
*Eunice Kennedy Shriver* National Institute
of Child Health and Human Development

# NATIONAL ADVISORY CHILDHEALTH AND HUMAN DEVELOPMENT COUNCIL

## *MEETING MINUTES*

September 18-19, 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

**September 18-19, 2019[1]**

The National Advisory Child Health and Human Development (NACHHD) Council convened its 171st meeting at 9:30 a.m. on Wednesday, September 18, 2019, at 6710B Rockledge Drive, Conference Rooms 1425 and 1427, of the National Institutes of Health (NIH) in Bethesda, Maryland. The meeting was open to the public on September 18 from 9:30 a.m. to 4:45 p.m. and on September 19 from 9:00 a.m. to 11:58 a.m. As provided in Sections 552b(c)(4) and 552b(c)(6), Title 5, U.S.C., and Section l0(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 on September 19 from 1:30 p.m. until 3:45 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)
Susan Bookheimer, Ph.D.
Atul J. Butte, M.D., Ph.D. (remote)
Michele Caggana, Sc.D., FACMG
Stephen A. Foley, M.D.
Catherine Gordon, M.D., M.Sc.
Richard D. Krugman, M.D.
Martin M. Matzuk, M.D., Ph.D.
Carmen L. Neuberger, J.D.
DeWayne M. Pursley, M.D., M.P.H.
Lesli Rotenberg (remote)
Timothy P. Shriver, Ph.D.
Annette Sohn, M.D.
Clifford Tabin, Ph.D.
Alan Thevenet N. Tita, M.D., M.P.H., Ph.D.
Anthony J. Wynshaw-Boris, M.D., Ph.D.

**Council members absent:**
Michael Boninger, M.D.
Alyce Thomas, RD

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

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

**Executive Secretary**
Della M. Hann, Ph.D.

[1] Members absent themselves from the meeting when the Council discusses applications from their own institutions or when a conflict of interest might occur. The procedure applies only to individual applications discussed, not to *en bloc* actions.

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

**Invited guests:**
Todd Macfarlan, PhD., Senior Investigator and Head, Section on Mammalian Development & Evolution, Division of Intramural Research
Kendra Haifley
Mustafa Khokha, M.D., Director, Pediatric Genomics Discovery Program; Associate Professor, Yale University School of Medicine
Helene Langevin, M.D., Director, National Center for Complementary and Integrative Health

## I. DAY 1: CALL TO ORDER AND INTRODUCTORY REMARKS

Dr. Bianchi began the meeting at 9:30 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 also 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 June 11, 2019, meeting minutes. The minutes were approved unanimously.

### C. Future Meeting Dates

Dr. Hann reviewed the future meeting dates:

January 23, 2020
June 11, 2020
September 10, 2020

## II. NICHD DIRECTOR'S REPORT AND DISCUSSION

Dr. Bianchi provided the Director's report.

### Updates on Selected Trans-NIH and NICHD Initiatives

A recent article published in *Science* summarized the influence and impact of Francis Collins, M.D., Ph.D., as NIH Director and described a number of major initiatives undertaken during his IO-year tenure. We often mention these major initiatives in the NACHHD Council's report because they challenge the status quo and because staff contribute significant time and effort to facilitate the research funded by these major projects. Additionally, a great deal of money flows through appropriations to multiple NIH institutes and centers (ICs) to support initiatives that

entail extensive collaboration by the ICs. Dr. Collins's decade of NIH leadership has been highlighted by four such programs:

- The Brain Research through Advancing Innovative Neurotechnologies® (BRAIN) Initiative, initiated in 2013
- The Precision Medicine Initiative, launched in 2015, which has since evolved into the *All of Us* Research Program
- The Cancer Moonshot℠, launched in 2016
- The Helping to End Addiction Long-term SM Initiative, or NIH HEAL Initiatives℠, begun in 2018

*HEAL Initiative*

NIH staff have been working for two years to conceptualize and fund the trans-agency HEAL Initiative, which consists of two main components: (1) enhanced pain management and (2) improved treatments for opioid misuse and addiction. NICHD's interest lies mainly in the effects of the opioid crisis on reproductive-age women, neonates and children, and people with physical disabilities. One of the six HEAL Initiative subprojects involves enhancing outcomes for infants and children exposed to opioids, especially through intrauterine exposure. The Advancing Clinical Trials in Neonatal Opioid Withdrawal Syndrome (ACT NOW) initiative has an overarching goal of optimizing health of infants exposed to opioids *in utero* and an overarching question: Among neonates with opioid withdrawal symptoms, to what extent can clinicians safely reduce or eliminate opioid treatment during the neonatal period? Starting with this simple question, the ACT NOW initiative has grown to encompass four interlinked studies that are to be funded. These include the ACT NOW Current Experience Study (manuscripts in preparation), two ACT NOW interventional trials (to be launched in calendar year 2019), and the ACT NOW Longitudinal Cohort Observational Study (discussed during this Council meeting).

An informal advisory group formulated a series of high-priority questions that could be addressed by the ACT NOW initiative and should be discussed with the multidisciplinary working group for the HEAL Initiative:

- How are clinicians treating infants now? How much variability exists in practices? These sorts of questions are the focus of the Current Experience Study.
- Do all infants need opioids for treating withdrawal symptoms, or would it be safe to treat some nonpharmacologically? What are the long-term consequences of different treatments? This line of research is the focus of the ACT NOW Eat, Sleep, Console (ESC) Cluster-Randomized Clinical Trial.
- For infants who do need opioids, is it safe for clinicians to wean them off medications earlier? What are the long-term consequences? The ACT NOW Weaning Randomized Clinical Trial is designed to answer questions about pharmacologic treatment of infants born to mothers who used opioids while pregnant.
- What happens to these infants over the long term? To what extent is neonatal opioid withdrawal associated with atypical neurodevelopmental outcomes? The ACT NOW Longitudinal Cohort Study will follow these infants. A pilot study will help to identify best practices to retain families in long-term studies. Neuroimaging studies will follow brain development of infants who were exposed to opioids in the womb.

The ACT NOW initiative studies will develop an evidence base for determining the standard of care for neonatal opioid withdrawal. Information on experience with current practices is available, and the two clinical trials (ESC and the weaning study) will collect data on nonpharmacologic and pharmacologic treatments from different but overlapping sets of hospital nurseries. A centralized data coordinating center will facilitate harmonization of data elements and extraction of information from the interventional and longitudinal trials, both of which

included a minimum of two years of clinical follow-up. Another program, called the HEALthy Brain and Child Development (HBCD) Study, is an ambitious study of brain and cognitive development of children ranging in age from neonates to age nine years that includes oversampling of infants exposed to opioids *in utero.*

Congress has appropriated $900 million for all six projects. Funds will also be available for a study of opioid prescribing for women recovering from cesarean section delivery.

### *Investigation of Co-occurring Conditions across the Lifespan to Understand Down syndrome (INCLUDE)*

The INCLUDE project resulted from a specific congressional directive to increase research on Down syndrome through a new trans-NIH initiative to study trisomy 21. INCLUDE will drive scientific studies to improve the health and neurodevelopment of people who have Down syndrome and to study typical individuals at risk for the certain co-occurring conditions, including Alzheimer's disease, cancer, cardiovascular disease, immune system dysregulation, and autism. The intent is not only to improve the lives of people living with Down syndrome but also to learn about conditions that affect the general population. For example, people who have Down syndrome are protected from developing solid tumors, and although many of them have problems with being overweight, they are at lower risk of atherosclerosis and myocardial infarction, compared with the general population.

The program has three objectives:

1. Conduct targeted high-risk, high-reward basic science studies on chromosome 21.
2. Assemble a large cohort of individuals with Down syndrome for comprehensive phenotyping and biomarker analysis.
3. Include individuals who have Down syndrome in existing and future clinical trials.

NIH funding for Down syndrome research had been relatively low and flat until the trans-NIH INCLUDE project led to a significant increase. The money for this project flows from the NIH Office of the Director to the ICs, but in addition, NICHD is adding money from its base funding. This bump in funding is attracting new researchers to work on Down syndrome.

During fiscal year (FY) 2018, $23 million in INCLUDE funding supported 49 supplements to existing NIH grants. The money was distributed among 14 institutes to support all three research objectives. Awardees are expected to share data. Study resources will benefit the study of Down syndrome and co-occurring conditions. NICHD funds OS-Connect®, which is a registry that allows people with Down syndrome and their family members who are interested in research participation to register and make their contact information available to allow researchers to contact them.

A congressional directive issued in the FY 2019 report read as follows: "continue to make investments in Down syndrome research that prioritize funding for both research grants and early-stage investigators that will expand the current pipeline of Down syndrome research, as well as implementation of the new trans-NIH initiative." In addition, Congress encouraged NIH ICs to increase overall funding for research on Down syndrome using non-INCLUDE funds from their own budgets. Consequently, NICHD is using an existing contract for its Pediatric Trials Network, which studies the formulation, dosing, efficacy, and safety of drugs and medical devices used in children in Phase I-IV clinical trials for many conditions. Network sites are located at more than 100 universities and children's hospitals. The plan is to use the network to leverage INCLUDE funds for supporting drug studies in individuals who have Down syndrome. In addition, one objective focuses on training investigators to overcome the specific challenges of including people who have intellectual and developmental disabilities (IDDs) in research.

Specific training opportunities will aim to increase the cadre of researchers in the next generation who are focused on IDDs.

Dr. Bianchi reported that during the Trisomy 21 Research Society conference held in June in Barcelona, Spain, several European Union (EU) attendees were intrigued by NIH efforts that led to the U.S. Congress' taking such interest in Down syndrome research and increasing funding for further study. Dr. Bianchi spoke as well about the meaningful participation of people with Down syndrome in the conference itself and in musical and dramatic presentations.

*Task Force on Research Specific to Pregnant Women and Lactating Women (PRGLAC)*

Dr. Bianchi announced that Phase I is completed. The report, available at https://www.nicbd .nih.gov/About/Advisory/PRGLAC, was submitted to Congress and Secretary of Health and Human Services Alex Azar in September 2018. Key among the 15 recommendations were the following:

- Changing the existing culture, which has limited the accumulation of knowledge on product safety, effectiveness, and dosing for pregnant and lactating women
- Protecting women *through* research instead of *from* research
- Removing pregnant women as a vulnerable population through the Common Rule
- Expanding the workforce of clinicians and researchers who possess expertise in obstetric and lactation pharmacology and therapeutics by removing regulatory barriers
- Continuing the task force, with a focus on implementation

The implementation of PRGLAC recommendations will likely be facilitated through extension of the charter; to this end, NICHD has already held two meetings and formed four working groups, comprising experts from federal agencies, industry, academia, and professional advocacy organizations. The four groups include a research and training group, a regulatory group, a communications group, and a drug discovery group. The working groups have been given their charges and will deliver their draft implementation plans with a set of 13 to 15 recommendations at a meeting scheduled for February 3--4, 2020.

## Staff Updates

New NICHD staff:

- Rodney Rivera, M.S., was named NICHD's associate director for administration and executive officer.
- Alison Cernich, Ph.D., was named the institute's deputy director.
- Theresa Cruz, Ph.D., is serving as the acting director of the National Center for Medical Rehabilitation Research.

## Fiscal Year (FY) 2020 Appropriations

Dr. Bianchi had little to report to the Council on FY 2020 appropriations aside from a statement that budget discussions are ongoing. She also confirmed that the federal government will be funded by Continuing Resolution through November 21, 2019.

## Council Discussion

Dr. Krugman asked how Dr. Bianchi had responded when people at the EU meeting asked her how Down syndrome has garnered so much attention and funding from the U.S. Congress over the past 4 years. Dr. Bianchi attributed the response to the sustained efforts of advocacy groups to educate Congress about the historic inadequacy of research funding for Down syndrome, which affects many people. Also, the personal touch was key. John Franklin "Frank" Stephens,

an actor with Down syndrome who is also a self-advocate, testified before Congress in 2016 and received a standing ovation.

Dr. Krugman asked about examples of IC-generated budget increases for diseases or other issues that were not stimulated by advocacy groups or Congress itself. Dr. Bianchi said that institute staff has the opportunity to shape science and also respond to needs identified by external advocacy groups. She spoke about staff efforts to identify and emphasize important issues. For example, in the new strategic plan, endometriosis research is identified as an aspirational goal, but not because of a push from any particular group. NICHD staff found that NIH was funding only about $6 million on research on the condition, although it affects 1 in 10 women.

Council members had no additional questions or comments.

## III. DIVISION OF INTRAMURAL RESEARCH REPORT

Dr. Stratakis, scientific director of NICHD's Division of Intramural Research (DIR), presented the division's annual report to the Council. DIR personnel include 900 staff including 60 investigators (55 tenured and five tenure track), 57 staff scientists, and more than 300 trainees. DIR is organized into 13 science-based affinity groups, covering the entire science portfolio of NICHD. The institute's clinical program is the fifth largest among the ICs of NIH. NICHD's intramural clinician scientists run more than 70 clinical protocols, about two-thirds of which are conducted at NIH's Bethesda campus, with the other third at other sites. NICHD also runs accredited medical training programs, including a new one in pediatric gynecology. The intramural program is overseen by Council and by the Board of Scientific Counselors (BSC). Dr. Stratakis highlighted recent changes to the BSC membership.

DIR's estimated FY 2019 budget is nearly $195 million, about half of which goes toward fixed costs, such as Clinical Center support (16%) and the management fund (20%). Other fixed costs include support for information technology and the animal program. The current administration has focused on increasing the portion of the budget that is more flexible-salaries and consumables-in order to hire new scientists, fund early-stage investigators, and start new programs and projects.

Currently the intramural program is expanding. Dr. Stratakis presented a number of staff changes in the intramural program:

- Dr. Bruce Howard retired.
- Dr. Bruce Simons-Morton retired. In addition to running his research program, Dr. Simons-Morton was notably NICHD's Associate Director for Prevention from 2015-2017.
- Dr. Kristina Rother has been appointed as Interim Director for the Pediatric Endocrinology Inter-Institute Training Program. Dr. Christina Tatsi was appointed Associate Director of the program. Dr. Stratakis also described efforts to bolster recruitment of pediatric endocrinology fellows to the program.
- Dr. Veronica Gomez-Lobo was recruited to develop a program in Pediatric and Adolescent Gynecology within the DIR.
- Dr. Fady Hannah-Shmouni and Dr. Marissa Lightborne were recruited to serve as co-chiefs of internal medicine. Dr. Hannah-Shmouni is also Associate Program Director, Inter-Institute Endocrinology Training Program.

Dr. Stratakis highlighted several honors from DIR staff including: Dr. Mary Dasso, who received the NICHD Mentor Award in 2018 and was also elected to the American Association for the Advancement of Science (AAAS); Dr. Meg Keil, who was elected to the American Academy of

Nursing; Dr. Juan Bonifacino, who was elected to the American Society for Cell Biology; Dr. Forbes Porter, who was elected to the Association for American Physicians; and Dr. Jack Yanovski, who received the Obesity Society's 2019 Thomas A. Wadden Award for Distinguished Mentorship. NICHD's junior faculty have been highly successful in receiving tenure with Dr. Todd Macfarlan, Dr. Edwina Yeung being awarded tenure in October 2018 and December 2018, respectively.

DIR investigators have the opportunity to compete in a number of funding opportunities, typically bringing in several million dollars in additional funding every year. The UOl program opens up the Clinical Center to extramural investigators who collaborate with DIR scientists. Intramural investigators have also successfully competed for additional funds to support their research as part of the Human Placenta Project and a Zika virus project within NICHD and from the NIH Office of AIDS Research, among others.

The DIR has several initiatives to train, support, and sustain individuals from groups traditionally underrepresented in science. The awardees range from high school students to postdoctoral fellows.

The Three-Minute Talks program offers fellows and graduates professional training in speech development and presentation delivery.

**Council Discussion**

In response to a question about the so-called "school tax", which is a significant expenditure, Dr. Stratakis explained that the NIH Clinical Center does not have its own budget; rather, it depends on support from the ICs that use the facility for clinical research. The DIR's support for the CRC will be approximately $31 million in FY 2019. Dr. Bianchi pointed out Clinical Center limitations on enrolling children younger than 3 and pregnant women are very restrictive for NICHD. She spoke of efforts to expand subspecialty support and add facilities to allow enrollment of these populations, as well as individuals with IDDs, to ensure representation of the populations of interest to NICHD.

Council members had no additional questions or comments.

## IV. HOW WE SHUFFLE OUR GENES IN THE GERMLINE AND WHY IT MIGHT MATTER FOR HUMAN FERTILITY

Dr. Stratakis introduced Todd S. Macfarlan, Ph.D., senior investigator and head of the Section on Mammalian Development and Evolution in the Division of Intramural Research. Dr. Macfarlan is interested in exploring how mammals evolved and how they develop *in utero.* This knowledge will help advance our understanding of human development, genetic disease, and infertility.

Dr. Macfarlan credited a fellow, Mohamed Mahgoub, Ph.D., with initiating this project. Dr. Mahgoub's interest lies in meiotic recombination, a process whereby chromatin material (DNA) from our parents is repackaged, causing mixing of alleles and generating genetic diversity. The process of exchanging parts of chromosomes via crossovers is critical for the proper alignment and segregation of chromosomes in our germ cells.

Meiotic recombination involves two specific processes. The first is generation of a double-strand break of DNA on one of the inherited chromosomes, and the second involves its repair by the other chromosome. This results in a shuffling of the two chromosomes. Meiotic recombination is not a random process; typically, about two to three crossovers occur per human chromosome. These crossovers are not randomly distributed; they occur in "hot spots," of which there are tens of thousands in the human genome. These crossovers (or lack of crossovers) in specific regions of chromosomes essentially determine which alleles and genes stay linked together, which has

dramatic consequences for allele distributions in human populations. To understand the consequences of failure in meiotic recombination, one must consider some statistics. A woman produces around five to seven million oocytes in her lifetime, and a man produces 500 billion sperm. If chromosomes do not properly align and segregate, the result can be missing or extra chromosomes, leading causes of miscarriage, childhood disease, and age-related syndromes. Crossover errors can happen in either the sperm or the egg. Estimating the prevalence of these errors is difficult, but a study using whole genome sequencing on oocytes from donors of different ages revealed that in young teens and in women older than 40, up to 50% of eggs have whole chromosome abnormalities.

Another type of chromosome problem is gross chromosomal rearrangements, with large regions missing or gained. The study mentioned earlier showed that this may occur in up to 10% of pre-implantation embryos and about 1% or 2% of pregnancies. About 1 in 20,000 live births has gross chromosomal rearrangements.

It turns out that there is high enrichment for gross chromosomal rearrangements at the regions of the genome called meiotic recombination hot spots. Dr. Mahgoub is interested in learning how hot spots are defined and distributed in different species. There are two primary patterns of hot spot distribution: the ancestral state and the evolved state. In the ancestral state, which is found in species such as plants, yeasts, and birds, crossovers typically occur right on top of genes, mainly near transcription start sites, at the front ends of genes. This state contrasts with the evolved state, in which crossovers happen away from genes because of a special factor called PR domain-containing protein 9 (PRDM9), which first emerged injawless vertebrates. PRDM9 determines where the hot spots occur. Many vertebrates and most mammals, including humans and mice, have hot spots located away from genes.

How does PRDM9 determine hot spots? PRDM9 has two key protein domains. It has a DNA-binding domain based on zinc finger proteins, which bind with very high specificity to DNA. The PR/SET domain is an enzymatic domain that puts methylation mark on chromatin molecules (histones) near the DNA binding site. Looking at the pattern of histone methylation across thousands of human hot spots reveals a pattern showing how PRDM9 binding is associated with double-strand breaks in DNA.

Interestingly, *Prdm9* knockout mice revert to the ancestral state. They do have hot spots, but double-strand breaks no longer happen at the Prdm9 binding site away from genes; instead they occur right at the start of genes. This finding means that the evolution of *PRDM9* itself was moving hot spots away from the ancestral state to the new state. One other interesting fact is that dogs lack the *Prdm9* gene; their hot spots are found at the genes, as in the ancestral state. There is a key difference between dogs and *Prdm9* knockout mice, however. The knockout mice are sterile, in contrast to dogs, which can breed. Due to some evolutionary quirk, dogs no longer need the PRDM9 system.

Another question was whether another factor is working with PRDM9 to move the "machinery" that makes double-strand breaks to other locations in the genome. Dr. Mahgoub took advantage of a large dataset of total gene expression profiles through different stages of mouse and human spermatogenesis. He developed an algorithm to search for genes that are strongly co-expressed with the *PRDM9* gene. One gene called *ZCWPWJ* had no known function and was most frequently co-expressed with *PRDM9.* ZCWPWl expression is highly enriched in the testes, but no other tissues. It is probably expressed in eggs, but eggs comprise only a small percentage of ovarian tissue, making it impossible to detect. ZCWPWl has two structural domains shown to bind to exact chemical signatures corresponding to the methylation marks near hot spots. PRDM9 is the protein that puts the methylation marks on the histones flanking a hot spot, and then ZCWPWl binds to the methylated histones and perhaps links to the cellular machinery that makes the double-strand break to cut the chromosomes, creating places where meiotic

recombination occurs. Experiments are under way to test this idea. In mice, Zcwpwl binds to places where there are hot spots in the genome.

*Zcwpw I* knockout mice are sterile. The males do not produce any sperm. It appears that not all chromosome pairs are properly synapsing without Zcwpwl. If chromosomes fail to synapse during development, the result is meiotic arrest and cell death. In the knockout mice, one observes an accumulation of double-strand breaks that cannot be quickly repaired. This repair is a key process in the crossover that allows the exchange of chromosome material. Using a mouse model developed at the National Cancer Institute, along with a protocol called end sequencing, the researchers showed that Zcwpwl is indeed necessary for repairing chromosome breaks.

Might defects in the *PRDM9* and *ZCWPWJ* system might lead to infertility in humans? There are some hints that that might be the case. First, mice lacking these proteins are sterile. Second, two small studies in Japan looked for mutations in the *PRDM9* gene and identified a few polymorphisms in some cases of azoospermia. This is an open question. Dr. Macfarlan and his colleagues developed a specialized platform to sequence the *PRDM9* gene and used it to screen an azoospermia cohort. They have 51 genotypes from azoospermia cases and 40 from controls. Even within this very small cohort, they found two entirely novel alleles that have not been described in human populations. Future studies will focus on determining whether these alleles could be causing azoospermia. The idea is to use *in vitro* models to see whether these alleles can bind to DNA. Perhaps it would be possible to restore fertility in these patients by simply removing the mutant allele, because both of these men were heterozygous for mutations that are thought to be dominant.

The *PRDM9-ZCWPWJ* system might be relevant to other human diseases. First, rare *PRDM9* alleles are associated with rare types of B-cell leukemia. Second, the *PRDM9* gene and its protein are reactivated in 10% of cancers although this gene should be turned off in all somatic cells. The affected cells then accumulate chromosome rearrangements at hot spots, leading to genomic instability of cancers in those sites. Third, expression of *ZCWPWJ* in cancer is associated with better survival. This seems to be true in many cancers, including pancreatic, cervical, lung, and urethral cancers. Having *ZCWPWJ* turned on might even provide a degree of protection against cancer.

**Council Discussion**

Dr. Tabin suggested referring to a derived state, rather than an evolved state, because yeast and birds are highly evolved. He also asked about possible reasons why *Prdm9* became fixed in the mammalian lineage. Dr. Macfarlan observed that dogs and marsupials, as well as some amphibians, have lost the Prdm9 system. It appears that the system arose once and then disappeared in many lineages. It does not seem to be essential; Dr. Macfarlan pointed out that **in** fact there might be some disadvantages to having *Prdm9,* which is a more flexible system. In species such as yeast and plants that lack *Prdm9,* hot spots are fixed. They occur **in** promoters and stay there. Those sites must be accurately repaired because they are genetic units that must remain functional. With the evolved state, hot spots are remote from genes, driving the evolution of the Prdm9 array. Alleles can be shuffled and unlinked, in a sort of diversity-generating system. Another possibility is that *Prdm9* may have emerged as a type of transposon defense. Experiments to address this possibility are under way.

Dr. Matzuk asked about whether prevalence of different human *PRDM9* alleles corresponds to differential susceptibility to different forms of cancer. Dr. Macfarlan said that part of the problem is that many large cancer trials are not accurately genotyping *PRDM9.* Typically, genotyping is done by exome capture, so genotypes for mini-satellite sequences are not accurate. One of Dr. Macfarlan's colleagues at NIH has initiated a project for using specialized sequencing protocols

to answer the question of *PRDM9* diversity among human populations in different patient cohorts.

Council members had no additional questions or comments.

## V. TOUR OF THE ZEBRAFISH FACILITY

The Council toured the DIR's zebrafish facility located on the main campus of NIH.

## VI. NEW NICHD STRATEGIC PLAN

Dr. Bianchi presented the new NICHD Strategic Plan. The plan is available online at https://nichd.nih.gov/sites/default/files/2019-09/NICHD_Strategic_Plan.pdf.

This is the first strategic plan for NICHD since the year 2000. It will guide institute activities for the next 5 years. The mission statement, which was recently revised, reads 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."

**Responding to Stakeholder Feedback**

Stakeholders, including the Council, provided valuable feedback on the draft strategic plan. Among the key changes that were made in response to stakeholders' comments were the following:

- Increasing the emphasis on developmental biology and model systems while broadening from a single-cell focus to a view based on genes and gene regulatory networks
- Articulating the importance of typical and atypical neurodevelopment, starting with the earliest developmental stages, and including more language on IDDs-early human development, the transition to adult care, and inclusion of people with IDDs in the development and testing of therapeutics and devices
- Clarifying the importance of reproductive health as a "window to future health" and underscoring the need to better characterize and define gynecologic and andrologic conditions
- Incorporating language on pre-pregnancy factors, reemphasizing the priority on placental biology and placental clinical research, including the "fourth trimester," and emphasizing research to address sudden unexpected infant death/sudden infant death syndrome and infant mortality
- Adding language on the need for a better understanding of puberty and the transition of adolescents, especially those with IDDs, physical disabilities, and chronic conditions, to adult health care systems
- Focusing on the development and validation of therapeutics and devices that affect NICHD's populations by integrating the use of clinical trial and real-world data to measure exposures and responses to therapeutics and devices

**Highlights of the Strategic Plan**

Dr. Bianchi presented some of the main components of the new strategic plan to the NACHHD.

*Research Themes and Aspirational Goals*

The five research themes in the strategic plan are as follows:

1. Understanding the Molecular, Cellular, and Structural Basis of Development
2. Promoting Gynecologic, Andrologic, and Reproductive Health

3. Setting the Foundation for Healthy Pregnancies and Lifelong Wellness
4. Improving Child and Adolescent Health and the Transition to Adulthood
5. Advancing Safe and Effective Therapeutics and Devices for Pregnant and Lactating Women, Children, and People with Disabilities

In addition, the strategic plan includes several crosscutting themes that are woven throughout the five research themes. These are global health, health disparities, prevention, nutrition, and infectious disease.

Ten aspirational goals are also presented in the plan to encourage scientists to aim beyond what is considered possible and strive to further advance research. The aspirational goals consist of the following:

1. *Limb regrowth:* Advance the ability to regenerate human limbs using emerging methods in developmental biology and rehabilitation.
2. *Personalized medicine for children:* Improve health outcomes for children through the development and application of personalized or precision medicine approaches and updated normative data on growth and development of children.
3. *Diagnosis, treatment, prevention, and cures for endometriosis:* Up to 10% of reproductive-age women in the United States experience endometriosis. This is an underserved area of research that has many interesting correlates related to pain, infertility, and predisposition to cancer.
4. *Predict pregnancies at risk for fetal loss:* Identify genome changes and exposure risks that explain or predict fetal loss using advanced technological approaches and population-based study methods.
5. *Advance and apply knowledge of the fetal-maternal immune relationship:* Use the growing understanding of immune factors in pregnancy and placental development to determine reasons for pregnancy rejection, mechanisms to prolong at-risk pregnancies, and ways to transfer this knowledge to other medical needs, such as organ transplantation.
6. *Improve the care of premature infants:* Enhance the survival and healthy development of preterm infants by exploring the role of environmental factors such as feeding methods and nutritional support, the role of human touch, and the role of environment, including music and lighting.
7. *Explore the risks of technology and media exposure on the developing brain:* Discover how technology affects developmental trajectories, health outcomes, and parent-child interactions in early childhood.
8. *Synthesize and personalize human milk:* Optimize infant survival by synthesizing human milk, capturing its components and properties, and individualizing it to the characteristics of the infant's mother.
9. *Build connections between atypical neurodevelopment and the risk of neurodegeneration:* Conditions such as Down syndrome are associated with atypical neurodevelopment and premature neurodegeneration, but there are other connections to explore and the possibility of identifying biomarkers of atypical neurodevelopment that could establish the likelihood of neurodegenerative disorders later in life.
10. *Train investigators in artificial intelligence and machine learning:* The next generation of scientists should be poised to harness the power of techniques to accommodate and interpret Big Data.

### *Scientific Stewardship Goals*

Several provisions of the 21st Century Cures Act relate to strategic plans and strategic planning. For example, IC strategic plans must use a common template. In addition, the act requires strategic planning to include consultations with the directors of the National Institute on Minority

Health and Health Disparities and the Office of Research on Women's Health to ensure that future activities of the ICs take into account women and minorities and focus on reducing health disparities.

The template includes a section on scientific stewardship-that is, how effectively the institute is using the tax money it receives. The first of NICHD's scientific stewardship goals is to promote an inclusive scientific workforce that fosters research training by focusing on early-stage investigators, opportunities for capitalizing on new methods and technologies, and recruiting and retaining a diverse biomedical and clinical research workforce. The second goal is to facilitate data sharing and access to biospecimens by supporting the accessibility, utility, and usability of NICHD-created or -sponsored data or biospecimens to enable secondary data analysis, thereby encouraging reproducibility while safeguarding privacy and confidentiality. The third goal is to partner with public and private entities and other federal agencies to enhance science. NICHD also leads trans-NIH and trans-U.S. Department of Health and Human Services (HHS) committees, task forces, and consortia. Fourth, we set research priorities by supporting strategic and operational planning efforts to help prioritize research and by continuing to rely on peer review, programmatic review by experts, and input from the Council and NICHD staff to identify and support meritorious programs and projects. The fifth stewardship goal addresses the alignment of resources to support science by using appropriate mechanisms and approaches and ensure timely responses to public health crises or emerging scientific opportunities. The sixth goal aims to improve clinical trial oversight and management by ensuring that trials have appropriate funding mechanisms, infrastructure, inclusion criteria, risk management, and provision for safeguarding research participants and their data. The seventh goal relates to program monitoring and evaluation to track, review, and report on NICHD research, training program activities, and accomplishments, by applying rigorous analytical approaches and techniques. The eighth goal is to facilitate transparency and communication by seeking new ways to reach the institute's audiences to convey the significance and value of the research it supports.

### *Management and Accountability Goals*

The first goal is to promote workforce development in order to balance and foster leadership, supervisory, technical, and scientific skills; preserve institutional knowledge; and encourage career development. Second, structural innovation will ensure that NICHD's infrastructure is responsive to staff needs.

Other management and accountability goals relate to (1) leading efforts on effective stewardship of resources and anticipating potential needs of the institute's workforce; (2) leveraging NIH-wide efforts aimed at enhancing a common infrastructure; (3) improving administrative efficiency while retaining accountability and quality of service; (4) advancing enterprise risk management by appropriately assessing internal and external risks; and (5) taking advantage of opportunities to adapt risk management procedures when confronted with unanticipated emerging issues.

## Moving Toward Implementation

NICHD has been working with a consulting group to develop a strategy model and metrics to measure progress toward goals. The strategy model is composed of tiered interrelated components that set the organization's path and direction. Each level of the strategy builds upon the preceding level to make the strategy actionable.

Objective measures will demarcate progress and performance against the goals in the strategic plan. Examples of measures to evaluate investigators' productivity include publications of investigators' laboratories and whether investigators are teaching, presenting at conferences, and recruiting diverse scientists for their laboratories. Other metrics could include the translation of

clinical trial results into clinical practice, patents issued, numbers of people trained, and diversity of the trainee population. Dr. Bianchi also provided examples of metrics to assess progress toward stewardship and management goals. These included numbers of underrepresented minorities in the trainee population, digital analytics showing how many people read press releases or engage with YouTube or Instagram videos, numbers of legislative milestones that are relevant to NICHD-funded programs, employee attrition rates compared with those of other ICs, and completion rates for continuing education courses.

**Performance Monitoring and Reporting Module Prototype**

NICHD staff are working with the NIH Office of Evaluation, Performance, and Reporting (OEPR) and the Division of Program Coordination, Planning, and Strategic Initiatives to develop a reporting module that will support NICHD's ability for metrics and transparent modeling of the planned performance. NICHD is the first of the ICs to partner with these entities within the NIH Office of the Director. NICHD selected OEPR's Strategic Plan Tracking System because OEPR already works across NIH to help harmonize the ICs' strategic plans with the NIH's overall strategic plan using the new common template in the 21st Century Cures Act.

With the Strategic Plan Tracking System's dashboard feature, staff can check metrics in real time. The data can be reported to the NACHHD and monitored over time. It would be a simple matter to instantaneously transmit the information to the NIH Office of the Director as well.

In closing, Dr. Bianchi thanked the institute's staff and the Advisory Council for the hard work necessary to create and refine the strategic plan.

**Council Discussion:**

- Dr. Bookheimer underscored the importance of neurobiology and the basic mechanisms of brain development. She recommended that the implementation plan take translation into account, going from basic models to systems-level neurobiological models and human biomarkers in infants and children to improve relevance of basic research. Dr. Bianchi said that the strategic plan is a framework and that translational science is woven in throughout the document. She agreed about the need to balance basic and clinical science. Theme 1 emphasizes developmental biology, and atypical neural development is articulated in theme 5.
- Dr. Bookheimer also noted that the longitudinal trajectory is not explicitly mentioned in the plan although it is relevant to many themes, including prematurity, drug exposure, environmental exposures, and early adversity, as well as genetic and other neurodevelopmental disorders. From a behavioral and cognitive approach, the outcomes are often not seen for many years after these events. Dr. Bianchi agreed about the importance of long-term outcomes, particularly with regard to the HEAL Initiative. Studying trajectories can also be accomplished through collaboration with other ICs; NICHD can deliver the datasets and biospecimens to other ICs in order to study the full trajectory.
- Dr. Tabin remarked on the importance of the implementation plan. Setting priorities, funding, and redirecting effort would be as important as the strategic plan itself. He encouraged NICHD leaders to rely on the Council when developing the implementation plan. Dr. Bianchi noted that until a strategic plan was in place, it was not possible to start on a detailed implementation plan. She said that in keeping with the goal of transparency, NICHD will keep everyone informed.
- Dr. Shriver supported the mention of IDDs in the strategic plan, but he expressed some disappointment that IDDs did not appear in the health disparities section. The strategic plan should be viewed as a way to accelerate scientific opportunities, not as an end point or closure of ideas. People who have IDDs should be considered an underrepresented

minority that has too often been excluded from research. NICHD should take a leadership role among the ICs in including children and adults with IDDs and physical disabilities in intramural and extramural research. Dr. Hann added that NICHD has taken the lead on a number of fronts, including autism and fragile X syndrome, to foster coordination of research efforts. Also mentioned was INCLUDE, which should help to tum the spotlight on IDD, which is an area in which the institute will remain active.

- Dr. Wynshaw-Boris asked about prenatal modeling in stem cells and animal models. Dr. Bianchi clarified that in addition to the high-level themes in the strategic plan, there were also sub-bullets, many of which were proposed by staff. Stem cell research is covered in one of the bullet points. The strategic plan is a brief document that provides a path and sets some priorities. The institute is clearly interested in funding cutting-edge technologies.
- A Council member asked about dissemination of the strategic plan. Dr. Bianchi explained that there is a full communications plan in place. Some people will receive printed copies, and there is a long mailing list of people who will receive electronic PDFs by email. A manuscript about the plan, to be submitted to a peer-reviewed journal, is in the works as well. Social media platforms are also a means of communicating about the strategic plan. The Council member suggested considering a YouTube video about the plan.
- Ms. Rotenberg would like to see more about early learning and school readiness as the strategic plan is implemented. Dr. Bianchi said that theme 4 would cover this stage of development.
- Dr. Butte recommended disseminating the plan to counselors of medical students who would be in a position to gauge how many students are going into pediatric medicine or obstetrical/gynecological medicine. As a statement of how NICHD views the future, the strategic plan could help trainees understand priorities in these fields. Dr. Bianchi supported this idea and suggested that Paul Williams, director of communications, would be in a position to explore the idea of disseminating the plan to medical schools and colleges.
- Members of Council praised NICHD staff on the excellent strategic planning process that culminated in the strategic plan, saying that staff members should be proud of their accomplishments.

Council members had no additional questions or comments.

## VII. CONCEPT CLEARANCE REVIEW AND DISCUSSION

NICHD staff presented the following concepts for review:

**In-Depth Phenotyping and Research Using IMPC-Generated Knockout Mouse Strains** (Mahua Mukhopadhyay, Ph.D., Developmental Biology and Structural Variation Branch) The Council members had no questions about this concept.

**Developmental Mechanisms of Human Structural Birth Defects** (Reiko Toyama, Ph.D., Developmental Biology and Structural Variation Branch) The Council members had no questions about this concept.

**Developmental Genotype-Tissue Expression (dGTEx) Project** (John Ilekis, Ph.D., Pregnancy and Perinatology Branch) Dr. Butte said that as a user of GTEx, he has found this resource to be very helpful, and he expressed his support for extending it to the pediatric developmental age group. He recommended ensuring that the project is diverse in terms of samples and populations. The Council members had no other comments or questions about this concept.

**Contraceptive Development Research Centers Program** (Christopher Lindsey, Ph.D., Contraception Research Branch) Dr. Gordon recommended including both adults and adolescents in this initiative because contraceptives can have effects in young adolescents different from those in adults. Dr. Tita asked whether there are plans to include any particular interventions, and Dr. Lindsey confirmed that requests for applications would be issued if the concept is cleared. The Council members had no other comments or questions about this concept.

**Population Dynamics Centers** (Rosalind King, Ph.D., Population Dynamics Branch) The Council members had no questions about this concept.

**Impact of Technology and Media Exposure on Early Childhood Development and Health Outcomes** (James Griffin, Ph.D., Child Development and Behavior Branch) Dr. Bookheimer confirmed with Dr. Griffin that the age group of interest is birth to age 5. Dr. Griffin said that the focus is on very early development because some basic and translational research has already been funded in this area, meaning that this initiative could tie everything together. Dr. Shriver sought confirmation that the research would include diverse populations, including children with IDDs. The Council members had no other comments or questions about this concept.

**Child Health Research Career Development Award** (Andrew Bremer, M.D., Ph.D., M.A.S., Pediatric Growth and Nutrition Branch) Dr. Tita asked whether this award could be extended to other disciplines that interface with NICHD, such as obstetrics/gynecology. Dr. Bremer said that it could go beyond that to serve as a model across NIH. In response to a question from Dr. Gordon, Dr. Bremer confirmed that special effort would be directed to encourage participation by underrepresented populations and women. Another Council member pointed out that more women than men are pediatricians and suggested weighting the number of awards by the number of people who are in a particular specialty. Dr. Bremer also explained that the awards are open to all aspects of pediatric research. The Council members had no other comments or questions about this concept.

**NICHD Research Education Programs** (Dennis Twombly, Ph.D., Office of Extramural Policy) In response to a comment from Dr. Gordon about this important pipeline initiative, Dr. Twombly said that the template for R25 programs includes sections about inclusion of underrepresented groups and women in these programs. The Council members had no other comments or questions about this concept.

**INCLUDE Project Cohort Development Awards** (Melissa Parisi, M.D., Ph.D., Intellectual and Developmental Disabilities Branch) Dr. Bookheimer asked whether the initiative would support deep phenotyping to make it easier to look across conditions, sites, and studies. Dr. Parisi confirmed that phenomics and deep phenotyping would be included. Dr. Shriver asked about integrating existing lines of research and ways that this initiative could help stimulate interest in IDDs in addition to Down syndrome. Dr. Parisi said that the hope is that Down syndrome will serve as paradigm for future research on IDDs. Approaching Down syndrome in a systematic way could help establish a framework for a broader approach to research on IDDs. The more that INCLUDE research is promulgated, the better the chances that inclusion will become standard and broadly acceptable throughout the research community. Dr. Shriver agreed about the importance of establishing a framework that could support a broad array of investigators in various fields. There are overlapping pathways that underlie many forms of intellectual disabilities, so if researchers start to understand some of those neurobiological bases, it could have effects on research on other related disorders. The Council members had no other comments or questions about this concept.

**Council Discussion**

Each of the concepts was approved unanimously.

## VIII. COMMENTS FROM RETIRING COUNCIL MEMBERS

Dr. Bianchi announced that Drs. Butte, Shriver, Krugman, and Pursley and Ms. Rotenberg were retiring from the Council effective on November 30 of this year. Dr. Bianchi presented them with certificates and letters of appreciation signed by Secretary Azar. Dr. Bianchi thanked the outgoing members for their commitment and contributions to the NACHHD.

Ms. Rotenberg said it had been an honor to serve, although she sometimes felt at a disadvantage because she did not understand much of the scientific language, but she was happy to contribute in small ways. She expressed enthusiastic support for the new strategic plan and the research concept on the effects of media exposure in early childhood.

Dr. Butte said that much had changed in his four years on the Council. Positives include new treatments for some genetic diseases, earlier diagnoses for more people, and undiagnosed diseases now getting diagnosed. However, some things are negative, such as prenatal opioid exposure, the return of childhood measles when the disease had been nearly eradicated, and families' inability to afford treatments that might cure their children. Where will NICHD be in the midst of all this change? Having a sound strategic plan is a start. Serving on the Council motivated Dr. Butte to think about the impact of research and how it is measured. He suggested that creating more accessible and affordable solutions through entrepreneurship might be a way to improve health. It is very easy for a group to get money to harm human health; for example, an e-cigarette maker raised $785 million regionally to fund its growth and development. Compare that with the $1.5 billion NICHD has to divide up every year. Each NICHD dollar needs to be spent wisely, and sometimes that means not continuing to spend it in the same ways. Dr. Butte encouraged the ongoing committee members to challenge NICHD staff and push beyond the status quo. More work needs to be done to reach more potential applicants who are very talented but think they do not have a chance to get funding from NICHD. They may not have much in the way of academic credentials, but they might be able to deliver solutions worthy of NICHD investment.

Dr. Krugman said that Council meetings had given him insights into how well this organization works. He has enjoyed being part of the Council. He particularly appreciates NICHD's emphasis on inclusion, and he pointed out that Dr. Bianchi is the first woman director of the institute. Dr. Krugman applauded NIH's interdisciplinary and trans-institute work, which is key in addressing topics such as human growth and development and neglected and abused children.

Dr. Shriver spoke of the need for the medical field to recognize the dignity, value, worth, capacity, and potential of individuals who have IDDs. From his work with people with IDDs and their families, it appears that about three-quarters of them would say that the most negative interaction they have had in their lives has been with a medical professional. These negative experiences exacerbate their pain, isolation, and loneliness, as well as the stigma attached to IDDs. Dr. Shriver said this not as an indictment or accusation but rather as a recognition that the field of medical research still does not understand the assets this population can bring to science, starting at the bench across the whole spectrum of research. The institute should constantly be challenging the scientific enterprise of NIH and, beyond NIH, recognizing the value of people who have IDDs. Dr. Shriver said that if he were channeling the spirit of his mother, Eunice Kennedy Shriver, he would say, "Don't forget that you have a sacred trust to science, research, biology, women, pregnancy, and reproduction. Everyone in this institute should see their mission as the need to recognize that the children who are most likely to be forgotten are in some ways the sacred trust of this institute."

## IX. DAY 1: CLOSING REMARKS

Dr. Bianchi adjourned the meeting for the day.

## X. DAY 2: CALL TO ORDER AND INTRODUCTORY REMARKS

Dr. Bianchi began the second day of the meeting at 9 a.m. She reminded the attendees that the meeting was being videocast live.

## XI. NICHD DIVISION OF EXTRAMURAL RESEARCH (DER) DIRECTOR'S REPORT AND DISCUSSION

Dr. Hann updated the NACHHD on recent DER activities.

**Extramural Policy Updates**

*Use of Human Fetal Tissue in Research*

In June, HHS issued a statement regarding the use of human fetal tissue from elective abortion. Regarding extramural research, current awards may continue research using fetal tissue. However, any new research that is being proposed through competing applications would now have to go through an ethics board. Intramural research has been directed to discontinue use of such tissue.

Two guide notices have been published:

- **NOT-OD-19-128: Changes to NIH Requirements Regarding Proposed Human Fetal Tissue Research.** This notice provides definitions to clarify the types of tissue that are subject to review by the new ethics advisory board.
- **NOT-OD-19-137: Clarifying Competing Application Instructions and Notice of Publication of Frequently Asked Questions (FAQs) Regarding Proposed Human Fetal Tissue Research.** This notice articulates what applicants need to consider and include in their proposal if they plan to use fetal tissue in research.

DER staff is working with the NIH Office of the Director to work through all the parameters and operational procedures. However, it is clear that any such applications will have to go to the ethics advisory board, which will recommend whether the application should be funded.

*Foreign Involvement*

Dr. Hann said that the Advisory Committee to the Director issued a report in December of 2018 indicating that in a few cases there have been peer review violations or failures to disclose either substantial foreign resources or significant foreign financial conflicts of interest that could distort funding decisions.

When NIH makes a grant, it is to an institution. The principal investigator writes the proposal and is responsible for the science, but the commitment and fiduciary responsibilities lie· with the institution.

In some cases, individuals on study sections were taking parts of applications and giving them to foreign institutions or foreign governments. Such actions are against NIH policy and values with regard to the integrity of the peer review process. One case cropped up in the news this week. It was under investigation by the Federal Bureau of Investigation.

Dr. Hann referred to NIH Guide Notice NOT-OD-19-114: Reminders of NIH Policies on Other Support and on Policies related to Financial Conflicts of Interest and Foreign Components.

### *Anti-Sexual Harassment*

Dr. Collins and Principal Deputy Director Lawrence Tabak, D.D.S., Ph.D., take the problem of sexual harassment very seriously. NIH is bolstering policies, guidelines, requirements, and communications to make our expectations clear to the NIH workforce and NIH-funded organizations. The anti-harassment policy is clear about expectations for NIH employees as well as contractors and grantee communities. More information is available online.

### *Concept Clearances at Council Meetings*

A few years ago, several policy irregularities came to light as a different IC was setting up a clinical trial being conducted under a major public-private partnership. Staff members involved in creating the funding opportunity announcement (FOA) were working very closely with individuals in the extramural community who then benefited from that FOA.

Funding opportunities need to support fair and open competition. Therefore, all concept clearance of FOAs must be done during open Council sessions or similar public external advisory sessions. The concept clearance presentation must address the outcomes of any workshop proceedings that informed the FOA development. Extramural scientists, including those who have attended a workshop, should not have a direct role in writing FOAs.

### *NI H's Second Inclusion Across the Lifespan Workshop*

The workshop is slated for September 2-3, 2020, in the Natcher Conference Center on the NIH main campus. A request for information will be issued soon. Inclusion of racial/ethnic groups and people of all ages is critical for research.

## Strategic Planning Implementation

The branch priorities are being revised now, with the goal of having them available by November. Applications submitted in January 2020 will be the first set to be funded. In support of open and fair competition, the institute leaders want to be clear regarding program priorities. In addition, NICHD staff needs to begin revising referral guidelines to see how NICHD's priorities intersect with, reinforce, or match the priorities of other ICs in order to negotiate and establish boundaries. The guidelines essentially dictate the types of applications that come into the institute. Once the guidelines are in place, institute staff will then start aligning all FOAs with the strategic plan.

Staff are also charged with developing initiatives and action plans for each scientific theme and aspirational goal articulated in the strategic plan. Action plans advance scientific stewardship, management, and accountability. The Council will be briefed on progress on action plans and initiatives during the January 2020 meeting.

## Staff Updates

Departing staff:

- Ruben Alvarez, Ed.D., of the Childhood and Development Behavior Branch accepted a position as deputy director of the Office of Technology Development and Coordination at the National Institute of Mental Health.

New NICHD staff:

- Clara Cheng, Ph.D., joined the Fertility and Infertility Branch.
- Melissa Copeland is serving in the Grants Management Branch.
- Tuba Fehr, Ph.D., joined as a program officer with the Developmental Biology and Structural Variation Branch.
- Sai Majji joined the Maternal and Pediatric Infectious Disease Branch.

- Amanda Price, Ph.D., is a new AAAS fellow in the Child Development and Behavior Branch.
- Aaron Pawlyk, Ph.D., is the new chief in the Obstetric and Pediatric Pharmacology and Therapeutics Branch.
- Jenelle Walker, Ph.D., M.S., is new to the Office of Global Health.

NICHD is currently seeking health science administrators and other staff across four branches-Pregnancy and Perinatology (PPB), Intellectual and Developmental Disabilities (IDDB), Obstetric and Pediatric Pharmacology and Therapeutics (OPPTB), and Pediatric Trauma and Critical Illness (PTCIB)-as well as within the Division of Extramural Research. More information is available at https://www.nichd.nih.gov/about/jobs and https://hr.nih.gov/jobs/global-recruitment.

**Council Discussion**

Dr. Tita inquired about plans for NICHD-supported networks and whether there would be opportunities for providing input for the implementation plan. Dr. Hann said that discussions were ongoing about how best to support networks in the context of the new strategic plan. She said that there will be opportunities in the next few months to acquire input from the field as planning activities start to take shape.

## XII. CONSIDERATION OF NICHD'S IMPLEMENTING AN OUTSTANDING INVESTIGATOR AWARD (R35)

Dr. Tabin served as co-chair of the R35 Working Group along with Dr. Twombly, deputy director of NICHD's Office of Extramural Policy. Other members of the Working Group were Council members Dr. Boninger, Dr. Gordon, and Dr. Wynshaw-Boris. NICHD staff made significant contributions in terms of providing background on previous reviews of the R35 funding mechanism and conducting analyses to understand the potential impact on NICHD if an R35 program is adopted.

**Background**

Dr. Tabin reviewed two types of grant mechanisms currently supported by NICHD:

- The ROI research project funding mechanism is the workhorse grant awarded in response to well thought-out proposals that have specific aims, preliminary data, and contingency plans. The RO**1** provides up to 5 years of support.
- The R37 Method to Extend Research in Time (MERIT) Award provides investigators who have superior records and a highly scored proposal with a five year award for a specific project, with the possibility of extension for up to five more years. The R37 is nominated by the IC after an RO1 application has gone through the traditional peer review process.
- An R35 Outstanding Investigator Award provides up to eight years of support to experienced investigators who have outstanding research productivity. With an R35, investigators can develop new longer-term innovative programs without the need to quickly generate the preliminary data required of a traditional funding mechanism. R35 awards minimize administrative burden and grant writing. These grants give flexibility (within some constraints) to allow investigators to pursue new research directions. Participating ICs can tailor R35 awards to suit their mission-specific needs. With an R35 award, all the investigator's existing grants are bundled together. The proposal is judged not so much on its specific aims and details, but more so on a visionary approach to solve long-standing problems.

The question of whether NICHD should offer R35 grants was discussed by the Council five or six years ago. The decision to not go forward at that time was based on the need for more information about financial impact and a desire to know about other ICs' experience with this funding mechanism.

**Experience of Other ICs with R35 Grants**

Dr. Tabin said that six institutes-the National Institute of General Medical Sciences (NIGMS); the National Institute of Environmental Health Sciences (NIEHS); the National Cancer Institute (NCI); the National Heart, Lung, and Blood Institute (NHLBI); the National Institute of Dental and Craniofacial Research (NIDCR); and the National Institute of Neurological Disorders and Stroke (NINDS)-currently have R35 grants. These institutes reported that the R35 mechanism has been a net positive. No other ICs are considering starting an R35 program, however. All the ICs require bundling of an investigator's grants, and all R35s have a duration of seven or eight years.

The ICs have set up their R35s in a variety of ways, but most require an investigator to have at least two RO1 grants or equivalents to bundle together in order to be eligible. The exception is NIEHS, which has a different approach. Most of the ICs cap at either $600,000 or $750,000, though NIGMS has a lower cap. The NHLBI is unique among the ICs in that investigators who have an R35 are allowed to apply for other grants. NIGMS issues many more R35 grants (798) than other ICs using this mechanism; NCI, with 133 R35 grants, was ranked second.

**Modeling the Effect of an R35 Program at NICHD**

Dr. Tabin suggested some criteria to consider when deciding whether to begin an R35 program:

- An R35 program would not make sense if it compromises other funding programs.
- It would have to be equity neutral, meaning that an R35 program would not disadvantage underrepresented groups.
- Funded applications must be congruent with the goals of the NICHD strategic plan.

To model the financial impact of an R35 program, Dr. Tabin said that the working group applied the following parameters:

- The total award amount should not exceed the average total of the most recent 4-year period.
- The maximum R35 would be capped at $750,000.
- R35s would provide eight years of support with an administrative review at the 5-year mark.
- All of an investigator's grants would be bundled.

Sarah Glavin, Ph.D., chief of the Science Policy, Planning and Evaluation Branch, and her staff analyzed the potential effects of an R35 program at NICHD. Only 40 investigators would qualify; of these, only 15 would be likely candidates. This group of investigators already has high grant-renewal rates (exceeding 80%), so they have little at risk. If all 15 were funded with R35 grants, the additional costs of the program would be low, in the range of $3 million to $6.9 million over **8** years if all 15 investigators were funded. To bring in more clinical investigators, one would need to raise the cap above **$1** million. If the criteria were broadened to bring in investigators who have one large RO1, the cost would change and the number of eligible investigators would increase; however, their renewal rates would be significantly lower than the group of 15. Of note, the administrative burden of implementing the program was not considered in the costs.

The working group considered the pros and cons of an R35 program. The downsides included the following:

- Only a limited set of investigators would apply for an R35, because most would not want to have a cap of $750,000. Likely applicants would all be in basic and translational science.
- The program would entail more work for the NICHD Review Branch and greater effort for grant management because of the significant work of consolidating and reissuing awards. The workload and associated costs could be highly significant if NICHD expanded beyond a pilot group of 15 investigators. The burden would be offset to some extent because the workload for renewing other grant mechanisms would be reduced.
- Projects do not undergo peer review for the duration of the R35 grants.
- An R35 program would not address important issues around diversity.

The potential upsides include the following:

- An NICHD R35 program could promote innovative work relevant to the strategic plan and allow outstanding investigators to pursue creative new research directions.
- An R35 supports the investigator as opposed to supporting a specific project or projects.
- The emphasis would be on an outstanding investigator record as a metric for future productivity.
- An R35 consolidates all NICHD grants into a single award, reducing the administrative burden on the investigator.
- Investigators would have a longer period of support (eight years).

**Summarizing the Working Group's Deliberations**

Overall, the R35 Working Group thought that an R35 program would be positive and exciting, but the members' enthusiasm was tempered by the potential downsides. Dr. Tabin declared a conflict of interest because he would be eligible for an R35 award. He noted that he declared his conflict when the working group first convened. Because of his declared conflict, Dr. Tabin declined to give any recommendation for or against implementing an R35 program and declined to participate in the subsequent discussion. For the record, Dr. Bianchi said she had been unaware of Dr. Tabin's conflict of interest until recently.

Two working group members gave their perspectives on a possible R35 program. Dr. Gordon said that the working group had lively discussions. On the whole, she feels very positive about an R35 program, bl.it she reiterated concerns about the potential burden on staff. Speaking on behalf of Dr. Boninger, who was not able to attend this meeting, Dr. Gordon said he also had an overall positive impression but shared the same concern about the staff burden. Dr. Wynshaw-Boris declared no conflict of interest, as he is not currently funded and so would not be eligible for an R35 award. He supported the idea of a pilot with 15 investigators to see if R35 awards live up to their potential and whether any of the cons lead to major problems. Dr. Wynshaw-Boris said that his colleagues who have R35s from other ICs have found the awards to be very positive: They give investigators a sense of pride and real commitment to the goals of the funding institute. Having an R35 program would ensure that the best investigators are working toward the goals articulated in the NICHD strategic plan.

**Council Discussion**

- A Council member said that it appears that R35 awards would support long-term projects with exceptional potential to advance healthcare and align with strategic plan goals. She sought clarification about whether investigators would be funded up to the R35 cap even if the total of their other consolidated grants was less than that. Would there be an

infusion of more money on top of that? Dr. Hann said her understanding was that if the total of consolidated grants was less than the cap, then the investigator would receive less than the cap amount. If the total exceeded the cap, the investigator would receive the cap amount, not more.

- If there is no additional money involved, how can the investigator have the flexibility to take on novel and riskier types of research? Dr. Hann said that R35 applications do not have specific aims; rather, they lay out an area of science and a vision. In addition, the longevity of the award offers advantages for the researcher, who would not have to spend time writing applications and instead could devote more time to working in the laboratory. Dr. Bianchi added that ensuring the security of a laboratory for eight years is a meaningful benefit. Many worthy investigators spend a great deal of time writing ROI proposals. Hiring and training activities remain steady over the life of the R35 while giving flexibility and creativity to the investigator.
- Dr. Butte said that the R35 mechanism smacks of the rich getting richer. The eligible investigators have figured out how to write grants and win awards. He asked about the makeup of the 15 investigators who would likely be eligible for the pilot. Dr. Butte also observed that the R35 mechanism is portrayed as reducing the burden on investigators, but they would still be free to apply for RO ls from other ICs. Dr. Wynshaw-Boris clarified that the R35 is a consolidation of grants; it does not provide more money. However, the R35 program could be perceived as enriching those who already receive substantial NIH support. Dr. Glavin said that the 15 eligible investigators were split between men and women in roughly the same proportion as the NICHD investigator pool. No data were available to look formally at minority status. She pointed out that there was a concentration within subject matter and within one branch, meaning that there would be a lack of diversity and breadth in the science that would be funded by the R35s.
- Dr. Bianchi explained that NIGMS has 798 R35 awardees, but NIGMS has no intramural branch. Also, NCI has a budget about six times larger than NICHD's, explaining why they are also an outlier in terms of the number of R35 awards.
- Dr. Krugman recommended that the pilot be contingent upon the institute's receipt of a budget increase. If the budget is flat for the next few years, the risk might be too great, especially with the administrative burden on NICHD staff.
- Dr. Twombly said that the system of applying for and renewing grants is a struggle for all. The R35 mechanism is attractive in terms of reducing that burden. However, Dr. Twombly had concerns about rolling multiple grants into one larger grant. Those funds would be locked in for a full eight years. Others in the field who are not eligible-probably more than 1,000 people who have ROI-equivalent grants-would wonder about the removal of funds from the pool to support investigators who already have substantial support. For this reason, Dr. Twombly had concerns about the possible perception of unfairness.
- Dr. Bookheimer pointed out that some types of investigators and science would be left out-for example, imaging and in-depth phenotyping in longitudinal studies, team scientists who work in centers and program projects, and integrative human and animal researchers.

Dr. Bianchi thanked the working group and said that NICHD will take this under advisement as further thought is given to possibly implementing an R35 funding mechanism.

## XIII. RARE PEDIATRIC DISEASES ARE COMMON AND DEMAND MECHANISM DISCOVERY TO UNDERSTAND THE DISEASE PROCESS

Dr. Khokha is a pediatric critical care physician. He spoke about the inordinate impact of birth defects and rare disorders on children. Birth defects are the number-one cause of infant mortality in the United States. Combined, rare disorders are surprisingly common, affecting about 2% of the population and represented in about 10% of hospital discharges.

For infants, congenital malformations are the most common cause of death. Indeed, congenital malformation is among the top three causes of death for all age groups in the United States, ranked behind only heart disease and cancer in adults.

Regarding the impact of birth defects, Dr. Khokha said that these conditions are among the top three causes of death among children up to age nine. In the first decade of life, birth defects are behind more deaths than any other cause. There is probably a genetic basis for many birth defects, but for the most part, birth defects' causes are unknown. Rare diseases and birth defects individually are rare, but combined they are very common and the major cause of childhood death.

With rare diseases, physicians struggle to make diagnoses and, in many cases, patients respond unpredictably to therapy. Families feel frustrated, isolated and desperate. They do not understand what happened, and they wonder what will happen with subsequent children.

DNA sequencing offers an extraordinary opportunity. This technology has become inexpensive, and it can identify candidate genes efficiently, providing insights into disease pathogenesis. However, sequencing is not enough. If a novel gene is found, then it is still a leap to figure out mechanisms and pathogenesis. Dr. Khokha said that tremendous opportunities are available today to convert descriptive diagnosis to molecular diagnosis, discover new biology, and return results to families desperate for answers. Dr. Khokha presented several examples of published research demonstrating that sequencing studies for individual patients led to identification of candidate genes, a fundamental understanding of a pathogenic process and, from there, to answers for families.

Clinicians are identifying and phenotyping patients and enrolling them in studies. By working with geneticists (for genome sequencing) and developmental biologists (for functional analysis), it is possible to think about genetic counseling. Dr. Khokha underscored the importance of returning information to families. Building an infrastructure to support clinical and basic science, genetic testing, and data analysis would improve our understanding of diseases and help patients and their families.

In summary, Dr. Khokha said that there are extraordinary opportunities but also major challenges:

- The impact of birth defects and rare diseases on children is massive but underappreciated by the general public.
- Resources are not proportional to the impact. Dr. Khokha recommended writing about the impact of rare diseases and birth defects for the lay press and alerting policymakers and funders.

Dr. Khokha recommended some solutions:

- Change the research metric by aiming to help patients today by returning results --- even research results-to patients.
- Emphasize patient-driven gene discovery. Patients are a powerful motivator for "new" biology. Patient phenotype can be a powerful guide for pathogenesis discovery. Using the phenotype can give rise to new discoveries for already studied genes.
- There is a need for animal models to convert clinical findings and candidate genes into basic science. Mouse models are expensive and are not high throughput. *Xenopus* (frog),

however, is powerful model. In just 1 week, the phenotype can be elucidated. Frogs have lungs and limbs, the genome is annotated, and an animal stock center exists (the National *Xenopus* Resource).

- We need to capitalize on return of results to patients by creating a basic science-clinical science infrastructure.

## XIV. RARE DISEASE IS DEVASTATING TO FAMILIES: HOPE FROM GENE DISCOVERY

Dr. Bianchi introduced Ms. Haifley. Hearing the voice of the patient personalizes all of NICHD's work, according to Dr. Bianchi, who thanked Ms. Haifley for being willing to share her story with the people in the room and those watching the videocast.

Ms. Haifley said that as a mother, she knew something was wrong with her daughter, Isabel. At one point, her daughter's oxygen saturation dropped to 58%. A heart catheterization revealed that Isabel had pulmonary hypertension and needed a lung transplant. She was placed on an oscillating ventilator. Meanwhile, Ms. Haifley joined every interstitial lung disease (ILD) group she could find. On day 12 of hospitalization, Isabel took a turn for the worse. Moreover, the family hit their insurance cap of $1 million dollars within 28 days. One social worker recommended that the Haifleys divorce so Isabel would be eligible for Medicaid, but Ms. Haifley was adamant that the family stay together. Isabel was accepted by a transplant facility, Texas Children's Hospital, and approved for Medicaid coverage, thanks to an exceptional woman Ms. Haifley found on Facebook.

Ms. Haifley spoke about feeling very alone and having to be an expert and an advocate for her daughter.

Isabel was transported to Houston, but while staff transferred her to the hospital's machines, they performed hand ventilation, causing serious problems. Isabel's aorta ruptured when staff performed cardiopulmonary resuscitation. Isabel died at the age of 2 years, 2 months, and 2 days. In honor of Isabel, the Haifleys started the Warrior Princess foundation to help other families struggling with rare diseases.

At that point, the doctors thought that Isabel's problem was not genetic. Ms. Haifley became pregnant again and gave birth to Silas. He had a bout with hypoxia during a respiratory illness. An echocardiogram revealed a minor abnormality, and a subsequent catheterization study revealed that he had pulmonary hypertension. When Silas began receiving bilevel positive airway pressure (biPAP), he went into cardiac arrest. He was not a considered a candidate for extracorporeal membrane oxygenation but was accepted by the Children's Hospital of Philadelphia for a lung transplant. Ms. Haifley took over his care and worked toward achieving home ventilation settings. Despite treatment, Silas died at the age of 19 months.

Ms. Haifley's father struggled with the loss of his two grandchildren and committed suicide.

Finally, the family reached a turning point when Dr. Khokha's team at Yale University reported their genetic sequencing results. Ms. Haifley and her husband found out they had different variants of the same gene, and Isabel and Silas had had both variants. Learning these findings was life-changing, and Ms. Haifley and her husband finally felt as if they could breathe again.

Dr. Khokha presented the Haifley family's pedigree, noting that when the family was referred to him, an older sibling was healthy, but two other siblings had been affected by interstitial lung disease at around one year of age and subsequently died. Ms. Haifley was pregnant at the time of the genetic consultation, and the fetus appeared healthy. Pathology reports indicated presence of alveolar proteinosis. Exome sequencing revealed that the mother and the father each carried

different variants of the *NARFL* gene. The proband and the other affected sibling had both variants; the older sibling who was well had one of the variants.

*NARFL* had never been associated with human disease until the Haifleys' pedigree was studied. The father's mutation is novel, and the mother's is very rare. Loss-of-function mutations appear to affect the lung. The youngest child, Stone, does not have either mutation and is healthy.

## XV. UPDATE FROM THE DIRECTOR OF THE NATIONAL CENTER FOR COMPLEMENTARY ANDINTEGRATIVE HEALTH (NCCIH)

Dr. Langevin presented some of the latest scientific research from the NCCIH and highlighted areas of common interest to NICHD and NCCIH. In terms of strategic priorities, NCCIH focuses on whole-person health by investigating treatments that originated outside of mainstream or conventional medicine. These are complementary therapies and practices that are meant to add to or complement, not replace, conventional medicine. Complementary medicine includes dietary, psychological, and physical interventions. Dr. Langevin noted that these categories overlap, and there is also overlap between complementary and conventional medicine-e.g., cognitive-behavior therapy can overlap with mindfulness-based stress reduction and relaxation therapy; physical therapy can include massage, and spinal manipulation. Yoga and tai chi have physical and psychological components. Acupuncture is intriguing in that it encompasses physical, device, and psychological components.

Integrative heath brings together complementary and conventional medicine to understand the whole person at a basic physiological level. Patients sometimes complain that they are treated like a disconnected set of body parts, which makes it hard to put the whole picture together. This organization of conventional medicine goes back in history and extends to how our medical schools and medical specialties are organized today. These body systems work together, although we do not always understand the connections between them. An example of this is the influence of breathing on digestion.

Science includes both analyses, or breaking things down into smaller parts, and synthesis, which puts information back together. Biomedical science is skewed toward analysis breaking the body down into different organ systems and then down to individual molecules. This yields a predominantly biochemical understanding and results in pharmaceutical treatments. Integration involves synthesis-getting back to the whole person. To balance analysis and synthesis, one needs to think about how a person functions across all levels in a biopsychosocial model.

Health involves the whole person. It is important, and we need to understand health promotion and restoration, disease prevention, and symptom management. NCCIH has until now focused on symptom management, especially pain relief, but also has had a long-standing interest in health promotion and disease prevention. Going forward, NCCIH will expand its focus to health restoration: return to health after an illness or exacerbation of a chronic illness. It is not enough just to treat disease; we need to restore health. That is the aim with many traditional healing systems, such as Chinese medicines.

With regard to self-care and health promotion, Dr. Langevin emphasized the importance of intervening early. Children can benefit from learning how to manage stress and cope in interactions with their peers. Children also suffer from pain. Teaching good posture habits, especially with computer use, is important. Poor posture can lead to musculoskeletal problems. Sedentary lifestyles and movement problems can lead to structural problems in the tissues.

According to Dr. Langevin, resilience is a very exciting line of research. Resilience may determine why people have different outcomes. In the face of a stressor, how do people push back, adapt, or even grow?

Mechanisms can have positive or negative effects when it comes to the restoration of health. Basic science may reveal mechanisms of repair, regeneration, and restructuring. These mechanisms may translate into recovery and resilience for the whole person. Negative mechanisms include inflammation, dysregulation, degeneration, fibrosis, thrombosis, and neoplasms.

Dr. Langevin also touched on the concept of health span: How long can people maintain a healthy state as they age? If one develops problems that require treatment, how can a person be supported and restored to as healthy a state as possible?

Key concepts in the NCCIH strategic plan are:

- Including complementary therapies and practices that use dietary, physical, and psychological approaches
- Addressing health promotion and restoration, disease prevention, and symptom management
- Supporting integrative research on whole-person health

Dr. Langevin asked how these concepts resonate with NICHD; there appear to be many areas of overlap and common thought.

**Council Discussion**

- Dr. Sohn spoke of her interest in studying adolescents who have grown up with HIV infection and chronic diseases to learn about their resilience and transition into adulthood. That is one of the institute's priorities in the strategic plan. Dr. Langevin said that predisease and disease can share common elements: such as an inflammatory burden in the body. People living with HIV have chronic inflammation, and the medicines they take also pose an additional inflammatory burden. To help with symptoms and help patients manage their lives, we need more research on how complementary and integrative medicine could help reduce the extent of inflammation. This is important at a basic physiologic level and whole-person level.
- Dr. Shriver spoke of the importance of ensuring that children with IDDs are included in studies of complementary therapies. He commented on positive psychology, noting that some large studies are focusing on children who are successful because they manifest what is popularly referred to as "grit." What is the role of grit in Down syndrome children and in their parents? There is a danger of overlooking important research opportunities by not including nontraditional subjects in studies, and little is known about the grit and resilience of children with disabilities. Dr. Langevin spoke about studies exploring the effect of music therapy on anxiety in children who have autism or in neonates that are exposed to stressful situations. Resilience applies across the spectrum in children with health problems and developmental difficulties.
- Dr. Gordon remarked on the benefits of yoga for children who have restrictive eating disorders. Dr. Langevin agreed that this topic was an intriguing line of research, and she emphasized the importance of applying scientific rigor to such investigations. NCCIH takes its scientific review as seriously as other ICs do, and studies must have proper controls and hypotheses. NCCIH hopes to fund more research on eating disorders.
- A Council member asked about opportunities for co-funding projects. Dr. Bianchi said that if there is a particular project or program under consideration for co-funding, staff reaches out to the potential funding partner to gauge interest and identify areas of

common interest. Dr. Langevin said that NCCIH, being a small center, considers collaboration to be vital. She noted that the HEAL Initiative is a trans-NIH effort.

## XVI. CLOSING REMARKS

Dr. Bianchi adjourned the meeting at 11:58 a.m., before the closed session.

## XVII. 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 l0(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 voting 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 442 primary applications requesting $124,946,004 in direct costs and $174,830,288 in total costs.

**Remarks**

## XVII. ADJOURNMENT

There being no further business, the meeting adjourned at 3:45p.m. on Thursday, September 19, 2019. The next meeting is scheduled for January 23, 2020.

I hereby certify that, to the best of my knowledge, the foregoing minutes and attachments are accurate and complete.[2]

/s/

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

• 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.

*/s/* _____ _____

Eugene G. Hayunga, Ph.D. Date

Acting Committee Management Officer, *Eunice Kennedy Shriver* National Institute of Child Health and Human Development