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The National Children's Study — End or New Beginning?

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On December 12, 2014, Francis Collins, director of the National Institutes of Health (NIH), announced his decision to terminate the National Children's Study (NCS), stating that the study "as currently designed is not feasible." Collins's decision was based on recommendations of an NCS Working Group of the NIH director's Advisory Committee. It also followed the report of an Institute of Medicine (IOM) panel opining that the NCS had "potential to add substantially to scientific knowledge about the impact of environmental exposures on children's health and development" but expressing concern over the study's design, inadequate management, and failed oversight.¹

The NCS was conceived in the late 1990s and authorized through the Children's Health Act of 2000. It was intended to be a prospective, epidemiologic, birth-cohort study that would follow a nationally representative cohort of 100,000 U.S. children from shortly after conception to 21 years of age and possibly beyond — a "children's Framingham study." The study was catalyzed by rising rates of chronic diseases in children — increases in asthma, autism, birth defects, dyslexia, attention deficit-hyperactivity disorder, schizophrenia, obesity, and diabetes that were too rapid to be of genetic origin — and by growing concern over children's exposure during vulnerable stages of early development to hundreds of new and untested chemicals.² The goal of the NCS, like that of the Framingham study, was to iden-

tify preventable risk factors for disease.

Strong emphasis on the environment was a core, congressionally mandated component of the study. Researchers planned to measure environmental exposures during pregnancy and early childhood through a combination of environmental monitoring and biomarkers. They intended to collect genetic and epigenetic information on each family. And they planned to create a large bank of environmental and biologic samples that could be used to examine the hypothesis that some diseases of childhood, adolescence, and adulthood result from prenatal and early postnatal environmental exposures.³

The NCS never fulfilled its promise. After 14 years and the expenditure of more than \$1 billion, only approximately 5000 mother-infant pairs had been recruited — all into pilot studies. The study was plagued by lack of focus and poor leadership. Two particularly disastrous decisions were a plan to enroll as much as 25% of the cohort before pregnancy and a plan to recruit families door-to-door rather than through hospitals or clinics. Both plans greatly increased costs. An inflexible, contract-driven management structure and an unwise decision to allow use of multiple incompatible data platforms inflated costs still further.

Meanwhile, other countries, including Norway, Denmark, and most recently China, are forging ahead. The Japan Environment and Children's Study (JECS), inspired in part by the NCS, has

been a particular success.⁴ Between 2011 and 2014, the JECS recruited 100,000 mothers and babies in 15 regional recruitment centers throughout Japan and made environmental measurements in a 10% subsample. Most recently, the United Kingdom has launched a prospective, life-long birth-cohort study involving 80,000 children.⁵

Despite our own deep involvement in the NCS and our strong hopes for its success, we believe that Collins was correct in deciding that the study in its current iteration must come to an end. The time has come to move on.

That said, the major questions that catalyzed the study remain unanswered. Why are rates of asthma, autism, birth defects, cancer, obesity, and other chronic diseases still increasing among U.S. children? What risks are conferred by exposures in early life to synthetic chemicals and other environmental stressors? Where will we obtain the data we need to design evidence-based programs for disease prevention in children analogous to the highly successful strategies for cardiovascular-disease prevention that emerged from the Framingham Heart Study?

Alternative study designs have been proposed for the NCS, but none have the ability of a large, national birth-cohort study with prenatal enrollment and long-term follow-up to assess associations between early-life exposures and later disease. Small, academically based studies do not have enough power to answer key questions. Large studies

based on linkages to extant environmental data fall short because too often these data do not accurately reflect individual exposures. And studies based on electronic medical records are hampered by a lack of good information on environmental exposures in too many health records.

We hope that the NCS will not be canceled. The need for a large, national, prospective, multiyear birth-cohort study of children's health in the United States remains too great. Termination of the NCS is too radical a remedy.

Instead, we would like to see the NIH preserve and reinvigorate the NCS by basing it in a coordinated national confederation of regional, academically based, prospective birth-cohort studies. The recruitment strategy, data platform, and management structure will need to be completely revamped, and new leadership put in place. As we envision such a study, participating institutions would collect, analyze, store, and share common core data under standard protocols, but each institution could also collect data specific to its population, environment, and geographic region. Some core elements such as data management and specimen archiving could be centralized for efficiency and quality assurance. A strong emphasis on the environment would be preserved, and there would be a robust invest-

ment in exposure biology. Data would be owned by individual academic centers, but data-sharing agreements would be essential for national analyses. And to answer big-data questions in children's health that go beyond the scope of even a large national study, investigators could pool data with researchers conducting similar studies in other countries.

Leadership will be critically important. At the NIH level, the study director will need to be a skilled and charismatic scientist highly experienced in the conduct of prospective birth-cohort studies. And the best way to select experienced leaders within U.S. academic institutions will be through competitive peer review with a firm requirement that each principal investigator have experience leading major epidemiologic studies. Grants or cooperative agreements would be a more effective funding mechanism than contracts and would permit greater flexibility.

The confederation could be based in or closely affiliated with the network of Centers of Excellence in Children's Environmental Health and Disease Prevention Research currently supported by the National Institute of Environmental Health Sciences and the Environmental Protection Agency.

We believe this approach would be effective, because it

combines the advantages of central coordination with the local knowledge and experience of competitively selected academic centers. It would be consistent with the recommendations made by the IOM panel and avert the more radical surgery favored by the NIH director's Working Group. Termination of the NCS in its current form is a serious setback for child health research in the United States. But it need not mark the end of either the NCS or efforts to understand the effects of early environmental exposures on health and development in U.S. children.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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