National Institutes of Health

Advisory Committee to the Director

National Children's Study (NCS) Working Group

FINAL REPORT – DECEMBER 12, 2014

Members: Russ Altman (co-chair), Philip Pizzo (co-chair), Robert Gibbons, Kathy Hudson, Renee Jenkins, Brendan Lee, Maureen Lichtveld, Marie Lynn Miranda, Cheryl Perry, Huda Zoghbi, Lyric Jorgenson (executive-secretary) *(full titles, affiliations, and biographies listed in Appendix A)*

EXECUTIVE SUMMARY

The origins of the National Children's Study (NCS) stem from the work of a wide community of investigators and a 1990s White House Task Force highlighting the paucity of evidence for evaluating the links between environmental exposure, development, and health outcomes in children and adults. The Children's Health Act of 2000 (P.L. 106-310) subsequently authorized the National Institute of Child Health and Human Development (NICHD) of the National Institutes of Health (NIH) to conduct a national longitudinal study of environmental influences (including physical, chemical, biological, and psychosocial) on child health and development. This Act defined the original and overall goals of the NCS.

In the ensuing 14 years, the NCS has struggled with concerns about its scientific methods, oversight and management structures, and increasing costs. The National Academies (NAS) reviewed the NCS extensively in 2008 and again in 2014. While these reviews endorsed the overarching concept of a longitudinal study examining the impact of environmental, behavioral, and social factors on child development, they also raised strong criticisms regarding the feasibility, suitability, and management of the NCS. Based on the 2014 NAS report and other persistent concerns, NIH Director Dr. Francis Collins convened the NCS Working Group of the Advisory Committee to the NIH Director (ACD) to address the future of the NCS. The Working Group's charge is to *evaluate whether the NCS is feasible*, as currently outlined, especially in light of increasing and significant budget constraints.

In its deliberations, the Working Group reviewed historical and contemporary documents about the NCS, including the 2008 and 2014 NAS studies, and other study-related documents and reports. In addition, the Working Group collected input from colleagues, the NIH and NCS leadership, and reviewers of the NCS design and its Vanguard data. Leaders knowledgeable about the NCS history, design, objectives, and feasibility were also engaged. These included experts in the fields of environmental science, child health and development, epidemiology, statistics, and longitudinal study design. The Working Group also received and deliberated upon public comments throughout the process.

Ultimately, the Working Group concludes that, while the overall goals and intent are meritorious and should be a priority for future scientific support, the NCS, as currently outlined, is not feasible. This conclusion is based on an evaluation of the aims, design, and management of the NCS. Specifically:

1. The current aims, design, and scope of the NCS are unlikely to achieve the goals of providing meaningful insights into the mechanisms through which environmental factors influence health and development;
2. The study does not incorporate approaches informed by new biological insights about factors that impact child health and new enabling technologies;
3. Even with the potentially valuable goal of a national probability sample, the NCS sampling design is overly complex, and the study design remains incomplete even after years of effort; and
4. The NCS investigative team and management are not well suited to the tasks inherent to such a study, and the management oversight by multiple committees is cumbersome, further slowing progress.

With the conclusion that the NCS is not feasible as currently outlined, the Working Group emphasizes that the NIH should champion and support new study designs, informed by advances in technology and basic and applied research across multiple disciplines, that could make the original and overall goals of the NCS more achievable, feasible, and affordable. The Working Group is convinced that the questions embodied in the Children's Act of 2000 remain important and concludes that available funds should be used to pursue alternative approaches that engage the broader scientific community and that could lead to superior study designs—designs that optimize the use of new scientific knowledge and enabling technologies. These approaches may substantially enhance our knowledge about the impact of environmental, biological, behavioral, and social factors on child and adult development, health, and disease.

INTRODUCTION

Purpose and Scope of this Report

This report summarizes the review, deliberations, analysis, and recommendations of the NCS Working Group of the ACD, which was convened by NIH Director Dr. Francis Collins in July 2014 to address the future of the NCS. Because there have been a number of thorough reviews of the NCS, including two by joint panels of the National Research Council and the Institute of Medicine (in 2008[1] and 2014[2], hereafter referenced as the NAS reports), this report does not attempt to recapitulate the well-detailed findings of prior reviews. Instead, this report addresses a specific charge that was presented to the NCS Working Group from the NIH Director:

> *The NCS Working Group is charged with evaluating whether the NCS is feasible, as currently outlined, especially in light of increasing and significant budget constraints.*
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> - *If "yes", the Working Group should assess how NIH can move forward to implement necessary changes, including some of those outlined in the NAS report.*
> - *If "no", the Working Group should identify whether there are new methods to answer key research questions that are most important to pediatric health today that capitalize on research and technology advances developed in the intervening years since the inception of the study.*

Background on the National Children's Study

At its inception, the NCS was envisioned to be a longitudinal birth cohort study focused on examining the influences of a broad array of environmental and biological factors on the health and development of children. The concept for the study has origins in the work of a wide community of investigators and a 1990's White House taskforce report noting the paucity of evidence for evaluating the links between environmental exposure, development, and health outcomes. Subsequently, the Children's Health Act of 2000 (PL-106-310) authorized the NICHD of the NIH to conduct a national longitudinal study of environmental influences (including physical, chemical, biological, and psychosocial) on children's health and development.[3] Specifically, the legislation states:

> *The Director of the National Institute of Child Health and Human Development shall establish a consortium of representatives from appropriate Federal agencies (including the Centers for Disease Control and Prevention, the Environmental Protection Agency) to—*
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> 1. *Plan, develop, and implement a prospective cohort study, from birth to adulthood, to evaluate the effects of both chronic and intermittent exposures on child health and human development; and*

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[1] The National Children's Study Research Plan: A Review (2008). National Research Council and Institute of Medicine, National Academies Press.
[2] The National Children's Study 2014: An Assessment (2014). National Research Council and Institute of Medicine, National Academies Press.
[3] http://www.gpo.gov/fdsys/pkg/PLAW-106publ310/pdf/PLAW-106publ310.pdf

2. *Investigate basic mechanisms of developmental disorders and environmental factors, both risk and protective, that influence health and developmental processes.*

The study shall--

1. *Incorporate behavioral, emotional, educational, and contextual consequences to enable a complete assessment of the physical, chemical, biological and psychosocial environmental influences on children's well-being;*
2. *Gather data on environmental influences and outcomes on diverse populations of children, which may include the consideration of prenatal exposures; and*
3. *Consider health disparities among children that may include the consideration of prenatal exposures.*

Impetus for Current Review of the National Children's Study

A 2014 NAS report reviewed the revised plan for the NCS and expressed concerns about the study's design, management, oversight structure, and anticipated cost. These concerns echo those voiced separately by scientists in the community, NIH leadership, and others. Much of the pilot work of the NCS Vanguard Study over the past several years has been focused on determining the optimal recruitment strategy. The question now is whether the NCS is sufficiently designed, specified, and organized to begin (at scale) with effective recruitment and data collection.

Many in the scientific community have pointed out that the scientific and technological landscape has dramatically changed since the NCS was first conceived. For example, the emergence of health care plans interested in research collaboration now permit study designs that were not feasible a few years ago. Rapidly developing "-omics" technologies are providing a level of subject phenotyping not previously achievable. In addition, multi-center collaborative networks show great promise for robust and cost-effective research in other large national projects. Harnessing these capabilities may address the escalating costs associated with the NCS, as the largest drivers of the budget are derived from characterizing the sample population, recruitment, and data/sample acquisition.

Congress, the public, and the entire scientific community consider it critical that resources be effectively leveraged to optimize advances in human health, especially in light of current NIH budget constraints. Since Congress first began providing funds for the NCS in 2007, approximately $1.3 billion has been allocated for the NCS. The impact of this funding is unclear—as is the degree to which the NCS feasibly can achieve the goals of the Children's Health Act of 2000.

Based on the 2014 NAS report and other persistent concerns, on June 16, 2014, the NIH Director put the NCS on hold, stating that the study is at an inflection point where critical questions must be answered in order to determine the best path forward. To assist in this task,

he formed a Working Group to advise the ACD and ultimately, the NIH, on the questions posed in the charge to the Working Group about the feasibility of the NCS.

Summary Findings and Recommendations Regarding the National Children's Study

The Working Group concludes that, while the overall goals and intent are meritorious and should continue to be a priority for future scientific support, the NCS, as currently outlined, is not feasible. This conclusion is based on an evaluation of the aims, design, and management of the NCS. Specifically:

1. The current aims, design, and scope of the NCS are unlikely to achieve the goals of providing meaningful insights into the mechanisms through which environmental factors influence health and development;
2. The study does not incorporate approaches informed by new biological insights about factors that impact child health and new enabling technologies;
3. Even with the potentially valuable goal of a national probability sample, the NCS sampling design is overly complex, and the study design remains incomplete even after years of effort; and
4. The NCS investigative team and management are not well suited to the tasks inherent to such a study, and the management oversight by multiple committees is cumbersome, further slowing progress.

The Working Group also notes that over the past 14 years the NCS has struggled with concerns about its scientific methods, its oversight and management structures, and its increasing costs. Consequently, there have been multiple iterations of the plan for the NCS, several of which have been accompanied by extensive reviews. These reviews consistently endorse the overarching concept for the study–a longitudinal pediatric study focused on examining environmental, behavioral, social and biological influences on child health and development. However many stakeholders, constituencies, and the greater scientific community have expressed concerns about and criticism of the feasibility and suitability of the NCS design—as well as its organization, management, and costs. At this time, the NCS has launched a pilot phase, referred to as the Vanguard Study, which has provided some information about the feasibility and cost projections for the Main Study. In evaluating the feasibility of the current NCS research plan, the Working Group finds this history to be important; a pattern of pervasive challenges has resulted in numerous delays and false starts for the study, which is proposed to begin in 2015. These challenges include difficulty in gaining scientific consensus and inability to create the detailed technical plan required for a multi-billion dollar research program.

The plan for the NCS as outlined in the Main Study Design and Methodology plan (July 2014) continues to be a longitudinal, observational study, following 100,000 children, prenatally or at birth to age 21 to examine the effects of a broad range of environmental and biological factors on children's health, growth, and development. Additional core elements of the NCS as currently proposed include the following:

- Establish a large research resource containing data, biological specimens, and environmental samples that researchers can use to answer fundamental questions about child health and development
- Use a national probability sample based on geography
- Recruit participants as early in pregnancy as possible or at birth and collect data at multiple times throughout pregnancy
- Stratify samples to achieve variability in socioeconomic status to support analysis of health disparities

The review of this plan by the Working Group raises substantial concerns. Although the NCS leadership has indicated its intent to begin the Main Study in 2015, the Working Group concludes that there is no detailed, step-by-step protocol for the NCS (a manual of standard operating procedures – MSOP). According to NCS leadership, constructing a fully operational and executable protocol would take at least 18-24 months. The Working Group lacks confidence that this can happen. Continued concerns about the scientific study design, complexity of sampling plan, and leadership mechanisms make the NCS not feasible at this time, particularly in light of increasing and significant budget constraints.

The Working Group concludes that these multiple concerns outweigh the varied and potential strengths of the NCS. The Working Group further observes that the resources needed to carry out the Main Study as currently outlined, including its duration of at least 21 years, raise serious concerns about the relative scientific merits and health impact of the NCS versus alternative, study programs aimed at achieving comparable goals and objectives. While the Working Group concludes that the NCS is not feasible, it also recognizes the importance of studies that address the extremely important questions articulated in the Children's Health Act of 2000—which require considerable rethinking and deliberation.

PROCESS, DELIBERATIONS, AND ANALYSIS

Implementing its Charge

To address the charge from the NIH Director, the Working Group met on four conference calls and two in-person meetings over five months to discuss the current status of the NCS, evaluate its strengths and weaknesses, assess its overall utility and feasibility, and propose options for next steps. To supplement its expertise, the Working Group sought input from colleagues, NIH and NCS leadership, reviewers of NCS design and Vanguard data, and numerous experts in fields such as pediatric research, environmental health, epidemiology, statistical analyses, and longitudinal study design (for a full list, see Appendix B). The Working Group studied the recent 2014 NAS report and other historical documents, including the established Vanguard and proposed Main Study protocols, along with internal documents regarding existing Vanguard data. Frequent and considerable communications between and among Working Group members took place between meetings. In addition, public comments were collected throughout the process and considered by the group throughout its deliberations.

Deliberations

The Working Group explored a broad range of stakeholder perspectives and a wide range of relevant documents in its deliberations. In particular, the Working Group focused on a critical assessment of the current NCS as outlined in the Main Study Design and Methodology plan (July 2014) and an analysis of the current NCS organization and management structure. In all interviews and documents, there was general agreement about the importance of a longitudinal cohort study to examine the role of an extensive range of environmental factors (interpreted broadly) on the health and development of children, as well as the impact of childhood exposures and health on long-term outcomes in the adult years.

Given the charge, the Working Group identified a series of scientific issues that were relevant to an assessment of the feasibility of the NCS as currently designed. These included:

- The scientific rationale for conducting a longitudinal study.
- The value of employing a design based on a national probability sample versus other approaches.
- The size and distribution of the participant population, including whether they are entered prenatally or later.
- The range and frequency of sampling procedures and how data are collected, stored, and made accessible.
- The evolving technologies used to measure environmental exposure and to measure behavior, disparity, biological development, and societal factors.
- Whether the study should be hypothesis driven (in part or in whole) and/or whether it was a platform study.
- The degree to which emerging scientific capabilities (e.g., genomics, epigenomics, microbiomics) and technologies (e.g., EMR, mobile monitoring devices, adaptive measurement and sampling) suggest study design alternatives that would strengthen the NCS study or make it less expensive.
- The organization and management of the study.
- The degree to which other environmental studies conducted internationally may complement or dovetail with some of the core questions posed in the NCS, and thus allow alternative designs to be considered to maximize scientific impact.
- The current costs of the NCS, as well as projected costs if the scope of the study is expanded or its length extended.
- Whether other study designs or management structures could address the core questions of the NCS in a simpler, faster, more representative, and less expensive manner.

During its deliberations, the Working Group identified strengths of the current NCS study design as outlined. Perhaps the most important of these include:

- There is a lack of an understanding of the impact of early life exposures on development and health, and a large longitudinal cohort design presents an opportunity to link environmental exposures to health outcomes in children. This is a critical need.
- There exists no similar study in the US currently that focuses on tracking the spectrum of human development from the prenatal period through childhood, adolescence and early adulthood.
- There exists no similar study in the US focusing on minority and disadvantaged populations and the impact of environmental exposures on children from these populations.
- The platform approach in the current design could provide flexibility to address current and as yet unknown hypotheses as science evolves over time.
- The current NCS design has flexibility to allow "add-on" studies that sample new environmental variables, taking advantage of the cohort and sampling infrastructure.
- The 2014 NAS report provides useful guidance addressing several technical weaknesses that allow the study to be strengthened before starting.
- The retention rates in the Vanguard study are reported to be high but this may reflect limited sampling making it less certain how this would impact a larger scale study.
- There are 112 papers resulting from NCS efforts so far, primarily papers about methodological design issues, but also including preliminary results related to environmental exposures.
- Most experts interviewed believed that the study should be continued in some form – although a number also raised very significant concerns and others offered that the study should be discontinued or changed significantly.
- The NIH has a history of supporting longitudinal studies that have served as valuable resources to the scientific community, providing numerous insights and mechanisms for biomedical discovery and translation.

While the strengths of the NCS are compelling, the study investigators, management, and the broader scientific community all suggested significant limitations of the NCS as currently designed. The Working Group found evidence to support the importance of these limitations in both its structured interviews and in the extensive documents that were reviewed. Among the most important of the limitations:

- The study design remains incomplete, even after years of effort, making it difficult to articulate what the "current study design" is. Neither the NAS panel nor the Working Group could obtain an appropriate manual of standard operating procedures (MSOP) capable of serving as the basis for initiating a comprehensive longitudinal study.

- Even considering the goal of recruiting a national probability sample, the sampling design is overly complex, leading to considerable delays and high costs.
- There is inadequate observational and field epidemiological expertise incorporated within the management and study design. This contributes to a sense that the design and management do not reflect current best practices for large longitudinal studies.
- The informatics substrate for consistently collecting, storing, and quality assuring NCS data is inadequate.
- The current management structure has too many stakeholder and scientific advisory mandates that inhibit flexibility, responsiveness, and consensus-driven science.
- Although a member of the Environmental and Child Health International Birth Cohort Group (ECHIBCG) representing colleagues conducting large birth cohort studies from China, France, Germany and Japan, the NCS has not been designed to coordinate with other global longitudinal environmental cohort studies. Thus it is unlikely that worldwide methodological experience and scientific progress will be fully leveraged.
- The NCS study design began at a time when NIH budgets were increasing, and does not reflect the need for low-cost recruitment and data collection strategies, possibly incorporating social media, electronic medical records, the Food and Drug Administration Sentinel Project, the Patient-Centered Outcomes Research Initiative, and other new efforts that did not exist in 1999 or in 2008.
- As noted above, the experts interviewed by the NCS Working Group who favored continuing the NCS almost universally recommended that it go forward with a "reboot" or "refined" or "redesigned" or "reconfigured" design, thus their support was typically conditioned on significant modifications to the current plan.

The Working Group weighed the strengths and limitations of the NCS listed above and concluded that, as currently outlined, the NCS is not feasible. Even with the adoption of, at a minimum, the NAS recommendations, the NCS is not sufficiently well developed or well-managed to warrant the substantial investment it would require. Most importantly, the NCS, as currently outlined, is unlikely to achieve the goals of providing meaningful insight into the mechanisms through which environmental factors influence health and development. At the same time, the Working Group concluded that abandoning the original goals of the NCS is not recommended, but that alternative strategies need to be explored and implemented. These might include a platform-oriented longitudinal study design or a series of smaller focused studies addressing the key issues originally envisioned when the NCS was first contemplated.

SUMMARY OBSERVATIONS AND RECOMMENDATIONS

There is little doubt that elucidating the interactions and impact of environmental, genetic, behavioral, and societal factors on child development is enormously important, and could lead to major improvements in child, adolescent, and indeed long term adult health. The major question is **not** whether elucidating these interactions is important, but whether the NCS, as it is currently designed, is likely to be able to do so. An NCS study would need to be designed to succeed in the context of rapidly emerging scientific developments and technologies, and must nimbly respond to new capabilities and theories. At the same time, it is likely that there will be significant financial pressures on the biomedical research enterprise in the coming decades, and so an NCS study must be designed for affordability and efficiency.

The Working Group acknowledges that there is a range of opinions about the relative importance of the issues summarized above, and the relative probability of different outcomes. Indeed, a number of knowledgeable experts are strong proponents for continuing the NCS. At the same time, the majority of these experts also recommended significant changes to the study design even as they indicated support for the NCS. In the end, the Working Group was left with the strong impression that most supported an NCS as they envisioned it, and not as it actually is today. There is clearly a strong view in the community (and indeed within the Working Group) that the general issues of environmental exposure on childhood development and health should be a national priority. There is also a strong view that the NCS represents an unusual opportunity to mount a major national initiative that could have provided a platform for answering compelling questions about the impact of the environment – particularly for minorities and disadvantaged populations who may disproportionately face historic burdens of health disparities.

The charge to the group, however, was to advise the ACD on the feasibility of the current design, and to examine alternatives in the case of a negative evaluation of feasibility. The Working Group's evaluation of the NCS has included a comprehensive review of the study's origins, evolution, and current status – examining its scientific plan, its management and oversight structures, and its cost projections along the way. The Working Group has carefully considered the recommendations of the NAS reviews of 2008 and 2014 and has consulted with numerous experts in children's health, environmental health, and epidemiology – including individuals involved in the initial creation of the NCS. The Working Group has received and read several letters from scientific and policy organizations. The Working Group has deliberated as a committee for several months, including both teleconference and in-person meetings. It is the clear conclusion of this group that the deficiencies noted by the 2014 NAS report and mentioned by expert consultants in combination with the analysis and deliberations of the Working Group provide strong evidence that the NCS is not feasible as currently outlined. Integral to this conclusion is the understanding that new approaches to addressing the critically important questions about the interactions of child health with environmental, biological, behavioral and societal factors should be given high priority.

The Working Group recognizes that its recommendations may have broad and deep scientific and programmatic consequences, and many research, advocacy, and governmental constituencies may be impacted. The Working Group further recognizes that the response from professional organizations, societies, academic leaders, investigators, and the public may be mixed – some negative, others supportive. However, the Working Group stresses that the recommendation that the NCS as currently outlined is not feasible is **not** a statement about the value of the transdisciplinary research questions motivating its formation, but rather about the feasibility of a specific study – the NCS – in providing robust and valid answers with its currently proposed design and structure. Thus the primary driver for the Working Group's recommendation is the evaluation of the likely scientific merit as currently proposed. In addition, the Working Group is not convinced that the current design embodied the most cost-effective strategies for achieving the goals of the Children's Health Act of 2000. There is a substantial risk for an expensive study with modest scientific value.

Accompanying the recommendation that the NCS is not feasible, the Working Group offers the following directions regarding next steps:

- The NCS is scientifically and logistically managed through a NICHD Program Office. This Office should be dissolved. Given the breadth and depth of the topics that reside around the NCS, a trans-NIH approach should be pursued, ideally convened and supported by the Office of the Director, with the goal of understanding environmental and behavioral influences on child health and development.

- The Vanguard Study has provided some useful information—primarily about the feasibility of different sampling strategies--and most of this has been published. The Vanguard Study has also collected some "test" data that may have value. The Working Group recommends that the NIH find a mechanism by which the Vanguard data can be archived and requested by investigators for secondary analysis, as long as this is consistent with the human subject consent protocol. The Working Group does not recommend that the Vanguard Study collect any further data.

- It is critical that future studies incorporate new biological and technological advances, which maximize our opportunity to elucidate the determinants of child health and the resulting impact on health and disease in adults. Future children's health research should examine the important interactions between child development and related environmental, behavioral, biological, and societal factors. Furthermore, supporting biospecimen collection and banking could facilitate a diverse array of contemporary, tailored investigations and provide built-in flexibility to deploy emerging scientific insights. Funds directed towards addressing questions, with the purpose of providing meaningful insights into the mechanisms through which environmental factors influence health and development, should support cutting-edge scientific methods that will achieve its goals.

- The working group emphasizes that time did not allow full consideration of the wide range of options regarding study designs that could best accommodate the recommended scientific strategies presented above. Hence, the comments that follow should be complemented by additional insights from the broader scientific community. In general, the group offers the following approaches for consideration:

    - A series of smaller focused studies designed as tailored explorations, including research targeting health disparate populations.

    - A multi-center collaborative network of scientific teams, who compete on responses to a well-considered funding announcement. This could provide a robust structure for meeting the goals of the Children's Health Act, and might attract the best researchers to be part of this larger effort. This structure would be capable of distributing responsibility for recruitment and data collection and would allow for the evolution of novel new approaches as opportunities arise.

    - A focused cohort design to facilitate longitudinal biospecimen collection and banking. This approach would resemble a biospecimen "core" and "repository" rather than the longitudinal strategy originally envisioned by the current NCS.

    - Probability sampling should be an integral feature of the methodological approach of scientific inquiry to explore critical gaps in children's health research.

The above are preliminary considerations by the Working Group for what might come next to address mechanisms through which environmental factors influence health and development. Clearly, a panel exclusively devoted to this question would yield more detailed alternatives for the future.

CONCLUDING REMARKS

The Working Group understands the importance of its charge and took very seriously the responsibility to fully consider the relevant issues surrounding the NCS. With the conclusion that the NCS is not feasible as currently outlined, the Working Group offers the additional recommendation that the NIH champion and support new study designs, informed by advances in technology and basic and applied research, that could make the original goals of the NCS more achievable, feasible, and affordable.

APPENDIX A – NCS WORKING GROUP BIOGRAPHIES

RUSS BIAGIO ALTMAN, MD (co-chair), is the Kenneth Fong Professor of Bioengineering, Genetics, & Medicine (and of Computer Science, by courtesy) and past Chairman of the Bioengineering Department at Stanford University. His primary research interests are in the application of computing and informatics technologies to problems relevant to medicine. He is particularly interested in methods for understanding drug action at molecular, cellular, organism and population levels. His lab studies how human genetic variation impacts drug response (e.g. http://www.pharmgkb.org/). Other work focuses on the analysis of biological molecules to understand the action, interaction and adverse events of drugs (http://features.stanford.edu/). He helps lead one of seven NIH-supported National Centers for Biomedical Computation, focusing on physics-based simulation of biological structures (http://simbios.stanford.edu/). Dr. Altman holds an AB from Harvard College, and MD from Stanford Medical School, and a PhD in Medical Information Sciences from Stanford. He received the US Presidential Early Career Award for Scientists and Engineers and a National Science Foundation CAREER Award. He is a fellow of the American College of Physicians, the American College of Medical Informatics, the American Institute of Medical and Biological Engineering, and the American Association for the Advancement of Science. He is a member of the Institute of Medicine of the National Academies. He is a past-President, founding board member, and a Fellow of the International Society for Computational Biology, and a past-President of the American Society for Clinical Pharmacology & Therapeutics. Dr. Altman is board certified in Internal Medicine, and has recently been certified in the first class of diplomats in Clinical Informatics. He recently chaired the Science Board advising the FDA Commissioner, and is on the NIH Director's Advisory Committee. He is an organizer of the annual Pacific Symposium on Biocomputing (http://psb.stanford.edu/), and a founder of Personalis, Inc. He won the Stanford Medical School graduate teaching award in 2000, and mentorship award in 2014.

PHILIP PIZZO, MD (co-chair), is the David and Susan Heckerman Professor and Founding Director of the Stanford Distinguished Careers Institute. Pizzo served as Dean of the Stanford School of Medicine from April 2001 to December 1, 2012, where he was also the Carl and Elizabeth Naumann Professor. He has devoted much of his career to the diagnosis, management, prevention and treatment of childhood cancers and the infectious complications that occur in children whose immune systems are compromised by cancer and AIDS. He has also been a leader in academic medicine, championing programs and policies to improve the future of science, education and healthcare in the US and beyond. Pizzo received his MD degree with Honors and Distinction in Research from the University of Rochester in 1970; and did his internship and residency at Children's Hospital Medical Center in Boston. Pizzo served as head of the National Cancer Institute's infectious disease section, chief of the NCI's pediatric department, and acting scientific director for NCI's Division of Clinical Sciences between 1973 and 1996, and then served as physician-in-chief of Children's Hospital in Boston and chair of the Department of Pediatrics at Harvard Medical School from 1996-2001. Pizzo is the author of more than 550 scientific articles and 16 books and monographs, including Principles and Practice of Pediatric Oncology, the Seventh Edition of which will be published in 2016. Pizzo has

received numerous awards and honors, among them the Ronald McDonald Charities "Award of Excellence" in 2009, and in 2012 the John Howland Award, the highest honor for lifetime achievement bestowed by the American Pediatric Society. He has been elected to a number of prestigious organizations and societies, including the Institute of Medicine of the National Academy of Sciences. He serves on a number of University and Foundation Boards of Directors.

ROBERT GIBBONS, PhD, is a Professor of Biostatistics in the Department of Medicine and the Department of Public Health Sciences at the University of Chicago Biological Sciences. He received his doctorate in statistics and psychometrics from the University of Chicago in 1981. He spent the first 30 years of his career at the University of Illinois at Chicago (1981-2010) where he directed the Center for Health Statistics, a consortium of 15 statisticians working in both theoretical and applied areas of environmetrics, chemometrics, biometrics, and psychometrics. In 2010 Professor Gibbons joined the faculty of the University of Chicago where he is Professor of Biostatistics in the Departments of Public Health Sciences, Medicine, and Psychiatry, and continues to direct the Center for Health Statistics. Support for his research includes numerous grants and contracts from the NIH, NIMH, ONR, NCI, and MacArthur foundation. Professor Gibbons is a Fellow of the American Statistical Association and a member of the Institute of Medicine of the National Academy of Sciences. He has authored more than 250 peer-reviewed scientific papers and five books. Professor Gibbons is a 2011 University of Chicago Pritzker Scholar, the 2012 recipient of the Rema Lapouse Award for contributions to Psychiatric Epidemiology from the American Public Health Association, and the 2013 recipient of the Long-Term Excellence Award from the Health Policy Statistics Section of the American Statistical Association.

KATHY HUDSON, PhD, is the Deputy Director for Science, Outreach, and Policy at the NIH, the world's largest biomedical research agency. Dr. Hudson leads the science policy, legislation, and communications efforts of the NIH and serves as a senior advisor to the NIH director. She is responsible for creating major new strategic and scientific initiatives for NIH and was a key architect of the National Center for Advancing Translational Sciences and the NIH BRAIN Initiative. She directs the agency's efforts to advance biomedical science through policy development and innovative projects and partnerships. Dr. Hudson's professional experience includes serving as the Acting Deputy Director of the National Center for Advancing Translational Sciences, NIH; the NIH Chief of Staff; the Assistant Director of the National Human Genome Research Institute, NIH; and the founder and Director of the Genetics and Public Policy Center at John Hopkins University. Also at Hopkins, Dr. Hudson was an Associate Professor in the Berman Institute of Bioethics, Institute of Genetic Medicine, and Department of Pediatrics. Dr. Hudson holds a PhD in Molecular Biology from the University of California at Berkeley, an MS in Microbiology from the University of Chicago, and a BA in Biology from Carleton College.

RENEE JENKINS, MD, is a Professor Emerita of the Department of Pediatrics and Child Health at Howard University College of Medicine in Washington DC She was Chair of the Department from 1994 to 2007. She is a Principal Investigator for the DC-Baltimore Research Center on Child Health Disparities, funded by the National Institute for Minority Health and Health Disparities in

collaboration with Johns Hopkins Division of General Pediatrics and the Children's National Medical Center. As Chair Emeritus, she established the College of Medicine's Office of Faculty Development. Dr. Jenkins has held leadership positions in several prominent national organizations, including the American Academy of Pediatrics (AAP), the Society for Adolescent Health and Medicine (SAHM), the Association of Medical School Pediatric Department Chairs, the National Medical Association, the Association of American Medical Colleges, and the American Pediatric Society. She served in major leadership roles as President of the SAHM (1989-1990) and President of the AAP (2007-2008). Dr. Jenkins has delivered 253 professional presentations and published 64 articles, and 17 book chapters and monographs. It's been her honor to serve on community boards, blue ribbon panels, and advisory committees within the District of Columbia and the greater Washington DC area. In addition to these local efforts, she provides expertise and advice to national committees and councils serving as a Member of the Advisory Committee to Director of the National Institutes of Health, a Member of the CDC Advisory Committee on Immunization Practice (ACIP) and a Member of the National Advisory Child Health and Human Development Council of the Eunice Kennedy Shriver National Institute of Child Health and Human Development. She was inducted into Alpha Omega Alpha Medical Honor Society in 1991 and the Institute of Medicine of the National Academy of Sciences in 2002.

BRENDAN LEE, MD, PhD, is the Robert and Janice McNair Endowed Chair in Molecular and Human Genetics, Professor and Chairman of the Department of Molecular and Human Genetics at Baylor College of Medicine. Dr. Lee co-directs the joint MD Anderson Cancer Center and Baylor College of Medicine Rolanette and Berdon Lawrence Bone Disease Program of Texas, and the Baylor College of Medicine Center for Skeletal Medicine and Biology. He is Founder and Director of the Skeletal Dysplasia Clinic at Texas Children's Hospital, and of the Medical Student Research Track at Baylor. As a pediatrician and geneticist, Dr. Lee studies structural birth defects and inborn errors of metabolism. Dr. Lee has received local and national recognition including election to the Institute of Medicine (IOM), Texas Academy of Medicine, Engineering, Science, and Technology (TAMEST), Association of American Physicians (AAP), the American Society for Clinical Investigation (ASCI), the TAMEST Peter O'Donnell Award in Medicine, the Society for Pediatrics Research (SPR) E. Meade Johnson Award for Pediatrics Research, the Michael E. DeBakey Excellence in Research Award, the American Philosophical Society's (APS) Judson Darland Prize for Patient-Oriented Clinical Investigation, and Best Doctors in America. Dr. Lee was also a former Investigator of the Howard Hughes Medical Institute prior to becoming Chair of the Department of Molecular and Human Genetics. The Department is the leading genetics program integrating basic, translational, clinical, and diagnostic laboratory activities performed by over 65 tenured and tenure-track faculty. It ranks #1 in total NIH funding and number of NIH grants by a wide margin.

MAUREEN LICHTVELD, MD, MPH, has 35-year experience in environmental public health and currently is Professor and Chair, Department of Global Environmental Health Sciences, Tulane University, School of Public Health and Tropical Medicine. Her research focuses on environmentally induced disease including asthma and cancer, health disparities,

environmental health policy, disaster preparedness, and public health systems. She holds an endowed chair in environmental policy and is Associate Director, Population Sciences, and Louisiana Cancer Research Consortium. Dr. Lichtveld has a track record in community-based participatory research with a special emphasis on persistent environmental health threats affecting health disparate communities living in disaster prone areas. As Director of the Center for Gulf Coast Environmental Health Research, Leadership, and Strategic Initiatives, Dr. Lichtveld serves as Principal Investigator of several Gulf Coast-associated environmental health research and capacity building projects ascertaining the potential impact of the Gulf of Mexico Oil spill: the NIH-funded Transdisciplinary Research Consortium for Gulf Resilience On Women's Health, addressing potential post- oil spill effects on vulnerable pregnant- and non-pregnant women; "Risk and Resilience in Environmental Health", a project designed to implement rapidly deployable community-based research, outreach and education; and the Gulf Region Health Outreach Program's Environmental Health Capacity and Literacy Project, aimed at strengthening individual and community resilience through an environmental health clinical referral network, emerging scholars, and trained community health workers navigating frontline health services. Dr. Lichtveld was elected President of the Hispanic Serving Health Professions Schools. She was honored as CDC's Environmental Health Scientist of the Year and twice named Woman of the Year by the City of New Orleans.

MARIE LYNN MIRANDA, PhD, is Professor and Samuel A. Graham Dean in the School of Natural Resources and Environment and Professor in the Departments of Pediatrics and Obstetrics & Gynecology at the University of Michigan. In addition to her administrative leadership responsibilities, Dr. Miranda directs the Children's Environmental Health Initiative (CEHI), which is a research, education, and outreach program committed to fostering environments where all people can prosper. CEHI emphasizes the environmental health sciences and social justice components of risks borne by children in the United States and internationally. CEHI received the USEPA Environmental Achievement Award in 2008. CEHI runs geospatial training programs both at the University of Michigan and nationally. CEHI is also leading a significant effort in developing geospatial informatics to support health care delivery and improvements in population health through its component center, the National Center for Geospatial Medicine (NCGM). NCGM is working in five different locations throughout the United States to apply geospatial methods to improve outcomes for disadvantaged populations. Dr. Miranda maintains a deep and abiding personal and professional interest in social and environmental justice.

CHERYL PERRY, PhD, is Professor at the University of Texas School of Public Health, the Rockwell Distinguished Chair in Society and Health, and Regional Dean of the Austin Regional Campus. Dr. Perry has over 36 years of experience in the design, development, implementation and evaluation of school and community programs for young people. These primarily have involved group-randomized trials funded by the NIH to prevent the onset of tobacco, alcohol and drug use; and to promote healthy eating and physical activity. She was the Principal Investigator of the Child and Adolescent Trial for Cardiovascular Health (CATCH), Project Northland, the Minnesota Smoking Prevention Program, DARE Plus, and Project MYTRI (India).

Dr. Perry served as the Senior Scientific Editor for the 1994 and 2012 Surgeon General's Reports on tobacco use among young people. She testified as a key witness for the State of MN in the state's tobacco trial in 1998. Dr. Perry is currently the Principal Investigator of the Tobacco Center of Regulatory Science on Youth and Young Adults, funded by the NCI/NIH. She has over 285 publications in the scientific peer-reviewed literature. She received her PhD in Education from Stanford University.

HUDA ZOGHBI, MD, is Professor of Pediatrics, Neurology, Neuroscience, and Molecular and Human Genetics at Baylor College of Medicine and serves as an Investigator with the Howard Hughes Medical Institute. She is also the Director of the Jan and Dan Duncan Neurological Research Institute at Texas Children's Hospital. Zoghbi's interest is in understanding healthy brain development as well as what goes awry in specific neurological conditions. She has published seminal work on the molecular basis of Rett syndrome and on late-onset neurodegenerative diseases. She trained many scientists and physician-scientists and is a member of several professional organizations and boards. Among Dr. Zoghbi's recent honors are the March of Dimes Prize in Developmental Biology and the Dickson Prize in Medicine. In 2000 she was elected to the Institute of Medicine, and in 2004 she was elected to the National Academy of Sciences.

LYRIC JORGENSON, PhD (executive secretary), is a Health Science Policy Advisor and Analyst in the Immediate Office of the Director at the National Institutes of Health under the Deputy Director for Science, Outreach, and Policy. In this position, she provides senior leadership, direction, and oversight of new, high impact NIH scientific initiatives across the NIH Institutes and Centers and conducts analyses on a wide variety of policy issues of high-priority to NIH and the United States Government. Most recently she has assisted in the creation of the National Center for Advancing Translational Sciences and was the lead staff on the Brain Research through Advancing Innovative Neurotechnologies Initiative at NIH. She has received numerous awards in recognition of her accomplishments and service. Dr. Jorgenson was previously an AAAS Science and Technology Fellow at the National Institutes of Health and earned a doctorate degree from the Graduate Program for Neuroscience at the University of Minnesota-Twin Cities.

APPENDIX B – STAKEHOLDER CONSULTATIONS

Expert Consultants

Nancy Adler, PhD – Vice Chair of the Department of Psychiatry and the Lisa and John Pritzker Professor of Psychology, Departments of Psychiatry and Pediatrics, University of California, San Francisco

Linda Birnbaum, PhD – Director of the National Institute of Environmental Health Sciences, National Institutes of Health

Robert Blum, MD – William H. Gates Sr. Professor and Chair of the Department of Population, Family and Reproductive Health, Johns Hopkins Bloomberg School of Public Health

Francis Collins, MD, PhD – Director, National Institutes of Health

Greg Duncan, PhD – Distinguished Professor in the School of Education, University of California, Irvine

Lynn Goldman, MD, MPH – Dean of the Milken Institute School of Public Health, George Washington University

Bernard Goldstein, MD – Emeritus Professor and Dean, University of Pittsburgh Graduate School of Public Health

Alan Guttmacher, MD – Director of the Eunice Kennedy Shriver National Institute for Child Health and Human Development, National Institutes of Health

Steven Hirschfeld, MD, PhD – Associate Director for Clinical Research and Director of the National Children's Study in the Eunice Kennedy Shriver National Institute for Child Health and Human Development, National Institutes of Health

Philip Landrigan, MD – Dean for Global Health, Professor of Pediatrics and Preventive Medicine, and Director of the Children's Environmental Health Center, Icahn School of Medicine at Mount Sinai

Michael Lauer, MD – Director of the Division of Cardiovascular Sciences in the National Heart, Lung, and Blood Institute, National Institutes of Health

Teri Manolio, MD, PhD – Director of the Division of Genomic Medicine in the National Human Genome Research Institute, National Institutes of Health

David Murray, PhD – Associate Director for Prevention and Director of the Office of Disease Prevention in the Office of the Director, National Institutes of Health

Stephen Rappaport, PhD – Professor of Environmental Health, University of California, Berkeley

Organizations and Stakeholders Submitting Unsolicited Comments

American Academy of Pediatrics

Consortium of Social Science Associations

Pediatric Policy Council

Society for Maternal-Fetal Medicine

The Teratology Society

Dean Baker, MD, MPH

Michael Bracken, PhD, Steven Buka, PhD, Jane Cauley, PhD, Maureen Durkin, PhD, Charlotte Hobbs, MD, PhD, and Nigel Paneth, MD, MPH