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Eunice Kennedy Shriver National Institute of
Child Health and Human Development
Scientific Vision Workshop
on Developmental Origins of Health and
Disease

February 14–15, 2011
Bethesda, Maryland

Workshop White Paper

by Workshop Organizers:
(in alphabetical order, by role)

Kjersti Aagaard-Tillery, M.D. (Co-chair)
Baylor College of Medicine

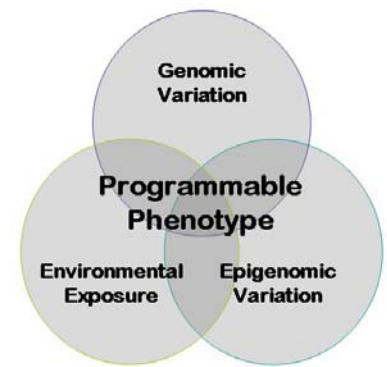
Kent L. Thornburg, Ph.D. (Co-chair)
Oregon Health & Science University

Ira M. Bernstein, M.D.
University of Vermont

David A. Washburn, Ph.D.
Georgia State University

NICHD Workshop: Developmental Origins of Health and Disease

Overview. Our nation faces a crisis of increasing chronic disease on an epidemic scale that will reduce the health and welfare of our citizens and will impose ever increasing financial burdens on society. The outcomes arising from chronic diseases have their roots in fetal and early childhood development. These include obesity, type II diabetes, insulin resistance, cardiovascular and atherosclerotic disease, dyslipidemia, and cognitive and behavioral disorders. Moreover, these diseases do not await adulthood to manifest, but rather appear now as chronic disorders in childhood and adolescents. Such disease burdens are predicted to affect the majority of young Americans in the coming few decades. The current focus of research infrastructure on what some view as reductionist science may limit our ability to conduct meaningful research that fully addresses the complexity of translating nearly three decades of understanding into public policy. We believe that we now have the scientific potential to significantly increase disease-free status of our society, but our ability to execute this change is hampered by lack of organizational structure and public support. In addition, mechanisms by which new scientific information can be translated and fully disseminated to the public are few.



Over the last several decades, the population-based morbidity and mortality from infectious diseases has significantly declined. Over this same interval, the burden of chronic metabolic, cardiovascular, and pulmonary disorders has exponentially increased to reach present epidemic levels. Because these relative states of health and disease have their origins in the critical windows of development, resolution ultimately falls within the purview of the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD), whose scientists could offer the greatest insights into their epidemiologic and mechanistic underpinnings. It is within the reach of NICHD clinicians and scientists to translate their understandings and cures to the public whom they serve.

Scientific Opportunities and Realizing the Opportunities by Key Concept

White paper organization: Under the four Key Concepts that framed the workshop, we have included three subtitles in each key concept section, with specific discussions of the overview (*framing the scientific opportunities*), the opportunities themselves (*scientific opportunities*), and methods that might be developed to enable these opportunities (*realizing the scientific opportunities*).

Key Concept 1 “Influence of Early Life Events on Health and Disease”

Framing the Opportunities

Evolutionary change is the result of natural selection, which alters heritable genetic traits over multiple generations. Natural selection is fundamentally different from programming in that natural selection acts upon genetic traits within a population that have survival value, and programming is the result of changes in gene expression patterns in the absence of alteration in the gene code but as a preserved response to the so-called histone code (or epigenome). In addition, emerging evidence points to a potential fundamental role of the emerging “second genome”-or microbiome metagenome-in laying down the developmental metabolic profile. *How do we study the influence of developmental exposures on later-in-life health and disease?* The main challenge in understanding the mechanisms that determine the developmental origins of health and disease (DOHaD) is that complex, integrated physiological systems among mammals are immersed in a complex environment that changes over time. Further, the characteristics that make up “normal health,” such as changes in height and weight, metabolic function, and neurodevelopment, as well as social and emotional function, are

quite diverse in the human population. There are few tools available to identify factors that represent risks for future healthy or deleterious outcomes.

While the study of programming holds great promise in understanding the biological propensities for disease, that promise is unlikely to be borne out in the present investigational environment, where independence and “silo-ed” thinking are more often rewarded than teamwork. Rapid progress will require an integrated, interdisciplinary approach to the study of human biological complexities that are the distinguishing features of the normal and abnormal states. Progress will require the expertise of basic, clinical, and translational scientists, pediatricians, maternal-fetal medicine specialists, physiologists, environmental biologists, biostatisticians, sociologists, behavioral scientists, health economists, health informatics experts, geneticists, microbiologists, and epidemiologists, at least. Given this background, states of health can be studied in various ways. The first is simply to define health as the absence of disease, but the collective opinion of workshop participants was that this negative definition was not as strong as other, positive definitions including: 1) Achieving growth/developmental milestones/standards; 2) Achieving an optimum standard (e.g., linear height at age 25); 3) Ability to maintain biological function over time; and 4) Ability to adapt in response to stress (i.e., robustness of the individual). In other words, health states lie on a continuum. Dichotomizing into “normal” vs. “disease” is necessary for clinical medicine, but the extent to which clinical or public health interventions in early human development are effective and cost-effective is not clear. It is possible that the same state can be healthful at one age and deleterious at another. “Normal” adaptations to an environmental condition can lead to disease and premature death later in life. The premise of programming is that an individual can have “normal” genes and simultaneously have gene expression patterns that lead to disease. This further complicates defining states of health. In a development context, health may be regarded as emergent rather than static, more about trajectory and process than a state of being at one point in time.

The Scientific Opportunities

Longitudinal analyses of anticipated healthy subjects and at-risk cohorts: The “life course approach” to studying cohorts would identify late-life factors that arise from early trajectories set by environmental conditions. Disease prevention should be a major theme of future investigations. Several types of such investigation should be considered, including efficacy studies in controlled settings, effectiveness studies in “real world” settings, and translational studies that apply findings in one setting to another. This last type should be informed by *implementation science*, which is not often applied in the developmental origins setting. Cohort studies should focus on: 1) Multi-level ‘omic scientific approaches (including and notably the developmental exposome and microbiome, 2) Growth trajectories in distinct identifiable populations, 3) Plasticity pathways; 4) Utilization of long-term cohorts in an innovative manner, including methods that allow for overlapping cohort designs, identification of better surrogate outcomes, and simulation of population and/or interventional approaches—including population-based cost-effectiveness analyses. Research studies should be designed to relate the process of aging to earlier patterns of growth *in utero* and during post-natal and childhood years.

Investigating phenotypic, genomic, and behavioral programming from multiple innovative angles:

Phenotypic programming refers to changes within individuals derived from expressed genes; patterns of gene expression that result from genomic, epigenomic, and metagenomic variation in response to environment. Risks for disease in adult life are influenced by these factors; thus, an improved understanding of the interplay among aspects of phenotypic programming will be important in order to determine relative risk of different disease states.

Genomic plasticity refers to the ability of genes to be differentially expressed according to environmental cues and is largely determined by changes in gene expression, epigenomic mechanisms, and fluctuations in the

metagenome. Genomic plasticity appears to be the mechanistic substrate for programming and may have evolutionary consequences; the genomic plasticity that is manifest during development may be crucial for survival under different environmental conditions, including nutritional, pharmacological, and toxicologic challenges.

The life approach model is important because it is based on the fact that people engage in behaviors that alter their phenotype as they age. Understanding the role of *both* maternal and paternal impact on behavioral plasticity was deemed to be important by workshop participants.

Define normative reference values: Innovative studies of “normal” fetal growth, neonatal anthropometry, and postnatal growth are needed and should include new ways to evaluate “optimal” prenatal and postnatal nutrition. Recent research in clinical obstetrics has developed customized growth curves incorporating maternal pregravid body mass indices and race/ethnicity. Understanding the influence of racial and ethnic differences and socioeconomic disparities in health is crucial for understanding developmental processes that lead to health decline with age. Studies assessing neonatal fat mass have demonstrated that two infants with the same birth weight can have markedly different lean and fat mass compartments, with different implications for future health. Defining normal weight, body composition, and growth for optimal developmental outcomes will allow researchers to share standards for measuring the impact of programming on future health.

Realizing the Scientific Opportunities

Leverage the current NIH Roadmap initiatives on the Epigenome and Human Microbiome Project: With regard to plasticity and programming, emphasis on leveraging opportunities within the current NIH Common Fund was regarded by the workshop, as a whole, to be both necessary and sufficient for many of the interrogations into DOHaD. Strong emphasis was placed on microbiome and epigenome research within this framework. It was pointed out by many present that NICHD-funded investigators are active and contributing members to multiple levels of these Common Fund initiatives.

Develop inter- and trans-disciplinary systems science approaches for DOHaD: Determinants ranging from the global to the genetic interact over time to become embodied in individual health trajectories. One response is reductionist: to deeply dive into mechanisms at the physiologic, cellular, molecular, and genetic levels, both *in vitro* and *in vivo*. Another response is to embrace the complexity by applying new methods, such as systems science (e.g., system dynamics, agent-based modeling), that have been used in basic biology, in organizational management, and other fields, but less in DOHaD. These approaches may identify the most promising levers for intervention in observational studies, and the most effective implementation approaches in intervention studies. *Interdisciplinary approaches* are the hallmark of DOHaD research, and need to be fostered. Barriers to facilitating investigators working together include administrative issues, including institutional review boards (IRBs), animal welfare standards, the Health Insurance Portability and Accountability Act (HIPAA), indirect cost agreements, and others. Some advances that can catalyze interdisciplinary approaches include: 1) Harmonizing measures across studies; 2) Infrastructure for data management, processing, programming, and sharing, to create tractable datasets for integrative analyses; 3) User-friendly bioinformatics tools; 4) Resource sharing, e.g., biosamples; new technology/bioengineering with a focus on imaging for accurate and objective measures of body composition, 5) Industry partnership for instrumentation, and 6) Improved biosampling (fetus, placenta) with a focus on single-cell and laser-capture technologies. Socioeconomic and behavioral factors may contribute to adverse outcomes, but these factors are ubiquitous in nature, subtle, and difficult to study. Behavioral studies may include the contributions of cognitive psychologists, behavioral scientists, anthropologists and economists. Such interdisciplinary approaches are necessary, as they will enable us to shed light on the meaning of various behaviors in the context of the individual, group, and culture, and will allow us

to develop strategies for sustainable changes in human behavior. Disease prevention strategies should include focused efforts on smoking (changing maternal behavior), alcohol consumption, and food preferences in childhood. Research considerations should include social inequality in specific populations, public policy (school nutrition), and rapid economic development tied to changes in diet and various socioeconomic factors. *Fostering transdisciplinary science* requires a new cadre of investigators trained in multiple disciplines. Trainees could be trained on one discipline but have facility in communicating with others, or could have deep knowledge in more than one discipline (e.g., epigenetics and physiology). This is not to imply that all individuals will necessarily have such breadth of training, but rather that a significant number may benefit from such multidisciplinary approaches. Focus on developmental process rather than disease-specific outcomes, and training in the new sciences (e.g., 'omics, systems science) will help. Training investigators from the developing world and from underrepresented groups in the U.S. is important. Training programs should involve elements of the following: multiple departments, schools, and universities, distance/interactive learning, multiple inter- and trans-disciplinary mentors, and short-term (e.g., NICHD/National Institutes of Health (NIH) summer courses), and long-term (e.g., degree-granting) programs.

Consider the value of comparative biology and unique human populations: Comparative biology and studies of unique human populations may be useful to examine the fundamental questions related to programming, adaptation, and maladaptation. The comparative studies would focus on non-human primates in particular, given their similar biology and tremendous ability for behavior adaptations. With respect to leveraging unique populations, one interesting population includes women of child-bearing age who have undergone bariatric surgery with corresponding changes in diet and the metagenome. Mothers may be followed during pregnancy, and such studies may yield findings with respect to changes in the metagenome and subsequent effects on the fetus. The concern with such studies refers to the generalizability of such investigations. Surrogate mothers may be another group that enables investigators to explore the impact of epigenomic and metagenomic variation on infants developing in mothers with different genetic backgrounds. The relative contributions of *in utero* programming, genetics, and early life exposures may be examined in different studies, including adoption studies and studies of twins separated at birth. Do the concepts of developmental origins or programming only apply to the *in utero* development or also to infancy? Developmental origins or programming may also apply to childhood, adolescence, and early adulthood. Long-term disease consequences including cancer risk may be related to phenotypic programming during fetal development or early childhood, in contrast to programming later in life resulting from specific environmental exposures.

Key Concept 2 “Environmental Impact on Development”

Framing the Opportunities

The central premise of the developmental origins of adult health and disease concept is that environmental cues affect key processes of development and lead to a phenotype that is either vulnerable for disease or resilient and healthy. Determining which environmental cues are sensed at specific stages of development and discovering the mechanisms by which environmental conditions affect development will be difficult. Important barriers to determining environmental impacts include distinguishing the roles of mother, placenta, and fetus in programming and determining early markers of disease non-invasively. Many current clinical conditions lend themselves to a better understanding of environmental effects on health and disease in clinical obstetrics and should be exploited. Examples that were brought to light included the effect of cesarean vs. vaginal delivery and preterm vs. term delivery on the gut flora (i.e., infant microbiome). Similarly, the assisted reproductive technologies (ART) setting provides a unique opportunity for a variety of studies, including, 1) assessing the effects of lifestyle and exposures on the likelihood of achieving a pregnancy, 2) evaluating longitudinal changes

in the maternal environment during pregnancy and later life, 3) assessing environmental effects on male sperm development, and 4) evaluating human correlates of experimental embryo transfer experiments to assess the effects of maternal metabolic environments on epigenetic events in the fetus.

The Scientific Opportunities

Go global: Global initiatives are needed to allow multi-institutional data to be obtained and analyzed. It was the overwhelming consensus among participants that the time is right for more global initiatives to address complex issues in relation to developmental origins of disease. For example: 1) Large multispecies collaborative experimental efforts could provide comparative data on environmental effects across a broad range of species. 2) Large-scale human research supported by multiple NIH institutes, and, potentially, other worldwide agencies could facilitate projects from many countries. For example, an initiative supported by NICHD, the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), and the National Institute of Environmental Health Sciences (NIEHS) that required interaction among scientists with different areas of expertise could set the stage for studies that would elucidate causes of metabolic disease in association with environmental contaminants, and thereby stimulate the development of intervention strategies.

Exploit existing opportunities: Many conditions in clinical obstetrics could be studied to determine environmental conditions that may relate to health and disease states in offspring. Examples include the effect of cesarean vs. vaginal delivery and preterm vs. term delivery on the gut flora of the neonate. In addition, offspring from ART programs provide a unique opportunity for studies including: 1) assessing the effects of lifestyle and environmental exposures on the likelihood of achieving a pregnancy, 2) assessing environmental effects on male sperm development, and 3) evaluating the influence of the maternal metabolic environments that manifest as epigenetic modifications in the fetus. Because phenotypic traits and the epigenomic footprints of the placenta provide a record of the intrauterine environment in which the fetus was grown, characterizing these features could include size and shape, cord insertion site, stereological histology, functional assessments like inflammatory mediators, signaling pathways, nutrient transporter activity, and biochemical markers like growth and angiogenic factors. Findings could be correlated with fetal growth patterns, maternal exposures, and long-term outcomes. A major problem determining the complexities of environmental exposures in human studies is obtaining adequate lifestyle and social information over time. Commercial entities have developed new methods of obtaining consumer web-based and electronic data that could be used to gather such data from specific population groups.

Consider the placenta as an integral part of the in utero environment: There is an increasing awareness that the placenta responds to and modulates maternal exposures, necessitating determination of maternal and fetal exposures separately. Indeed, it is plausible that the fetal programming effect of many maternal exposures is mediated—at least in part—by changes in placental function. For example, down-regulation of placental 11 β -HSD2 (resulting in increased fetal exposure to cortisol) and decreased activity of key placental nutrient transporter (limiting fetal nutrient availability) play an important role in mediating the restricted fetal growth and programming effects of maternal under-nutrition and reduced utero-placental blood flow. It is possible that the placenta has a limited repertoire of molecular responses to a wide variety of maternal exposures, which could explain why different maternal exposures have similar fetal outcomes. It was generally felt that the placenta is understudied. How can we measure the dynamic function of the placenta? Placental functional measures *in vivo* using advanced imaging technologies, single-cell experimentation, and high-throughput technologies for genomic/epigenomic/metagenomic and transcriptomic technologies are tools that could be used.

Placental opportunities: Opportunities that focus on the placenta as a unique measure of environmental influences should consider the following: How can we measure the dynamic function of the placenta at different gestational age points in a prospective and non-invasive manner across time, taking into account exposure measures? To what degree can the placenta serve as a diary of the pregnancy? Is this also true for amniotic fluid? Can additional amniotic fluid measures be considered, i.e., drug metabolites, nutritional byproducts, and the microbiome? Can placental biology be related to surrogate markers of maternal and child health, and robustness later in life?

Placental physiology: Our current understanding of the physiology linking maternal environment with fetal programming is limited. Yet the mother and the placenta play a central role in modulating the environmental signals delivered to the fetus. For example, maternal pancreatic function and peripheral insulin resistance determine whether a given dietary glucose load results in fetal hyperglycemia. The placenta's response to environmental signals may determine fetal programming. Maternal nutrition during pregnancy and lactation may affect mobilization of stored toxins, such as lead and fat-soluble chemicals, into the fetal compartment and into breast milk. Unraveling the effects of the maternal and placental phenotype on fetal exposure will require an integrative approach to reproductive physiology. Lastly, the placenta provides an opportunity for "phenotyping" the intrauterine environment to understand the impact of environmental exposures on fetal development. Placental phenotyping could include structural (stereology) and functional assessments (e.g., inflammatory mediators, signaling pathways, and nutrient transporter activity), and should be correlated with maternal exposures and maternal, fetal, and longer term outcomes.

Define the earliest reliable markers and modifiers of metabolic disease, and understand the role of the environment on these markers: DOHaD epidemiologic research has linked developmental exposures with health outcomes in late adulthood. It is not currently feasible to link prospectively-collected perinatal data with such outcomes, and therefore, intermediate markers and study of diseases with onset in childhood are needed. Fairly robust markers exist for obesity, hypertension, and glucose and lipid homeostasis. However, epidemiologic work suggests tradeoffs with increasing birth weight, for example between cardiovascular disease (CVD) and breast cancer risk. Measuring these tradeoffs requires ways to assess early markers of risk for multiple diseases across the life course. In addition, more work is needed to assess DOHaD outcomes beyond CVD and the metabolic syndrome, including outcomes related to immune function and the microbiome, neurobehavior, and reproductive endocrinology.

Consider the gestational age at birth as a unique environmental exposure: Gestational age at birth is associated with long-term differences in phenotype, even among infants born after 37 weeks gestation. Potential mediators include nutrition, infection, hormone exposures, drug exposures, early neonatal behavioral interactions, etc. Many of these might be amenable to intervention if their role were understood.

Explore multimodal interventions prior to conception (i.e., in adolescence) as environmental contextual clues: Interventions during pregnancy have had limited success in altering developmental programming, and single-exposure interventions (e.g., diet, physical activity, substance use) have not been promising. Preconception multimodal interventions, beginning as early as a mother's childhood or adolescence, may be needed. Multimodal interventions focusing on the areas of health and well-being most important to populations at highest risk could mitigate the effects of low socioeconomic status (SES) on DOHaD outcomes.

Realizing the Scientific Opportunities

Develop social networking- and communication-based tools to quantify associations between exposures or behaviors and outcomes: Social networking sites and internet search engines can profile consumer behavior and market to precise demographic groups. Such technology also holds promise for measuring behavior, SES,

environmental exposures, and other environmental determinants of health. Moreover, internet search engines have been used to monitor outbreaks of influenza with greater precision than that of the Centers for Disease Control and Prevention. Studies are needed to determine whether similar approaches can be used to identify families for study. For example, this approach could be used to engage families with specific environmental exposures childhood diseases such as asthma, preeclampsia, gestational diabetes, reproductive experiences, and other factors and conditions.

Develop new technologies for human studies: New technologies that enable us to understand social influences on behavior and how such influences are mediated through biochemical changes need to be exploited. The development of new technologies to capture the frequent behavioral changes that pregnant women and children make is essential. For example, a woman's diet may change markedly during pregnancy. To capture diet accurately during critical periods of fetal development, new methodologies for collecting comprehensive, real-time dietary information are essential. Given the rapid changes in technology (e.g., online viewing has replaced broadcast television for most adolescents and young adults), new methodologies must account for and utilize new information technologies. A major problem in estimating complex exposures in human studies is obtaining adequate lifestyle information and follow-up data. Commercial entities have developed new methods of obtaining consumer data that should be incorporated. Geographic information system technologies could also be exploited to estimate exposures. Similarly, we need to exploit new communication technologies (e.g., text messaging, email) to provide rapid, real-time feedback to study participants. Steps need to be taken to educate institutional review boards (IRBs) about the potential utility of these data sources in research studies.

Leverage unique exposure models that occur “naturally” with deployable standardized tool kits: Exposures to environmental stressors, such as the Dutch famine, provide opportunities to investigate the role of environmental exposures in fetal programming. Disasters such as the BP oil spill allow scientists to assess the effect of an exposure, with a precise time of onset, that affects ongoing pregnancies and their outcomes, both at birth and beyond. Assisted reproductive technology (ART) provides opportunities to measure the effects of genotype, in combination with the *in utero* and postnatal environment, on development. Studies of donor egg, donor sperm, and gestational carrier pregnancies, compared with ART pregnancies using the intended parents' gametes, would allow us to answer key DOHaD questions. This approach would necessitate the development of “Exposure Measure and Environmental Assessment Tool Kits for Ready Deployment.” These would be uniform “data collection kits” or “environmental assessment tool kits” to be deployed when profound, immediate, discrete environmental exposures occur. Examples include interrogating the BP oil spill as an immediate proxy of petrochemical effects, and H1N1 and subsequent disruptions in the microbiome. Ultimately, this approach would create opportunities at an NIH-wide level for developing comprehensive tool kits of social and behavioral measures, cross-population studies, biologic measures and exposure measures, and epigenomics. Moreover, leveraging opportunities in the community might include the Clinical and Translational Science Awards program (CTSA) and the National Children's Study (NCS), as well as nontraditional community advocacy groups and community-based research efforts.

Develop new methods for assessing fetal exposure: New tools are needed to determine what signals the fetus is exposed to and how these signals affect fetal development. Such tools could include non-invasive, safe bio-monitoring methods (see above). Understanding the developmental effects of fetal exposures requires the development of a variety of new tools, including: 1) non-invasive, safe biomonitoring methods (e.g., prenatal imaging, detection of drugs in blood, analysis of placental tissue), 2) methods for sharing existing data sets and merging new ones, 3) methods for unfocused examination of human samples to detect contaminants, 4) improved biobanking of relevant tissues (e.g., placenta, stillbirth, autopsy material), and 5) improved interfaces with bioinformatics.

Support long-term follow-up of clinical studies: Randomized clinical trials of prenatal interventions could test the causal effect of exposures during development on health and disease. In addition, many large birth cohort studies in the U.S. and throughout the world have rich biobanks along with exposure data with which to test DOHaD hypotheses. Funding approaches are needed to support follow-up of existing cohorts and the establishment and maintenance of long-term cohorts. Such long-term follow-up should be planned at the inception of new studies. For example, registration of clinical trials could require specification of plans to allow long-term follow-up.

Establish an international clearinghouse of datasets, bio-banks, and cohorts: Participants in the workshop noted multiple missed opportunities for collecting longitudinal data in the current clinical infrastructure in the U.S. For example, a woman who is undergoing ART will provide multiple blood samples and extensive data to her reproductive endocrinologist, her obstetric provider, and her infant's neonatologist or pediatrician, yet linking these records and specimens is prohibitively complex. Issues of patient privacy and HIPAA, as well as discordant electronic medical records and clinical labs across disciplines, prevent meaningful longitudinal studies using already-collected clinical data. Publically available directories of datasets such as dbGaP (database of Genotypes and Phenotypes, <http://www.ncbi.nlm.nih.gov/gap>) provide researchers with an index of available data, and with access to genotype and phenotype information for analysis. A similar database, indexing DOHaD cohorts, including measured exposures and outcomes, availability of biobank samples, and contact information for access, would accelerate the pace of research in this area.

Encourage public participation in trials in innovative ways, recognizing most of our population of interest is young and will engage in research if recruited in non-traditional ways. Marketing campaigns are needed to engage reproductive-age women to participate in both observational and intervention trials during pregnancy. We need to develop and test online strategies, similar to the Susan Love Army of Women, to identify interested families and test the feasibility of novel study designs, such as by-mail specimen collection during pregnancy.

Develop international standards for meaningful and translatable research: Varied methods have been used to measure maternal diet, physical activity, behavior, psychological profile, and social stressors. Moreover, cohort studies have used a variety of methodologies to collect, process, and store biospecimens. Development of international consensus standards for such work, including standards for study design, would facilitate collection of high quality data and specimens and facilitate combining cohorts for analysis of rare outcomes. This approach could build on the existing PhenX toolkit (<https://www.phenxtoolkit.org/>).

Foster independent research studies on environmental exposures: Measuring the effects of environmental exposures on developmental outcomes should be conducted free from corporate or political pressures.

Develop meaningful and relevant animal models on environmental exposure: Currently, there are few relevant animal (i.e., primate and higher order mammals) models for preterm birth or preeclampsia, and this dearth of animal models limits our ability to study important translational questions. For example, what is the effect of an environmental exposure *in utero* in late pregnancy vs. after birth, in a preterm infant? And what are the consequences, for mother and child, of expectant management of severe preeclampsia, remote from term, vs. induction of labor?

Address scientific and workforce challenges: Realization of the recommendations above would require the development of: 1) new models and initiatives to support multi-disciplinary science, 2) new or improved animal models for human diseases, 3) new training and career development strategies to ensure the success of new research models and the inclusion of young investigators, 4) partnerships with industry to develop improved methods of collecting detailed lifestyle and exposure information, 5) multinational collaborations to provide a broader spectrum of environmental exposures, and 6) an environment protected from self interested parties.

Key Concept 3 “Understanding Complex Molecular Interactions”

Framing the Opportunity

A pressing knowledge gap in the developmental origins field is the lack of understanding of how gene expression is affected by the environment. Within that larger question are issues related to how epigenetic mechanisms integrate with other biological processes, including the regulation of cellular function and interactions with the microbiome. The degree to which genetic vs. epigenetic inheritance underlies disease vulnerability and biological resilience across generations remains a looming question as do the roles of maternal vs. paternal contributions to biological propensities for disease. In the past decade the ability to characterize the human genome has improved enormously. There is now an unprecedented opportunity to identify genetic markers that predict disease in association with known environmental conditions in early life. However, despite technological advances, genome wide association studies have not been as successful as needed in identifying genotypes that predict disease. While there is no doubt that genes do not act in isolation and that certain single nucleotide polymorphisms (SNP) can predispose to deleterious outcomes, the penetrance of such SNPs is usually low. It is more likely that SNPs act in concert with variations in other genes and environmental exposures to determine the transcriptome, proteome, and metabolome and that these together confer risk for healthy or disease outcomes. It is highly likely that epigenetic modification of gene expression is determined by environmental exposures. The resulting genetic modification is termed the exposome. Hence the epigenome is predicted to be an excellent reflection of environmental exposures and together with genotype will characterize an individual’s risk for disease.

Comprehensive longitudinal study of large, national cohorts, with extensive molecular characterization, identification, and quantification of the effect of specific environmental exposures on pregnancy outcome and long term health in offspring, would enable early diagnostic and therapeutic interventions in pregnancies at risk and could improve the health of individuals in post-natal life. The National Children’s Study (NCS) could be modified to include more data that relate directly to developmental origins of disease. Early intervention in adolescent populations prior to conception would result in better informed women and men prior to pregnancy so as to permit identified, modifiable factors, such as elevated body mass index (BMI), micronutrient deficiencies, and smoking, to be addressed. This research program could ultimately result in healthier gametes, better fertility, and improved life-long health across the population in the next generation. A positive outcome of such research would engender public trust in such research, as working for the public good.

The Scientific Opportunities

Leverage intervention trials under way for follow-up analyses: This topic was discussed by nearly every breakout group on every key concept. They all recognized the need to leverage ongoing intervention trials that take place proximal to or during pregnancy so as to enable long-term follow up of both mother and offspring. It would be very time- and cost-efficient to leverage intervention trials already under way before and during pregnancy or at critical early developmental windows (i.e., Maternal and Fetal Medicine Units and Neonatal Research Network programs and global trials) to include long-term follow-up of offspring and to expand biobanks and data collected. Trials in non-Caucasian populations in the U.S., particularly trials in African American, non-white Hispanic, and other disadvantaged populations that have a greater risk for poor pregnancy outcomes should be included. Furthermore, there are trials in other countries, including in developing countries, where the parental environmental exposures are different than those in middle class white populations in the U.S. It was felt that long-term follow up should be considered mandatory and funding mechanisms should be designed accordingly.

Enable intervention trials in human and relevant animal populations: Workshop participants emphasized the importance of engaging in intervention trials in pregnancy aimed at established modalities. These included building off of current initiatives such as the U.N. “1000 Days Movement” and undertaking community-based initiatives on established nutritional and exposure parameters (adequate nutrition, and minimization of bisphenol A exposure). Anticipated “soon to be there” interventions included probiotics and prebiotics.

Identify healthy and unhealthy epigenomic profiles during the life course of an individual: While definitions of healthy and unhealthy are yet to be established, the new epigenomics technologies provide the opportunity to identify healthy and unhealthy epigenomic profiles during the life course of an individual. The imperative to establish these over the life course is predicated on the understanding of early critical windows of development when the individual is vulnerable to environmental factors that program fetal and placental development and influence perinatal and long-term health outcomes. Furthermore, epigenetic status may be modified at later developmental times into late adult life by additional environmental exposures. Advanced technologies make it possible to characterize the epigenome, genome, proteome, metabolome, and even microbiome of individuals across the life course, and the use of these technologies will become less expensive with time. If these analyses are performed on samples from a large cohort recruited at different centers around the country and if information on environmental exposures is also collected, this approach would provide a unique opportunity to understand molecular and environmental interactions. The approach provides a second opportunity to expand and develop multidimensional computational technology to organize and analyze the complex interactions between environment, genome, epigenome, proteome, metabolome, and microbiome.

Determine environmental exposures prior to and during pregnancy in the mother and father (paternal contribution to DOHaD) that affect the epigenome in the offspring and determine their association with intrauterine growth restriction (IUGR) and poor health in post-natal life: Cohorts of pregnant women around the nation should be recruited prospectively with their partners and objective and reliable physiological and biological markers of specific exposures should be developed and applied. A large online database of clinical, psychosocial, and dietary factors should be established across the cohorts to permit standardized collection of information and markers across populations, including those at risk of poor outcomes. An extensive biobank, with associated infrastructure to assess the epigenome, genome, proteome, metabolome, and microbiome for both women and men, will be required. If possible, the same data should be collected for the grandparents of the fetus. Other discussed opportunities would capitalize on nearly unique or unique male attributes, such as the male contribution to ART.

Describe the potential for a GOHaD initiative (gamete origins of health and disease): Periconceptual DOHaD models (or GOHaD) would enable studies of how programming is induced in gametes. For example, the maternal diet influences the oocyte/embryo milieu, leading to altered energy metabolism that in turn leads to epigenomically-regulated compensatory responses and changes in the developmental program. Participants thought that these models could be readily employed in the development of applied interventional strategies.

Consider all non-nuclear genomic mechanisms of inheritability: All breakout groups agreed that the DOHaD field is defined by non-traditional genomics, e.g., cellular mechanisms, including epigenetics, and microRNA (miRNA) as well as mitochondrial DNA (mtDNA) variation. A special emphasis on mtDNA variants and related mechanistic underpinnings was identified as important, given the high rate of mutability and maternal inheritance of an individual’s mtDNA genome. It was felt that researchers were becoming specialists in a single form of epigenetic modification without integrating the different forms of gene expression regulation. Understanding how the different epigenetic mechanisms work together would broaden the options in intervention strategies. It would also illuminate how epigenetic changes contribute to physiological “options” for the organism in a controlled way—rather than as an apparent random loss of normal markings. Expanded

scientific opportunities would encourage “blue skies” research that would go beyond more traditional, discovery-laden research.

Innovative research employing metagenomics in concert with epigenomics in characterizing the DOHaD microbiome: Understanding the human fetal, placental, maternal microbiomes in relation to neonatal and early childhood development was felt by many participants to be pivotal to future mechanistic studies.

Realizing the Scientific Opportunities.

Enable collection of biologic material for mechanistic studies: It was agreed that biological samples should be collected to provide resources for future research and that such samples should include: stem cells from amniotic fluid, cord blood and tissue and placenta across gestation, e.g., chorionic villous sampling and term collection. The placenta is often a mosaic, so collection needs to be full thickness, chorionic and basal plates, and villous tree from multiple sites. Samples need to be fixed for morphological assessment and frozen and held at -80°C for molecular studies. The villous tree is the site of hormone synthesis for maintenance of pregnancy and nutrient, gaseous, and waste exchange and is, therefore, an important site for putative epigenetic effects that program the fetus. Maternal serum, plasma, peripheral blood mononuclear cells (PBMN), DNA, urine, and cervical fluid should be collected across gestation, and a first trimester collection is critically important because early gestational placental morphogenesis and invasion of the maternal uterine vasculature establish the maternal blood supply to the placenta and lay the foundation for sufficient feto-maternal exchange in late gestation, when the fetus is rapidly increasing its growth. Impairments at this early stage predispose to pregnancy complications and poor fetal growth and hence fetal programming of disease in later life. It is already possible to quantify placental analytes in maternal blood at 12 weeks to predict risk for Down syndrome. This technique and others could be used to predict risk for poor fetal growth. Various research groups around the world and in the U.S are engaged in this research now. Additionally, since the father contributes one copy of every gene to the fetus and placenta, he should be sampled (as well as grandparents if possible) for his (their) serum, plasma, PBMN, and DNA. Methods to extract fetal/placental RNA, miRNA, and DNA from maternal plasma have been developed but need further refinement. These samples should be used to establish molecular interactions across gestation and develop a picture of feto-maternal interactions. Samples collected longitudinally should be the subject of high-throughput epigenomic, genomic, transcriptomic, proteomic, metabolomic, and microbiomic characterization. This will require standardized techniques and pipelines and infrastructure that are accessible and interactive, with user-friendly informatics to engage multidisciplinary teams of researchers (clinicians, research nurses, scientists, bioinformaticians, statisticians, computational technologists, systems biologists, and physiologists).

Enhance technological opportunities: Since pregnancy is a dynamic process and includes significant changes in placental differentiation and function across gestation and because placental sampling is not without risk, it is imperative that new non-invasive imaging modalities be developed so that serial placental functional sampling, and quantitative visualisation of maternal exposures at the feto-maternal interface with a variety of environmental agents, become possible. Furthermore, ultrasound technologies need to be improved or, better, a new imaging system needs to be developed to make it possible to measure accurately body composition and dimensions of various compartments of the fetus across gestation. Currently, many cases of IUGR are not diagnosed until after delivery. Better imaging would improve our understanding of normal and abnormal fetal growth patterns and identify the at-risk fetus earlier in gestation than is currently possible. Imaging or other techniques should be developed to enable assessment of factors such as maternal stress, nutritional status, and diet.

Leverage existing databases and models: Notably, with respect to ART, workshop participants suggested combining current Society for Assistive Reproductive Technologies (SART) database(s) with international ART registries to enable integrative queries across population subgroups and with distinct availability of ART resources. For example, in European and Israeli communities there is government support for ART, which enables a distinct socioeconomic group to partake of these resources. Examples of supporting innovative animal models included studies in both primates and mammals, such as the collaborative cross mouse facility (<http://csbio.unc.edu/CCstatus>). Mechanistic studies would include emerging 'omics technologies, and integrate human exposure models.

Leveraging current Roadmap initiatives and creating big “team science” approaches focused on DOHaD mechanisms. Participants emphasized that both human and animal studies in current Road Map initiatives (Human Microbiome Project (HMP) and epigenomics) are inherently focused on DOHaD issues. Bringing in researchers with expertise in each of these arenas would leverage better science.

Address scientific and workforce challenges: Training of cross-disciplinary scientists and physicians will be required to meet the research requirements of the field. Among the necessary combinations of disciplines will be computational biology, statistics, genetics, epigenetics, systems physiology, and nanotechnology. Studies of large cohorts recruited from across the nation with full 'omics characterization and meticulous determination of environmental exposures would require broadly trained specialists in addition to clinicians and research nurses. There is a need for multidisciplinary networks of investigators who could collaborate on multinational studies. Immediate attention to training the next generation workforce would hasten the time when such studies could be under way. The development of large biobanks will require that better, faster, cheaper, 'omics technologies that can use smaller-volume samples also be developed. Ideally, these techniques should become available at the single cell level.

Key Concept 4 “Scientific Policy and Social Issues as Means of Translation”

Framing the Opportunity

For the first time since World War II, we have the likelihood of being less wealthy and less healthy than our preceding generation. Many of the chronic diseases affecting the health of our country have been shown to have their origins in the perinatal time period. While basic mechanistic research will continue to provide valuable insights into the prevention and treatment of these conditions, the complexity of these discoveries requires a multidisciplinary team approach for optimal interpretation and application. Likewise, the bio-psychosocial-economic contributions to both the origin and progression of chronic health conditions do not lend themselves well to study by the current reductionist system of scientific inquiry. How do we communicate the urgency of this message to the population for the common good?

Most of the chronic diseases affecting the health of resource-rich countries have been shown to have their origins in early life. The complexities of chronic diseases require a multidisciplinary team approach for optimal experimental strategies to determine the DOHaD processes. The bio-psychosocial-economic contributions to the origins and progression of chronic health conditions are not likely to be discovered by a reductionist system of scientific inquiry. Thus, the current biomedical research system requires re-engineering to maximize the potential of new technologies and better understanding of disease origins to improve health. Core narratives for scientific discoveries need to be developed and disseminated widely to raise public awareness, solidify public support for health interventions, and move the public to action. Public support must then be used to generate public-private funding mechanisms to provide the scientific infrastructure necessary to translate new discoveries into healthier, longer lives for citizens. The NICHD, along with other institutes, should build strategic plans in

concert with media experts to educate the public about the role of childhood and maternal nutrition in providing the substrate for a healthy baby. Workshop participants acknowledge the need for a balance between studies of core biology and those of environmental context for the advance of DOHaD. Similarly, they reflected that there likely exists a funding balance between “big-science” team projects and traditional single-investigator approaches. Large multidisciplinary and multi-investigator studies with diverse national or international samples are costly and difficult, but yield valuable data that can be used to answer many DOHaD questions. That said, there remain many questions that can be addressed perfectly well with small samples and a focused research team. Investigators need to consider when it is useful to sample and compare populations with different cultures, environments, exposures, and circumstances, and to remain sensitive to potential unintended adverse consequences of such investigations on those populations (e.g., the “blaming the mother” error of dispositional rather than situational attributions and policies that further stigmatize vulnerable populations). NICHD’s guidance on this issue would also be valuable. Public support must be used to generate public-private investments—including innovative long-term funding mechanisms—that can support the workforce and infrastructure necessary to translate these discoveries optimally into healthier, longer lives for our citizens.

The Scientific Opportunities

Optimizing communication aimed at the common good: Our field appears to be failing spectacularly in this area. DOHaD already has a large number of important messages to communicate, but to date those messages have not been disseminated effectively. For example, we know the importance of proper nutrition not only for the health of pregnant women (and women who may become pregnant), but also for their offspring’s long-term health. DOHaD research also instructs us that it is likely that the earliest stages of pregnancy are the most crucial. The messaging and policy implication of this is that programs that intervene only during pregnancy are not going to provide sufficient benefit. Thus, we laud programs like federal Women’s, Infants, and Children’s food program (WIC) that have established national programs and priorities for at least minimum levels of nutrition of women and children, but programs are needed that extend the comparable benefit to reproductive-age women in general. At the same time, we need to focus not only on decisions that girls and young women make in regard to nutritional and environmental exposures, but also on the choices that are available to women, especially women of lower socioeconomic status. This means that the policy issues implied by DOHaD include the existence of “food deserts,” inequitable toxic exposures, and the difficulties of finding opportunities for physical exercise in certain environments. All of this leads us to suggest that it may be time to invest work toward a goal like a Surgeon General proclamation on embryonic sensitivity.

Workshop participants envisioned a cycle of translation and communication in which DOHaD research leads to discovery, which leads to effective dissemination of findings, which leads to change (behavioral change, social change, environmental change, attitude change), which informs policy, which then provides support for another cycle of discovery. Three audiences should be targeted for this dissemination:

- a. *The public:* As has been discussed above, the public is one important audience. DOHaD research is yielding important findings, but neither behavior nor social policy is changing sufficiently to reverse trends of increasing obesity, cancer, diabetes, heart disease, and other chronic conditions. Although further research is needed to understand underlying mechanisms completely, we believe that we are failing to disseminate what we do know effectively to the public.
- b. *The policy makers:* A second audience for our message should be policy makers. Because we have not succeeded in communicating the importance of our research to the public and to policy makers, we have failed to generate political traction to advance DOHaD as a funding priority. We recommend a focus on cost drivers—

like mental health, chronic disease, frailty, and cancer—that should compel funding of DOHaD research. Every dollar of investment into DOHaD discovery can yield many dollars of savings in the areas of these cost drivers. The findings of DOHaD studies do not require a trade-off of proximal benefits for long-term costs; rather, we should communicate that epigenetic programming can yield healthier, smarter babies that develop into healthier adults with longer productive lives. To engender political traction and sustained funding, we need to communicate in ways that rally the public in support of our science, and to make DOHaD research a contemporary “space race” that provides a common motivation to policy makers, scientists, and the general public and that drives our discipline forward.

c. The scientific community: Finally, we must do a better job of dissemination to ourselves, i.e., to scientists in DOHaD research, to physicians, and to related disciplines. We recommend continued development of procedures for promoting interdisciplinary training of scientists, and for building multidisciplinary teams of scientists studying DOHaD problems. We recommend two measures for improving the dissemination of DOHaD science to change public behavior and to develop an appropriate workforce. First, we laud funding programs that ask investigators not only to report on scholarly products (publications, presentations, experiment results) of their research, but also to indicate one or two of the most exciting or important findings or implications for health. A policy like this will encourage NIH-funded scientists to think about the send-home messages from taxpayer-supported investigations.

Acknowledge the limits of reductionist approaches: Core approaches need to be developed for communicating scientific discoveries and opportunities to raise public awareness, move the public to action, and solidify public support for health interventions. This public support must then generate public-private investments—including innovative long-term funding mechanisms—that can support the workforce and infrastructure necessary to translate these discoveries optimally into healthier, longer lives for our citizens. Such demonstrated improvements in health and well-being will, in turn, generate new narratives that can generate further health investments.

Integrate dissemination to the public into concepts of translational research: The ultimate in “translational research” describes full scale public dissemination and public policy revision. What is the role of scientists, government, and environmental and community advocates in creating vital linkages within our society so as to stimulate action? Is there enough of a sense of urgency for multidisciplinary research ultimately to engage in meaningful community discussions? Such developments will build on traditional social science concepts of acceptance and framing, along the lines of “science is progress,” “science is good,” and “science benefits human health.” When are policies across entities in opposition to one another, and when do they work in concert to benefit the public? Progress on health issues requires political traction and cautious evaluation of relative benefits. Results must then be communicated to the public in order to optimize partnerships for both the engagement of research and the communication of its outcome, thus leading to discussions of the “dissemination cycle” of our scientific discoveries to all stakeholders.

Consider racial and ethnic and socio-economic class sensitivities: Because chronic disease rates are high among many minority populations, extra effort needs to be given to studies among people of those populations. Such studies need to be sensitive to the needs and privacy of individuals while gathering the quality of data needed to understand special needs of people in these groups.

Realizing the Scientific Opportunities

Establish an Office of Dissemination for DOHaD research: This Office was envisioned by participants as, preferably, a unit at “arms-length” from NIH, so as to facilitate interfaces among Institutes, NIH-funded investigators, policy makers, and media organizations. Much more than just a media relations office for

generating press releases and similar reports, this Office of Dissemination should work with communication professionals in social marketing—the types of professionals who are already employed by the pharmaceutical and fast-food industries to influence consumer behavior. In this way, NIH and the Office of Dissemination (or whatever it is called, including perhaps under the proposed new NIH National Center for Advancing Translational Sciences) will become an important nexus for improved messaging between DOHaD investigators and our target audiences. At the same time, scientists will recognize their translational responsibility for their research, such that each discovery is accompanied by a commitment to change behavior and to improve health in light of that discovery.

Minimize regulatory and compliance hurdles that hamper progress and collaboration: Under federal regulations for protection of human research subjects, pregnant women, fetuses, and neonates together comprise a special category of research participants that require additional protections (45 CFR 46 Subpart B, 46.203). As a result, investigators pursuing DOHaD research activities may be stymied by IRBs that invoke interpretations of the regulations by the federal Office for Human Research Protections as obstacles above and beyond regulatory intent. However, to the extent that DOHaD research activities are not categorized as greater than minimal risk (e.g., blood draws), these additional protections should not inhibit the IRB approval process. Another issue is that IRBs may interpret the term “vulnerable,” with regard to pregnant women, as “incompetent” and not adequately capable of providing informed consent for themselves, their fetus, or their infant. Some IRBs incorrectly require paternal consent in studies that do not require it, thereby fostering a paternalistic atmosphere. In general, IRBs are typically not regarded as partners in the research endeavor, but as adversaries to the research process. Understanding and adopting best practices of the more effective IRBs, can streamline the process while maintaining high ethical standards and protections. In addition, policies that promote reciprocity among institutions can foster interdisciplinary and multi-site work. The IRB and other regulatory/oversight bodies serve essential functions in this research, and this functional significance is threatened by administrative inefficiencies. Similarly, an Institutional Animal Care and Use Committee (IACUC) can be a barrier to research. Again, the problem is not that regulations and oversight exist, but rather that the local IACUC can create obstacles to research through mission drift, bureaucracy, and inconsistency. Although research protocols require stipulation that proposed research does not unnecessarily duplicate previous work, and peer-reviewed publication and funding practices ensure that work isn’t duplicated unnecessarily, there is no comparable procedure for eliminating redundancies and inefficiencies in local compliance (IRB and IACUC). The result of the increasing burden of compliance and reporting requirements (including also HIPAA, and the National Science Foundation’s administration of statutory Responsible Conduct for Research rules) is that large portions of each scientist’s time and effort are invested in administrative tasks that are ancillary to the actual science. NIH should facilitate streamlining, reliance agreements, and best practices that reduce the paperwork demands for investigators without compromising protection for human and nonhuman-animal participants and the scientists who study them.

Engage the larger community and greater collective conscience: Armed with decades of knowledge, but given the limits of reductionist science, we need to now develop “ideas, teams, and tools.” The ideas will modify the upstream contributing factors to improve health and reduce the disease burden in society, thereby enhancing educational outcomes and economic prosperity. The teams will reshape the culture, moving from single or multi-investigative led initiatives to full public and policy engagement. The tools will start with a process map to achieve healthier, longer lives in partnership with communities. Such tools will deploy core partnerships and focused discussions into communities. An innovative tool suggested by workshop participants was “science bonds,” to support a sustainable and innovative research workforce and products.

Summary of Scientific Opportunities from the Vision Meeting

Over the prior two decades, the population-based morbidity and mortality from infectious diseases has significantly declined. Over this same interval, the burden of chronic metabolic, cardiovascular, and pulmonary disorders has exponentially increased to reach present epidemic levels. Because these relative states of health and disease have their origins in the critical windows of development, their resolution ultimately falls within purview of NICHD, whose scientists could offer the greatest insights into their epidemiologic and mechanistic underpinnings. It is within the reach of NICHD clinicians, scientists, public policy makers, and chosen representatives to translate their understandings and cures to the public to whom they serve. The consensus among participants of the workshop and reviewers of its outcome is that this is the critical moment in time fully to facilitate this work.

**NICHD Scientific Vision Workshop
on Developmental Origins of Health and Disease
February 14–15, 2011
Bethesda, MD**

Participant List

Special thanks to the workshop participants, who contributed to the ideas in this white paper:

Kjersti Aagaard-Tillery, M.D., Ph.D.

Baylor College of Medicine
Houston, TX

Rui Chen, Ph.D.

Baylor College of Medicine
Houston, TX

David J. Barker, M.D., Ph.D.

Oregon Health and Science University/
University of Southampton
Southampton, United Kingdom

Lane Christenson, Ph.D.

Kansas University Medical Center
Kansas City, KS

Marisa S. Bartolomei, Ph.D.

University of Pennsylvania School
of Medicine
Philadelphia, PA

Edward B. Clark, M.D.

University of Utah
Salt Lake City, UT

Sheri A. Berenbaum, Ph.D.

Pennsylvania State University
University Park, PA

Sherin U. Devaskar, M.D.

University of California, Los Angeles
Los Angeles, CA

Ira M. Bernstein, M.D.

University of Vermont College of Medicine
Burlington, VT

Janet DiPietro, Ph.D.

Johns Hopkins Bloomberg School
of Public Health
Baltimore, MD

Patrick M. Catalano, M.D.

Case Western Reserve University
Cleveland, OH

Francine H. Einstein, M.D.

Albert Einstein College of Medicine
Bronx, NY

Aaron B. Caughey, M.D., Ph.D., M.P.H.

Oregon Health and Science University
Portland, OR

**Caroline Fall, M.B.Ch.B., D.M., FRCP,
FRCPCH**

Southampton General Hospital
Southampton, United Kingdom

John R.G. Challis, Ph.D., D.Sc., FRSC

University of Toronto/
Michael Smiths Foundation for Health
Research
Vancouver, Canada

Alison E. Field, Sc.D.

Harvard Medical School
Boston, MA

Tom P. Fleming, Ph.D.
University of Southampton
Southampton, United Kingdom

Matthew W. Gillman, M.D.
Harvard Medical School
Boston, MA

William A. Grobman, M.D., M.B.A.
Northwestern University Feinberg School of
Medicine
Chicago, IL

Jane E. Harding, D.Phil.
University of Auckland
Auckland, New Zealand

William W. Hay, M.D.
University of Colorado Denver School
of Medicine
Aurora, CO

Patricia Hunt, Ph.D.
Washington State University
Pullman, WA

Alan A. Jackson, M.D.
University of Southampton
Southampton, United Kingdom

Thomas Jansson, M.D., Ph.D.
University of Texas Health Science Center
at San Antonio
San Antonio, TX

Mark A. Klebanoff, M.D., M.P.H.
Nationwide Children's Hospital
Columbus, OH

Michelle Lampl, M.D., Ph.D.
Emory University
Atlanta, GA

Robert H. Lane, M.D.
University of Utah School of Medicine
Salt Lake City, UT

Ronald Magness, Ph.D.
University of Wisconsin–Madison
Madison, WI

Aleksandar Milosavljevic, Ph.D.
Baylor College of Medicine
Houston, TX

Kelle H. Moley, M.D.
Washington University School of Medicine
St. Louis, MO

Leslie Myatt, Ph.D.
University of Texas Health Science Center
at San Antonio
San Antonio, TX

Nancy Potischman, Ph.D.
National Cancer Institute
National Institutes of Health
Rockville, MD

Nancy A. Press, Ph.D.
Oregon Health and Science University
Portland, OR

Janet W. Rich-Edwards, D.Sc., M.P.H.
Brigham and Women's Hospital
Boston, MA

Claire Roberts, Ph.D.
University of Adelaide
South Australia, Australia

Michael G. Ross, M.D., M.P.H.
University of California, Los Angeles
Torrance, CA

Tracey Rouault, M.D.
Eunice Kennedy Shriver National Institute
of Child Health and Human Development
National Institutes of Health
Bethesda, MD

George R. Saade, M.D.
University of Texas Medical Branch
Galveston, TX

Carmen Sapienza, Ph.D.
Temple University School of Medicine
Philadelphia, PA

John Schimenti, Ph.D.
Cornell University College of Veterinary
Medicine
Ithaca, NY

Rebecca A. Simmons, M.D.
University of Pennsylvania
Philadelphia, PA

Alison Stuebe, M.D.
University of North Carolina at Chapel Hill
Chapel Hill, NC

Susan Taymans, Ph.D.
Eunice Kennedy Shriver National Institute
of Child Health and Human Development
National Institutes of Health
Bethesda, MD

Kent L. Thornburg, Ph.D.
Oregon Health and Science University
Portland, OR

Michael W. Varner, M.D.
University of Utah
Salt Lake City, UT

James Versalovic, M.D., Ph.D.
Baylor College of Medicine
Houston, TX

Lawrence Wallack, Ph.D., M.P.H.
Portland State University
Portland, OR

David A. Washburn, Ph.D.
Georgia State University
Atlanta, GA

Elizabeth Wehr, J.D.
Eunice Kennedy Shriver National Institute
of Child Health and Human Development
National Institutes of Health
Bethesda, MD

Sherman M. Weissman, M.D.
Yale University School of Medicine
New Haven, CT

Michelle A. Williams, Sc.D.
University of Washington School of Public
Health
Seattle, WA

Lubu Zhang, Ph.D.
Loma Linda University School of Medicine
Loma Linda, CA