Eunice Kennedy Shriver National Institute of Child Health and Human Development

NATIONAL ADVISORY CHILD HEALTH AND HUMAN DEVELOPMENT COUNCIL

MEETING MINUTES

June 11, 2019

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE

***EUNICE KENNEDY SHRIVER* NATIONAL INSTITUTE OF CHILD HEALTH AND HUMAN DEVELOPMENT**

NATIONAL ADVISORY CHILD HEALTH AND HUMAN DEVELOPMENT COUNCIL SUMMARY MINUTES

June 11, 2019[1]

The National Advisory Child Health and Human Development (NACHHD) Council convened its 170th meeting at 8:00 a.m. on Tuesday, June 11, 2019, at 6710B Rockledge Drive, Conference Rooms 1425–1427 of the National Institutes of Health (NIH) in Bethesda, Maryland. The meeting was open to the public from 8:00 a.m. to 1:00 p.m. As provided in Sections 552b(c)(4) and 552b(c)(6), Title 5, U.S.C., and Section 10(d) of Public Law 92-463, for the review, discussion, and evaluation of grant applications and related information, the meeting was closed to the public from 1:00 p.m. until 5:00 p.m.

Dr. Diana W. Bianchi, Director, *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD), presided.

Council members present:
Diana W. Bianchi, M.D. (Chair)
Michael Boninger, M.D.
Atul J. Butte, M.D., Ph.D. (remote)
Barbara Collura, M.A
Stephen A. Foley, M.D.
Melissa Gilliam, M.D., M.P.H.
Catherine Gordon, M.D., M.Sc.
Richard D. Krugman, M.D. (remote)
DeWayne M. Pursley, M.D., M.P.H.
Lesli Rotenberg (remote)
Annette Sohn, M.D.
Clifford Tabin, Ph.D.
Alyce Thomas, RD

Council members absent:
Timothy P. Shriver, Ph.D.

National Advisory Board on Medical Rehabilitation Research Council liaison:
Kenneth Ottenbacher, Ph.D., OTR

***Ex officio* members present:**
Patricia Dorn, Ph.D.
Aaron M. Lopata, M.D, M.P.P.

Observers (pending members) present:
Michele Caggana, Sc.D., FACMG
Martin M. Matzuk, M.D., Ph.D.
Carmen L. Neuberger, J.D.
Alan Thevenet N. Tita, M.D., M.P.H., Ph.D.
Rebeca Wong, Ph.D.
Anthony J. Wynshaw-Boris, M.D., Ph.D.

Executive Secretary
Della M. Hann, Ph.D.

Others present:
Constantine Stratakis, M.D., D.Sc., Director, Division of Intramural Research, NICHD
Members of Staff, NICHD
Members of Staff, NIH

Ad-hoc Reviewers:
Kimberly K. Leslie, M.D., Chair, Department of Obstetrics and Gynecology, Carver College of Medicine, University of Iowa Health Care (remote)
Vassilios Papadopoulos, D.Pharm., Ph.D., D.Sc. (Hon.), Dean, School of Pharmacy, University of Southern California (remote)

I. CALL TO ORDER AND INTRODUCTORY REMARKS

Dr. Bianchi began the meeting at 8:00 a.m. The meeting was videocast live.

A. Review of Confidentiality and Conflict of Interest

Dr. Hann reminded Council members that they are required to read and sign the confidentiality agreement and nondisclosure rules on the Council member website before evaluating any NIH grant applications. Council members also received a conflict-of-interest certification form, which they were required to sign before the closed session. Dr. Hann reminded the Council members that they are required to recuse themselves and leave the room if there is a specific discussion involving any organizations or universities for which they are in conflict, in addition to those listed on the Council Action document. Council members are not allowed to serve on the NIH peer review panel while serving as Council members. It is NIH policy that individuals may not serve on both the first and second levels of peer review.

B. Council Minutes

Dr. Hann moved to approve the January 24–25, 2019, meeting minutes. The minutes were approved unanimously.

C. Future Meeting Dates

Dr. Hann reviewed the future meeting dates:

September 18–19, 2019
January 23, 2020
June 11, 2020
September 10, 2020

II. NICHD DIRECTOR'S REPORT AND DISCUSSION

Dr. Bianchi provided the Director's report.

Fiscal Year 2020 Appropriations

Dr. Bianchi testified at the fiscal year (FY) 2020 House Appropriations Committee hearing along with Francis S. Collins, M.D., Ph.D. (NIH), Anthony S. Fauci, M.D. (National Institute of Allergy and Infectious Diseases [NIAID]), Gary H. Gibbons, M.D. (National Heart, Lung, and Blood Institute [NHLBI]), Douglas R. Lowy, M.D. (National Cancer Institute [NCI]), and Nora

D. Volkow, M.D. (National Institute on Drug Abuse [NIDA]). At this hearing, Dr. Bianchi fielded questions on maternal mortality, the Task Force on Pregnant Women and Lactating Women (PRGLAC), newborn screening, postpartum depression, and pediatric research.

Lawmakers expressed strong bipartisan support for NIH funding. The House Appropriations Subcommittee on Labor, Health and Human Services, Education, and Related Agencies marked up a bill that included the following:

- $41.1 billion for NIH
- $1.580 billion for NICHD (an increase of $80 million over FY 2019)
- $12.6 million for the Gabriella Miller Kids First Pediatric Research Program

The House Appropriations Full Committee markup was held on May 8; five of the 12 appropriations bills, including Labor-HHS, were packaged together for consideration on the House floor. Senate markup is expected in June.

Updates on Selected NICHD Initiatives

Maternal Mortality

Maternal mortality is a significant issue. Every 12 hours, a woman in the U.S. dies from complications of childbirth. A recent analysis by the Centers for Disease Control and Prevention (CDC) indicated that maternal death can happen up to a year after delivery. Currently, the Centers for Medicare & Medicaid Services (CMS) allows maternal coverage for only 60 days following delivery. Many women who need coverage do not see a physician after their Medicaid coverage ends. Over time, heart disease and stroke are important comorbidities. The incidence of maternal mortality is much higher in African American women.

NICHD has made maternal mortality a priority and is updating its research agenda on this topic.

- NICHD sponsored a Community Engagement Forum on Improving Maternal Health on April 8, 2019. The forum featured Dr. LaQuandra Nesbitt as the guest speaker and attracted more than 400 participants. The Facebook Live recording received 11,000 views within the first week after the forum.
- NICHD staff authored a manuscript on the "Importance of Research in Reducing Maternal Morbidity and Mortality" that was accepted for publication by the *American Journal of Obstetrics & Gynecology*.
- NICHD sponsored a workshop, Maternal Mortality in the United States: Future Research Directions, on May 2–3, 2019. Discussions addressed data quality and trends, disparities, social determinants, and clinical causes.
- NIH is establishing a working group with CMS to explore opportunities to use CMS data to address research questions.
- NICHD is supporting a National Academies of Sciences, Engineering, and Medicine (NASEM) study on the choice of birth settings, risk factors, social determinants that influence risk, and maternal health outcomes.
- NICHD will hold a workshop on comorbid conditions (e.g., obesity, hypertension, diabetes) in early 2020.

PRGLAC Recommendations

Each year, 6.3 million women in the United States become pregnant, and more than 90% of these women take medications. However, for 98% of medications, there are insufficient data to determine teratogenicity risk, and 98% of dosing studies do not include pregnant women. Studying pregnancy is complex, and liability issues are a concern. Even less is known about

lactation. Women must consider the benefits of breastfeeding versus taking medications, but there are limited assays to assess the impact of medications in breast milk.

NICHD was charged with advising the Secretary of the U.S. Department of Health and Human Services (HHS) regarding gaps in knowledge and research for pregnant and lactating women. After four meetings, PRGLAC submitted a report to HHS and Congress in September 2018. Key recommendations included the following:

- Change the existing culture that has limited scientific knowledge of therapeutic product safety, effectiveness, and dosing for pregnant and lactating women.
- Protect pregnant women through research instead of from research.
- Remove pregnant women as a vulnerable population through the Common Rule.
- Expand the workforce of clinicians and researchers with expertise in obstetric and lactation pharmacology and therapeutics.
- Remove regulatory barriers.

The complete recommendations are available online at https://www.nichd.nih.gov/About/Advisory/PRGLAC

The HHS Secretary agreed to allow continued work in this area and to extend the PRGLAC charter until March 2021. The full PRGLAC Task Force will hold two meetings per year and establish four working groups to address subsets of the recommendations. Federal partners will be included in all PRGLAC working groups. One major partner is the U.S. Food and Drug Administration (FDA), which has issued draft guidances on scientific and ethical considerations for inclusion of pregnant women in clinical trials, study design considerations for clinical lactation studies, and post-approval pregnancy safety studies. The recently established FDA Perinatal Health Center of Excellence (PHCE), funded 14 proposals from across the FDA.

The NIH INCLUDE Project

The INCLUDE (INvestigation of Co-occurring conditions across the Lifespan to Understand Down syndromE) project is a trans-NIH research initiative that was awarded $22.2 million in FY 2018. Its purpose is to investigate conditions that affect individuals with Down syndrome and the general population. NICHD issued four funding opportunity announcements (FOAs) in FY 2019; awards will be made in September 2019.

A new NICHD project will leverage the institute's Pediatric Trials Network to establish an infrastructure for Down syndrome clinical trials and develop training programs on effective ways for practitioners to work with individuals with intellectual and developmental disabilities (IDDs).

Data and Specimen Hub (DASH)

DASH is a centralized resource for researchers to store de-identified data and to access data and associated biospecimens from NICHD-supported studies. This resource can help investigators meet NIH's data sharing requirements for their own studies and accelerate scientific findings to ultimately improve human health. The goal of DASH is to facilitate secondary analyses. Data sharing was launched in August 2015, and a new function for DASH is the management of requests for biospecimens.

Institute and Center (IC) Leadership at NIH

Debara L. Tucci, M.D., M.S., M.B.A., is expected to become the new Director for the National Institute on Deafness and Other Communication Disorders (NIDCD) in September 2019. Dr. Bianchi said that with Dr. Tucci's appointment, 10 of the 27 IC directors are women.

NICHD is currently hiring for several positions:

- Executive Officer. The hiring process is in the final stages.
- Deputy Director. The search committee has completed interviews.
- Extramural Branch Chief Positions: Pregnancy and Perinatology, Obstetric and Pediatric Pharmacology and Therapeutics, and Child Development and Behavior.
- Medical and Program Officers in the Division of Extramural Research.

Council Discussion

Dr. Gilliam asked whether discussions had taken place about postpartum contraception and birth spacing. Dr. Bianchi said that the issue had not come up specifically but that the topic is very much part of the discussions on strategic planning.

Council members had no additional questions or comments.

III. INTRODUCTION OF NEW MEMBERS

Dr. Hann invited the new members to briefly introduce themselves.

Michele Caggana, Sc.D., FACMG, is the Deputy Director of the Division of Genetics, Director of the Newborn Screening Program, and the head of the Genetic Testing Quality Assurance Program at the Wadsworth Center of the New York State Department of Health in Albany, New York.

Martin M. Matzuk, M.D., Ph.D., is the Robert L. Moody, Sr. Chair in Pathology and Immunology in the Department of Pathology and Immunology at Baylor College of Medicine in Houston, Texas.

Carmen L. Neuberger, J.D., is the executive vice president and general counsel of Phoenix Children's Hospital in Phoenix, Arizona.

Alan Thevenet N. Tita, M.D., M.P.H., Ph.D., is a tenured professor and Director of the Department of Obstetrics and Gynecology at The University of Alabama at Birmingham.

Rebeca Wong, Ph.D., is the P. & S. Kempner Distinguished Professor and vice chair for research in the Department of Preventive Medicine & Community Health at the University of Texas Medical Branch in Galveston, Texas.

Anthony J. Wynshaw-Boris, M.D., Ph.D., is the James H. Jewell M.D. '34 Professor of Genetics and the chair of the Department of Genetics and Genome Sciences at Case Western Reserve University School of Medicine in Cleveland, Ohio.

IV. DIVISION OF EXTRAMURAL RESEARCH REPORT

Dr. Hann provided updates on the inclusion of IDD populations in clinical research, the long-term support for meritorious investigators, and NICHD staff.

Inclusion of IDD Populations in Clinical Research

NICHD is exploring this issue in response to Council comments on the potential exclusion of IDD populations from NICHD's extramurally funded clinical research. This research includes not only clinical trials but also epidemiologic and behavioral research for these populations.

Funding estimates for Research, Condition, and Disease Classification (RCDC) categories for FY 2018 across NIH include:

- $5.048 billion for women's health
- $4.499 billion for pediatrics
- $515 million for IDDs
- $419 million for pregnancy
- $354 million for sexual and gender minorities

A random sampling of 273 NICHD-funded clinical trials was analyzed to determine whether IDD populations were excluded and, if so, to what extent. The results showed that about 89% of the studies did not exclude these populations. There were no differences observed across intervention type, phase of trial, or age range of participants. The results were comparable to those of other published research that examined this issue.

Several ongoing efforts are underway to continue to address this issue, including the following:

- The Inclusion Governance Committee, a trans-NIH group that focuses on the NIH policy for inclusion of women, children and IDD populations in research involving human subjects
- INCLUDE
- NICHD's Intellectual and Developmental Disabilities Branch (IDDB), which provides leadership across NIH in studying research and research training aimed at understanding, preventing, and ameliorating intellectual and related developmental disabilities

Discussion

Dr. Sohn asked whether it was surprising that 89% of NICHD studies did not exclude IDD populations. Dr. Bianchi said that an examination of studies across NIH showed that 58% of studies showed exclusions and noted that NICHD's efforts are more inclusive.

Providing Long-Term Support for Meritorious Investigators

Dr. Hann said that the issue of long-term support for meritorious investigators was explored in response to the Council's comments on the potential use of alternative support mechanisms for these investigators. A previous Council working group examined using the Outstanding Investigator Award (R35) grant mechanism back in FY 2015 and FY 2016. These years were budgetarily difficult, and the payline at NICHD was restricted. The Council did not recommend pursuing the R35 at that time but recommended revisiting the issue.

Dr. Hann reviewed several grant mechanisms used to fund NIH research projects:

- **R01 (Research Project):** Supports discrete, specified, and circumscribed projects to be performed by the named investigators; provides up to 5 years of support.
- **R37 (Method to Extend Research in Time [MERIT] Award):** Provides a 5-year award, with the possibility of extension for up to 5 additional years, for investigators with distinctly superior records; provides up to 10 total years of support.
- **R35 (Outstanding Investigator Award):** Provides long-term support to experienced investigators with an outstanding record of research productivity and encourages

investigators to embark on long-term projects of unusual potential; provides up to 8 years of support. The R35 is designed to:

- Provide long-term support to principal investigators to conduct innovative and high-impact research
- Reduce administrative burden and grant writing
- Provide flexibility to principal investigators to pursue new research directions (limited constraints)
- Give participating NIH ICs the opportunity to tailor the award to suit their mission-specific needs

Six NIH institutes currently use the R35 awards: the National Institute of General Medical Sciences (NIGMS), NCI, NHLBI, the National Institute of Neurological Disorders and Stroke (NINDS), the National Institute of Environmental Health Sciences (NIEHS), and the National Institute of Dental and Craniofacial Research (NIDCR). In terms of eligibility, the primary focus is the investigator's history of R01 support. NIGMS requires an investigator to have two concurrently funded R01s or one large one. The lengths of the awards vary from 5 to 8 years. When investigators accept an R35, they also relinquish other research grants with that institute.

The relative citation ratios for NICHD's R01 and R37 awards confirmed that the MERIT awards accomplish the goal of supporting highly meritorious research. Another analysis showed that the R37 awards lean more toward nonhuman research: 55% of NICHD R37 awards do not involve human subjects, compared with 32% of NICHD R01 awards. An analysis of other participating ICs showed a heavy commitment to nonclinical research for R01 and R35 awards (72% for R01s and 85% for R35s).

Most NICHD principal investigators have only one R01 award. Only 159 have two awards, 24 have three, and six have four or more.

Discussion

Dr. Tabin said that top investigators resubmit grant applications almost every cycle, which puts a burden on them as well as the study sections that receive the applications. He said that the main advantage of the approach described is consolidation. Investigators might turn away two or three R01s and less total money but would have long-term support with just a single application and the flexibility to pursue the directions the research takes over time. Dr. Tabin said he was very much in favor of supporting the best science while freeing people from the need to write and evaluate many grants.

Dr. Sohn asked whether the NHLBI criteria for two R01s were intentionally aimed at giving awards to more midlevel investigators or younger investigators. Dr. Hann said that some of the institutes run a concurrent program devoted to newer investigators; the dollar amount is generally lower. She said that one of the comments raised early in the development of the program was that it mainly considered investigators with a history, but there was also a need for opportunities for newer investigators.

Dr. Hann indicated that given Council's interest, that they may want to form a a working group to examine this issue further. She asked who would be interested in participating and Dr. Wynshaw-Boris, Dr. Gordon, Dr. Tabin, and Dr. Boninger all volunteered.. Dr. Bianchi proposed that Dr. Tabin chair this working group. Dr. Bianchi also indicated that Dr. Dennis Twombly, NICHD, would serve as co-chair of the working group.

Staff Updates

Departing staff:

- Minki Chatterji, Ph.D. has accepted a position as a program officer for the HBCD Consortium at NIDA.
- Rosemary Higgins, M.D., is currently Associate Dean for Research at George Mason University.
- Meredith Temple-O'Connor, Ph.D., has accepted a position as Director of Science Policy at the National Center for Advancing Translational Sciences (NCATS).
- Katerina Tsilou, M.D., joined the FDA.

New NICHD staff:

- Vicky Haines joined the Grants Management Branch.
- Clay Mash, Ph.D., is a health science analyst with the National Center for Medical Rehabilitation Research (NCMRR).
- Ronna Popkin, Ph.D., is a program official in the Population Dynamics Branch (PDB).

NICHD is currently seeking program officers across four branches—the Pregnancy and Perinatology Branch (PPB), IDDB, Obstetric and Pediatric Pharmacology and Therapeutics Branch (OPPTB), and Pediatric Trauma and Critical Illness Branch (PTCIB)—and a Branch Chief for PPB. More information is available at https://www.nichd.nih.gov/about/jobs

Council members had no additional questions or comments.

V. 2019 STATEMENT OF UNDERSTANDING

Dr. Hann said that the Statement of Understanding between NICHD and the NACHHD Council is posted on the Council website and provides a short synopsis of the Council and its membership and structure.

Council members voted and unanimously approved the statement of understanding.

VI. STRATEGIC PLANNING UPDATE

NICHD Strategic Plan Responding to Stakeholder Feedback

Dr. Bianchi said that the goals of NICHD's strategic plan were to identify NICHD's priorities, determine partners and collaborators, and inform future investments in research, training, and infrastructure. The core principles are transparency, decisions informed by evidence, and stakeholder participation. NICHD funds about 18% of all child health research conducted by NIH. NICHD collaborates with other ICs on child health research through the Trans-NIH Pediatric Research Consortium.

NICHD issued a Request for Information (RFI) to solicit feedback on the new strategic plan and received 924 comments, many touching on multiple themes. Proposed strategic plan themes include:

- Understanding early human development
- Setting the foundation for a healthy pregnancy and lifelong wellness

- Promoting gynecological, andrological, and reproductive health
- Identifying sensitive periods to optimize health interventions
- Improving health during the transition from adolescence to adulthood
- Ensuring safe and effective therapeutics and devices

These themes are not final. A summary of the report is available at https://www.nichd.nih.gov/sites/default/files/2019-06/RFI_NICHD_SP_Response_Sum.pdf

Revisions to the strategic plan will reflect a synthesis of input from many sources. Cross-cutting themes relevant to all research subjects and priorities will include global health, health disparities, prevention, nutrition, and infectious disease. The final strategic plan will include an introduction explaining the broad applicability of these cross-cutting themes, although the themes may not be stated explicitly in each individual research topic or priority. A final version of the strategic plan will be shared in September 2019.

The strategic plan evolved in response to stakeholder feedback in several areas (showing suggestions by topic):

- Developmental biology and animal models
    - Increase emphasis on a variety of model systems to understand typical developmental processes.
    - Expand from a single cell focus and encompass a broader view of genes and gene regulatory networks.

- Neurodevelopment and intellectual and developmental disabilities
    - Include a focus on typical and atypical neurodevelopment from the earliest developmental stages.
    - Incorporate individuals with IDDs throughout the plan, from early human development to transition to adult care, and include them in the development and testing of therapeutics and devices.

- Reproductive health
    - Include a clearer emphasis on reproductive health as a “window to future health.”
    - Investigate developmental processes that result in abnormalities of the female and male reproductive tracts.
    - Clarify the need for better characterization and definition of gynecological and andrological conditions.
    - Retain emphasis on fertility and infertility, with a specific role for methods to manage fertility.

- Healthy pregnancies
    - Incorporate prepregnancy factors.
    - Reemphasize placental biology and placental clinical research.
    - Include the “fourth trimester.”
    - Ensure an emphasis on research to address Sudden Unexplained Infant Death (SUID)/Sudden Infant Death Syndrome (SIDS) and infant mortality.

- Child development
    - Articulate continued support for studying typical and atypical child development.

- Investigate social and environmental factors in the development of the child and adolescent.
- Emphasize life stage transitions for individuals with intellectual, developmental, and physical disabilities.
- Provide a stronger emphasis on the impact of and treatments for the exposure to violence, stress, and trauma.

- Adolescent development

  - Clarify areas of emphasis.
  - Include a specific concentration on a better understanding of puberty.
  - Incorporate adolescents' transition to the adult health care system, especially for people with intellectual, developmental, and physical disabilities and people with chronic conditions.

- Safe and effective therapeutics and devices

  - Continue to focus on development and validation of drugs and devices that affect NICHD's populations.
  - Use conclusions from PRGLAC to influence the research agenda.
  - Integrate the use of clinical trial and real-world data, such as electronic health records and research registries, to measure exposures/responses to therapeutics and devices.

Discussion

Dr. Wynshaw-Boris asked whether human induced pluripotent stem cell (iPSC) models were part of the plan. Dr. Bianchi said that although iPSCs may not be mentioned explicitly, they are a technology that is absolutely relevant to NICHD's work.

Dr. Tabin asked about use of organoid technology to study the formation of human organ development. He said that although such technology cannot be used to the exclusion of animal models, it will have a much stronger resonance. Dr. Bianchi said that she agreed and that this is becoming the standard of research.

NICHD Refreshed Mission and Vision Statements

The current NICHD mission statement is as follows:

> "The mission of the NICHD is to ensure that every person is born healthy and wanted, that women suffer no harmful effects from reproductive processes, and that all children have the chance to achieve their full potential for healthy and productive lives, free from disease or disability, and to ensure the health, productivity, independence, and well-being of all people through optimal rehabilitation."

Dr. Gordon described the processes for revising the mission and vision statements. The Mission and Vision Statement Working Group included Dr. Bianchi; Dr. Gordon; Richard Ellenson; Lesli Rotenberg; Dr. Alison Cernich; Dr. Stéphane Philogene; Mr. Paul Williams; and Dr. Elizabeth Baden.

For the mission statement revision process, parameters were established to comply with congressional language, contain the words "research" and "training," be unique to NICHD, and be concise. The process included a review of mission statements from other organizations (i.e., NIH ICs and top nonprofits). Each member of the working group independently drafted potential mission statements. The group discussed draft statements and whittled the list down from 27

possibilities to two top candidates. Members considered several variations of the two top choices before arriving at the proposed language

For the vision statement revision process, the established parameters were that the statement be clear, concise, inspirational, memorable, forward-looking, and unique to NICHD. The process involved brainstorming ideas which led to drafting top two mission statement choices. The working group discussed these draft statements, selected words and phrases that resonated, and constructed a new option with group consensus. The goal was to have a statement concise enough to also serve as a tagline. The working group determined that the vision statement should be broad, not call out individual diseases or topics, and be inclusive of NICHD's populations and the full spectrum of NICHD research, though without listing everything explicitly. Important words or phrases included "research and training," "understanding human development," "adolescence," and "optimizing abilities."

The revised NICHD mission statement is as follows:

> "The *Eunice Kennedy Shriver* National Institute of Child Health and Human Development leads research and training to understand human development, improve reproductive health, enhance the lives of children and adolescents, and optimize abilities for all."

The revised NICHD vision statement/tagline is the following:

> "Healthy pregnancies. Healthy children. Healthy and optimal lives."

Council members had no additional questions or comments.

VII. ENDOMETRIOSIS: A FUNDAMENTAL EXAMPLE FOR WOMEN'S HEALTH DISCOVERY

Dr. Bianchi introduced Stacey Missmer, Sc.D., professor of obstetrics, gynecology, and reproductive biology at the College of Human Medicine, Michigan State University.

Dr. Missmer said that endometriosis is characterized by endometrial-like tissue that grows outside of the uterus, typically in the peritoneal cavity, but also in more distal sites such as the lung, heart, and brain. This inflammatory disorder is estrogen-dependent and progesterone-resistant. High levels of cytokines and other inflammatory factors may be involved in the growth of the characteristic endometriosis plaques.

Endometriosis is a major health issue associated with pelvic pain and infertility. One in 10 women has endometriosis during the reproductive years. In the United States, costs of the disease are estimated at $69 billion, taking into consideration the costs of diagnosis, treatment, and losses associated with decreased quality of life and work productivity. These costs are similar to those associated with Crohn's disease, rheumatoid arthritis, and diabetes mellitus. Women with endometriosis also have a higher risk of ovarian cancer, autoimmune disease, and cardiovascular disease.

Symptoms of endometriosis include severe menstrual cramping (dysmenorrhea), pelvic pain not associated with menses, painful intercourse (dyspareunia), painful urination (dysuria), and painful defecation (dyschezia). About one-third of patients with endometriosis report life-changing associations with work, school, home, and social activities.

The peak age at first consultation for symptoms is in the early 30s. However, about two-thirds of patients have an onset of symptoms before age 30, indicating that the disease's impact begins

long before the formal diagnosis. This is an important consideration for adolescents, for whom the disease can greatly affect social functioning.

The pathogenic hypothesis suggests that effluent menstrual fragments move up the fallopian tubes. Although this phenomenon may occur to some degree in all women, those with endometriosis probably experience an atypical quantity of fragments.

Endometriosis has been associated in some studies with low birth weight, diethylstilbestrol (DES) exposure, premature delivery, early age at menarche, a lower body mass index (BMI), possible sun sensitivity, shorter menstrual cycles, lower waist-to-hip ratio (WHR), nulliparity, dysplastic nevi/moles, and some environmental and dietary factors.

Delayed diagnosis is a major issue. The average time from start of symptoms to diagnosis is about 7 years. Patients consult an average of eight clinicians before being referred to an appropriate specialist. Many primary care physicians are unaware of the disease and believe that pelvic pain associated with menstruation is normal.

Endometriosis is characterized by significant heterogeneity, with a huge variation in the appearance and location of lesions, the propensity for scarring, and the risk of infertility.

Current therapeutic options for endometriosis are limited and may include over-the-counter pain medications or opioids, oral contraceptives, gonadotropin-releasing hormone (GnRH) agonists, surgical excision or ablation, hysterectomy, and oophorectomy. Because of hormones' potentially strong side effects, there is a need to explore nonhormonal pathways.

The World Endometriosis Research Foundation (WERF) Endometriosis Phenome and Biobanking Harmonization Project (EPHect) is a research initiative that currently involves 25 centers in 17 countries and another 12 emerging centers in nine additional countries. The ultimate vision includes placing the diagnosis in the hands of first-line health practitioners, defining the true prevalence of the disease, shortening the interval from diagnosis to effective treatment, modifying infertility or comorbidity risks, identifying biomarkers, and using the large number of samples and data.

In summary, endometriosis is a widespread, significant disease affecting millions of women. Identifying critical windows of etiologic physiology may allow prevention and cure. Identification of informative subtypes may help predict risk, treatment selection, and prognosis. Large collaborative and diverse research studies with multidisciplinary teams will drive the science forward.

Discussion

- Ms. Collura asked about finding an appropriate caregiver for a patient with endometriosis after she has had treatment for infertility and is no longer being treated by the reproductive endocrinologist who diagnosed the condition. Many women only find out about endometriosis when they have trouble conceiving, and Dr. Collura wondered about their care options after pregnancy and for the rest of their lives. Dr. Missmer said that if the woman did not realize she had endometriosis until the fertility treatment, the pathway needs to engage around pain management. Managing pain while trying to conceive is very difficult, especially because the primary treatment for endometriosis is ovarian suppression. Organizations such as the International Association for the Study of Pain are recognizing that reproductive endocrinologists and fertility specialists, who are the primary physicians caring for endometriosis, are not formally trained in pain management. She said that this is a huge disconnect that needs to be addressed.

- Ms.Collura said that she was part of an international group working on core outcomes for clinical research in endometriosis; these outcomes will be announced shortly.
- Ms. Thomas asked about the role of cruciferous vegetables in the diet. Dr. Missmer said that while an increased risk of diagnosis of endometriosis has been reported with a high intake of cruciferous vegetables, she would hesitate to say there is a causal relationship. She said that one hypothesis may be an association of cruciferous vegetables with increased GI symptoms and bloating that would then lead a patient to a diagnosis of endometriosis.
- Ms. Neuberger asked whether any links have been found between endometriosis and peritoneal cancer. Dr. Missmer said there were not but that only one study would have addressed that; four studies have shown a very strong protective effect for cervical cancer.
- Dr. Gilliam asked about the diagnosis of endometriosis in early adolescence. Dr. Missmer said that there are heated debates about the adolescent diagnosis and whether surgical intervention is beneficial or harmful. She said that the International Pelvic Pain Society would argue for treating the symptoms. There is currently no evidence that a diagnosis and excision of the lesions would confer a benefit over treatment with oral contraceptives or another remediation for these patients.

VIII. VOICE OF THE PARTICIPANT

Dr. Bianchi introduced Erica, a woman with endometriosis, to provide the voice of the participant. The Council regularly asks participants to address the meeting.

Erica said that when endometriosis first interrupted her life, it affected all aspects of her life. She was slow to admit to the pain and even slower to accept help. It was a topic that she hated talking about.

She started having periods late, at age 17 in 1999. Her parents were excited, but she only felt pain and confusion. She was told she was experiencing cramps, which were normal and would go away.

Erica took a gap year after high school and worked in Honduras, where she met Manuel, a toddler who became like a son to her. The experience stabilized her. She felt sure that she could love any child and that fertility was irrelevant.

She returned to the United States to finish college. When her pain increased, she went to the medical center in her small town and saw a doctor who was a family friend. He talked with her for about an hour and suspected endometriosis. She started using oral contraceptives, and when the pain persisted, she saw a specialist in a larger town, who gave her a pamphlet with slightly more information.

At age 23, Erica underwent a laparoscopy and cauterization. Recovery did not go well, and she experienced heavy bleeding and decreased activity for several months. When she relocated to a new area, she found an obstetrician/gynecologist who prescribed Lupron and Depo-Provera. Although her pain and symptoms decreased with Depo-Provera, her moods changed. She ended her 5-year relationship with her partner.

Erica pursued a career in bilingual education and moved to the Washington, D.C., area. Her doctor prescribed Xanax and Lexapro to help with her anxiety and moods. She learned that her aunt also had endometriosis and fibroids. Her aunt told her that at age 27, she had had a full hysterectomy, which solved her problems.

Erica's pain was so intense at times that she would pass out. She experienced twisting sensations and a feeling of lower deep heat. She said that she "lived on Vicodin." Anticipation of the pain brought on anxiety. She frequently visited the emergency room, where she was given morphine to ease the pain, as well as vaginal checks, which added to the pain.

In 2007, Erica searched for a local ob/gyn with a recent understanding of endometriosis. She found a doctor at the George Washington University Hospital (GWUH) whom she found to be kind, attentive, clever, convincing, and driven to help her find relief. She said this doctor helped to keep her sane. She discussed the possibility of a hysterectomy if it would ever be considered necessary.

Erica said that at this time, she was in pain almost daily. She kept a journal, where she noted that she would "prefer death." She pleaded for more treatment. In December 2008, she was taking Depo-Provera shots every 10 days. She felt that her options were limited. Doctors did not want to perform a hysterectomy on someone so young, noting that a hysterectomy might not even cure her pain. She found it nearly impossible to maintain a relationship or initiate a new one while sick.

By April 2009, Erica's doctor was still reluctant about a hysterectomy, but Erica was insistent and had the surgery. She said she felt joy going into surgery and remembered smiling. However, recovery was not easy. Her hormones "went wild," and she began to have gastrointestinal problems. She was advised to avoid anti-inflammatory agents. It was suggested that she might have developed Crohn's disease.

In October 2011, Erica said, she withdrew from people. Another doctor said he would be happy to remove an endometrial growth and she went through a procedure, but it turned out to be a misdiagnosis; she had a simple bladder infection.

Erica decided to take a break and try to heal. She tried acupuncture to help her manage stress. She reconnected with her doctor at GWUH, who guided her through the steps of finding new specialists.

Erica said that the impact of a long-standing illness has been profound. "Pain changes you," she said. "Endometriosis stole my joy and limited my ambition." Because she did not want to be seen as someone who needed to be taken care of, "relationships faded away. I pushed close friends away."

Erica had used all her sick days at work and couldn't afford to take any more days without pay. Although her job involved taking care of people, she felt she became a shadow of herself and was at the brink of suicide. To avoid sinking into negativity, she "turned her brain off." If people asked how she was, she replied that she was fine. She said she was lucky in that her bosses rallied for her support; she was never fired.

Erica is continuing to work on her master's degree. In 2013, she was named teacher of the year in her locale. She bought her first car and is debt-free and saving money. She continues to volunteer in Honduras, where Manuel is now 19 years old. She teaches English as a second language to immigrants from around the world. Much of this she accomplished while sick.

In conclusion, Erica said that some things that may help a person with endometriosis include:

- Understanding "danger parameters" (i.e., knowing when a symptom is normal rather than one that would require an office visit). This can save time, stress, and money.
- Having an overall plan with short- and long-term goals.

- Knowing the best way to contact a doctor.
- Choosing doctors who will write out notes.
- Considering alternative therapies such as acupuncture.
- Living a healthy lifestyle and remaining active.
- Engaging in positive self-talk.

Erica also recommended that women with endometriosis have a patient advocate and keep a journal to bring to every appointment. Counseling also helps, along with an understanding that exams hurt and it is not easy to talk while in pain. Emergency rooms should have a treatment plan for endometriosis, and caregivers need to find time for a patient in pain.

Erica thanked Dr. Missmer for her passion in research and Dr. Bianchi for choosing to address this topic.

IX. CONCEPT CLEARANCE REVIEW AND DISCUSSION

NICHD staff presented the following concepts for review:

Fertility and Fertility Preservation for Patients with Diseases that Previously Precluded Reproduction (Susan Taymans, Ph.D., Fertility and Infertility Branch). The Council members had no questions about this concept.

Small Research Grants for Establishing Basic Science–Clinical Collaborations to Understand Structural Birth Defects (Reiko Toyama, M.D., Developmental Biology and Structural Variation Branch). The Council members had no questions about this concept.

Natural History of Disorders Screenable in the Newborn Period (Tuba Fehr, Ph.D. Intellectual and Developmental Disabilities Branch). Dr. Butte asked whether this effort would work in collaboration with state governments and state screening programs. Dr. Fehr said that it would not. She said that there are state programs that coordinate these efforts, but this particular initiative is for research projects only. Investigators may choose to collaborate with a state program, but this is not required for this initiative.

Small Research Grants for Analyses of Gabriella Miller Kids First Pediatric Research Data (James Coulombe, Ph.D., Developmental Biology and Structural Variation Branch). Dr. Butte said he was in favor of this concept, noting that it would fund individuals who actually use the data.

NICHD Biomedical Informatic Resource Grants (Dr. Coulombe, Developmental Biology and Structural Variation Branch). Dr. Butte said that he would encourage data and tools to be open-source as much as possible, from the NIH perspective.

Archiving and Documenting Child Health and Human Development Datasets (Regina Bures, Ph.D., Population Dynamics Branch). Dr. Butte said that he really loved this concept because it addressed a large number of people who want to contribute to DASH and who have great datasets but may not have the funding. Dr. Sohn asked whether this opportunity would be open to international datasets funded by NICHD, noting that there may be legal implications. Dr. Bures said that the opportunity would be open for all NICHD-collected data. She said that the principal investigators usually apply because they have access to the data and are able to be identified.

Human–Animal Interaction (HAI) Research (Layla Esposito, Ph.D., Child Development and Behavior Branch). Dr. Sohn said that she saw a news clip about the use of animals for supporting rehabilitation of veterans and thought it was great, noting that it helped the public understand more about the work of NICHD. She said that she would be interested in learning more about the collaboration with Mars, Inc., and whether there are opportunities at NICHD to build similar public–private partnerships. Dr. Hann agreed and said that at a future meeting this could be added to the agenda. Dr. Krugman said that an opportunity also exists to explore not only assistive relationships but also abusive ones, where there may be an overlap of animal and child abuse. He said that this may be the only recent concept that has an opportunity to encourage work in the child maltreatment area. Dr. Esposito said that this consideration is within the scope of the request for this funding opportunity.

Genomic Expert Curation Panels (Danuta Krotoski, Ph.D., Intellectual and Developmental Disabilities Branch). Dr. Butte said that ClinGen came about because too many genome sequencing companies had proprietary databases of variants and their meanings for human health and disease. He said that these are incredibly important efforts spanning multiple institutes, he was glad to see that expert panels could be funded in this way, and he was a "big fan" of the concept. An attendee asked about the potential for other partners to participate. Dr. Krotoski said that a number of ICs are interested in partnerships and that she would like to see this eventually become a complete trans-NIH effort. Dr. Gilliam agreed that input is needed from expert panels, especially for data on newborns and asymptomatic individuals. Dr. Bianchi said that she would also add considerations for fetal life and early loss, noting that many mutations may be unknown because genetic contributions to reproductive health are not being recognized.

Council Discussion

Each of the concepts was approved unanimously.

X. CLOSING REMARKS

Dr. Bianchi adjourned the meeting for lunch at 12:05 p.m., before the closed session.

XVI. CLOSED SESSION

This portion of the meeting was closed to the public in accordance with the determination that it concerned matters exempt from mandatory disclosures under Sections 552b(c)(4) and 552b(c)(6), Title 5, U.S. Code and Section 10(d) of the Federal Advisory Committee Act, as amended (5 U.S.C. Appendix 2).

Update: Division of Intramural Research (Closed to Extramural)

Review of Applications

The session included a discussion of procedures and policies regarding voting and confidentiality of application materials, committee discussions, and recommendations. Members absented themselves from the meeting during discussion of and votes on applications from their own institutions or other applications in which there was a potential conflict of interest, real or apparent. Members were asked to sign a statement to this effect. The Council considered and approved 503 primary applications requesting $ 187,755,022 in direct costs and $ 249,695,127 in total costs.

Remarks

XVII. ADJOURNMENT

There being no further business, the meeting adjourned at 4:00 p.m. on Tuesday, June 11, 2019. The next meeting is scheduled for September 18–19, 2019.

I hereby certify that, to the best of my knowledge, the foregoing minutes and attachments are accurate and complete.//[1]

/s/ 8/2/19

Diana W. Bianchi, M.D. Date
Chair, National Advisory Child Health and Human Development Council, Director, *Eunice Kennedy Shriver* National Institute of Child Health and Human Development

_____ _____

Eugene G. Hayunga, Ph.D. Date
Acting Committee Management Officer, *Eunice Kennedy Shriver* National Institute of Child Health and Human Development

[1] These minutes will be formally considered by the Council at its next meeting, and any corrections or notations will be incorporated in the minutes of that meeting.