and adolescents: a systematic review. *Journal of Medical Internet Research*. 2017; 19:e176.