

*ADVISORY COMMITTEE TO THE NIH DIRECTOR*

# **National Children's Study Working Group Report**

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***Co-Chairs, NCS Working Group***

*ACD Meeting, December 12, 2014*

# Overview of Report

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- Brief History of the NCS
- Impetus for Current Review
- Charge to the Working Group
- Working Group Process, Deliberations, and Analysis
- Working Group Findings and Recommendations
- Concluding Remarks
- Discussion

# Children's Health Act of 2000\*

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*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 and the Environmental Protection Agency) to*

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

# Children's Health Act of 2000\* *(cont.)*

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*The study shall*

- *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;*
- *Gather data on environmental influences and outcomes on diverse populations of children, which may include the consideration of prenatal exposures; and*
- *Consider health disparities among children that may include the consideration of prenatal exposures.*

# Since 2000...

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- Long and tumultuous evolution
- Planned to be launched in two phases:
  - The **Vanguard Study** (*pilot study launched in 2009 to evaluate the feasibility, acceptability, and cost of different recruitment strategies, study procedures, and outcome assessments for use in the Main Study*)
  - The **Main Study** (*not yet initiated*)
- Up to \$1.3 billion have been appropriated for NCS

## Since 2000... *(cont.)*

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- Multiple iterations of the plan; reviews consistently
  - **Endorse overarching concept** of a longitudinal study focused on examining environmental, behavioral, social, and biological influences on child health and development
  - **Express concern about the feasibility and suitability** of the NCS design – as well as its organization, management, and costs

# Impetus: “*Persistent Concerns*”

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- Persistent concerns expressed in a 2014 NAS report, echoed by scientists, NIH leadership, and other stakeholders regarding
  - Study design
  - Management and oversight structures
  - Escalating costs of the NCS
  - Need to consider evolving scientific and technological landscape
  - Newer models for conducting robust and cost-effective research

# Impetus: *NCS Put on Hold*

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“I am putting the main study on hold, effective immediately, in order to determine the best path forward. We are at an inflection point where critical questions need to be answered:

- Is this study, as currently outlined, actually feasible in the face of significant budget constraints?
- If yes, how do we move forward to implement necessary changes...?
- If no, are there new methods to answer key research questions...?”

Francis Collins, June 16, 2014

**ACD working group established to address these questions**

# ACD NCS WG: *Roster*

*\*indicates ACD member*

**\*Russ Altman (*co-chair*)** – Stanford (computational sciences)

**Philip Pizzo (*co-chair*)** – Stanford (pediatrics)

**Robert Gibbons** – U Chicago (biostatistics)

**Kathy Hudson** – NIH (policy/genetics)

**\*Renee Jenkins** – Howard U (pediatrics)

**Brendan Lee** – Baylor College of Medicine (pediatrics)

**Maureen Lichtveld** – Tulane U (environmental health policy)

**Marie Lynn Miranda** – U Michigan (pediatric environmental health)

**Cheryl Perry** – U of Texas Health Sciences Center (behavior and prevention)

**Huda Zoghbi** – Baylor College of Medicine (developmental genetics)

**Lyric Jorgenson (*exec. sec.*)** – NIH (policy, developmental neuroscience)

# ACD NCS WG: *Charge*

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- The NCS Working Group of the ACD is ***charged with evaluating whether the NCS is feasible***, as currently outlined, especially in light of increasing and significant budget constraints
  - ***If “yes,”*** assessing how NIH can move forward to implement necessary changes, including some of those outlined in the NAS report
  - ***If “no,”*** identifying 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
- The NCS Working Group of the ACD will present a final report for consideration by the ACD at its December 11–12, 2014, meeting

# ACD NCS WG: *Process*

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- Met 6 times since July (2 in-person) but with lots of communications between meetings
- Explored a broad range of stakeholder perspectives and a wide range of relevant documents
  - 2008 and 2014 NAS reports
  - Vanguard and Main Study protocols
  - Internal analyses
  - Experts in pediatric research, environmental health, epidemiology, statistical analyses, and longitudinal study design
  - Received public comments
- Discussed the current status of the NCS, its strengths and weaknesses, and its overall utility and feasibility

# ACD NCS WG: *Analysis*

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- Focused on the NCS as outlined in the NCS Main Study Design and Plan of July 2014
- Designed to be a longitudinal, observational study following 100,000 children, prenatally or at birth, to age 21 to examine a broad range of environmental and biological factors on children's health, growth, and development
- Additional core elements:
  - Established to be a large resource containing data, biological specimens, and environmental samples
  - Uses a national probability sample based on geography
  - Recruits participants as early as possible in pregnancy or at birth
  - Stratifies samples to achieve variability in socioeconomic status

# ACD NCS WG: *Analysis of Feasibility*

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- Scientific rationale for a longitudinal study
- Value of national probability sample
- Size and distribution of participant population
  - Prenatal or later?
- Range and frequency of sampling procedures
- Data collection, storage, and accessibility
- Evolving technologies for measuring variables
- Desirability of hypothesis-driven vs. platform-based study

# ACD NCS WG: *Analysis of Feasibility* (cont.)

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- Emerging scientific capabilities
- Omics and mobile monitoring
- Organization and management
- Complementarity for analysis with other international studies
- Current and projected costs
- Alternate study designs or management structures

# ACD NCS WG: *Analysis of Strengths*

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- Critical need for understanding environmental early life exposures on development and health outcomes
- No existing US study focused on environmental exposures and
  - Tracking the spectrum of human development
  - Assessing the impact on children from minority and disadvantaged populations
- Platform approach could provide flexibility
  - Address current and as yet unknown hypotheses as science evolves
  - Allow “add-on” studies that sample new environmental variables

# ACD NCS WG: *Analysis of Strengths* (cont.)

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- 2014 NAS report provides useful guidance on technical weaknesses
- Value from the Vanguard
  - Potentially high retention rates
  - 112 papers published
    - 26 drew scientific observations from the database
- Most experts interviewed believed that the study should be continued in some form, but many also raised serious concerns and recommended a reboot or discontinuation
- NIH has a history of supporting longitudinal studies that have served as valuable resources

# ACD NCS WG: *Analysis of Weaknesses*

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- Design remains incomplete, even after years of effort
  - Difficult to articulate what the “current study design” is
- Sampling design is overly complex, leading to considerable delays and high costs
- Inadequate observational and field epidemiological expertise in management
  - Sense that the design does not reflect best practices for a longitudinal study
- Inadequate informatics substrate for collecting, storing, and ensuring sample quality
- Management structure has too many stakeholder and advisory mandates inhibiting flexible and consensus-driven science

# ACD NCS WG: *Analysis of Weaknesses* (cont.)

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- Lack of interoperability for coordination with other global longitudinal environmental cohort studies limiting fuller leveraging of scientific progress
- Design does not reflect need for low-cost recruitment and data collection strategies and other new efforts that did not exist in 1999 or in 2008
  - Social media and EMRs
- Most of the experts consulted who favored continuing the NCS indicated that it should go forward with a “reboot” or “be refined,” “redesigned,” or “reconfigured,” and some recommended it be discontinued

# ACD NCS WG: *Findings*

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## *The Working Group Reached Unanimity in its Core Finding*

While the overall goals of examining how environmental factors – defined broadly – influence health and development are meritorious and should be a priority for future scientific support, **the NCS, as currently outlined, is not feasible.**

# ACD NCS WG: *Findings* (cont.)

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- **Conclusion based on an evaluation of the aims, design, and management of the NCS. Specifically:**
  - The current aims, design, and scope are **unlikely to achieve the goals of providing meaningful insights** into the mechanisms through which environmental factors influence health and development;
  - The study **does not incorporate approaches informed by new biological insights** about factors that affect child health and **new enabling technologies**;
  - 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
  - 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.

# ACD NCS WG: *Recommendations*

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- The NICHD NCS Program 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
- Vanguard Study data should be archived and available for request by investigators for secondary analyses
- The Vanguard Study should not collect any further data

# ACD NCS WG: *Recommendations* (cont.)

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- Future studies must incorporate new biological and technical advances
- Future studies are needed to address the interactions between child development and related environmental, behavioral, biological, and societal factors
- Supporting biospecimen collection should permit contemporary tailored investigations and provide flexibility to deploy emerging scientific insights
- Funds should be provided to achieve these goals

# ACD NCS WG: *Recommendations* (cont.)

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- Time did not allow full consideration of the wide range of options regarding optimal study designs
- In general, the working group offers the following approaches for consideration:
  - **A series of smaller focused studies** designed as tailored explorations
  - **A multi-center collaborative network of scientific teams**, who compete on responses to a well-considered funding announcement
  - **A focused cohort design to facilitate longitudinal biospecimen collection and banking**
  - **Probability sampling should be an integral feature** of the methodological approach

# Concluding Remarks

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The Working Group understands the importance of its charge and took very seriously the responsibility to fully consider the relevant issues surrounding the NCS

# Concluding Remarks

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*With the conclusion that the NCS is not feasible as currently outlined:*

The Working Group recommends that **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

*ADVISORY COMMITTEE TO THE NIH DIRECTOR*

# DISCUSSION