Eunice Kennedy Shriver National Institute of Child Health and Human Development

National Advisory Child Health and Human Development (NACHHD) Council

Meeting Summary

September 4–5, 2024

NIH Bethesda Campus, Building 35A (September 4)

Bethesda, MD

6710B Rockledge Drive (September 5)

Rockville, MD

U.S. Department of Health and Human Services (HHS)

National Institutes of Health (NIH)

Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD)

The NACHHD Council convened its 186th meeting at 9:30 a.m. ET on Wednesday, September 4, 2024, at the NIH Bethesda Campus, Building 35A, in Bethesda, Maryland. It was a hybrid meeting that was open to the public from 9:30 a.m. to 5:00 p.m. ET. The Council reconvened on Thursday, September 5, 2024, at 6710B Rockledge Drive in Rockville, Maryland, for another session open to the public from 9:00 a.m. to 9:30 a.m. ET. The Council then met in a session that was closed to the public from 9:30 a.m. to 12:45 p.m. ET. As provided in Sections 552b(c)(4) and 552b(c)(6), Title 5, U.S.C., and Section 10(d) of Public Law 92-463, sessions for the review, discussion, and evaluation of grant applications and related information are closed to the public.

NICHD Director Diana W. Bianchi, M.D., presided.

Council Members Present[1]

Anna Aizer, Ph.D., M.S. (virtual)
Diana W. Bianchi, M.D. (Chair)
Shari L. Barkin, M.D., MSHS (virtual)
Christina M. Bucci-Rechtweg, M.D.
Marcelle Ivonne Cedars, M.D.
Cynthia Gyamfi-Bannerman, M.D.
Ethylin Wang Jabs, M.D.
Catherine E. Lang, Ph.D.
Yvonne A. Maldonado, M.D.
Genevieve S. Neal-Perry, M.D., Ph.D.
David H. Rowitch, M.D., Ph.D.
Ignatia Barbara Van den Veyver, M.D.

Council Members Absent

Susan L. Brooks, J.D.
Damien Fair, Ph.D.

Ex Officio Members

Patricia Dorn, Ph.D.

Department of Defense

Gayle Vaday, Ph.D.

Health Resources and Services Administration

Rui Li, Ph.D.

Executive Secretary

Rebekah Rasooly, Ph.D.

National Advisory Board on Medical Rehabilitation Research Council Liaison

José L. Contreras-Vidal, Ph.D.

In each section of this meeting summary, the number in parentheses that follows each heading refers to the time stamp on either the Day 1 NIH VideoCast or the Day 2 NIH VideoCast. Please go to that point in the recording to listen to the full presentation.

[1] Council 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.

I. Call to Order and Introductory Remarks (0:05)

Dr. Bianchi opened the meeting and welcomed the members of the NACHHD Council and all in-person and online attendees. She briefly reviewed the agenda and logistics for speaking during the meeting.

Review of Confidentiality and Conflicts of Interest (1:46)

Rebekah Rasooly, Ph.D., the Council's executive secretary, reminded NACHHD Council members that they are required to read, agree to, and sign the confidentiality and nondisclosure rules for special government employees on the Council member website before they evaluate any NIH grant applications. Before the meeting, Council members received and signed the required conflict-of-interest certification forms. Dr. Rasooly also reminded Council members that they are required to recuse themselves and leave the meeting before any discussion that involves organizations or universities for which they are in conflict, in addition to those listed in the Council action document. Council members are not allowed to serve on any NIH peer-review panel while they serve as Council members, because NIH policy indicates that individuals may not serve on both the first and second levels of peer review. Furthermore, during closed sessions, Council members must turn off cloud-based voice services (e.g., Alexa) that can capture confidential information.

Council Minutes (2:55)

Dr. Rasooly said that a correction to the June 3–4, 2024, NACHHD Council meeting minutes had been posted on the Council website. The correction was to the numbering (but not the text) of the Pregnant Women and Lactating Women Implementation Working Group (WG) cluster B recommendations. Catherine E. Lang, Ph.D., made a motion to approve the corrected minutes. Cynthia Gyamfi-Bannerman, M.D., seconded the motion. Council members voted to approve the minutes.

Future Meeting Dates (4:23)

Dr. Rasooly announced that future Council meetings are scheduled for January 13–14, 2025 (virtual); June 9–10, 2025 (6710B Rockledge Drive); September 9–10, 2025 (NIH Bethesda Campus, Building 45); January 26–27, 2026 (virtual); June 8–9, 2026 (6710B Rockledge Drive); and September 1–2, 2026 (NIH Bethesda Campus, Building 45).

II. NICHD Director's Report (5:18)

In her report, Dr. Bianchi described the fiscal year (FY) 2025 appropriations bills and pending presidential transition; provided updates on ongoing women's health, pediatric, and rehabilitation research initiatives; shared progress on various extramural training programs; and gave kudos and staffing updates.

FY 2025 Appropriations Bills and Presidential Transition (6:35)

The FY 2025 House Appropriations Bill includes $48.6 billion for NIH, which would be an increase over the FY 2024 enacted level of $47.1 billion. The bill also includes a proposed reorganization of NIH from 27 to 15 institutes and centers (ICs). In the proposal, NICHD would be merged with the National Institute on Deafness and Other Communication Disorders (NIDCD) to become the "National Institute for Disability Related Research," and the proposed budget for the new institute would be $2.3 billion (this is the approximate combined FY 2024 total for NICHD and NIDCD). The House Committee on Energy and Commerce took public comments on the proposed reorganization through August 16, 2024.

The FY 2025 Senate Appropriations Bill includes $50.3 billion for NIH, which would also be an increase over the FY 2024 enacted level of $47.1 billion. The Senate bill further provides $20 million of additional funding for the Implementing a Maternal health and PRegnancy Outcomes Vision for Everyone (IMPROVE) Initiative and $76 million of additional funding for the Office of Research on Women's Health (ORWH). Beyond budgeting, the Senate bill would create 10-year term limits for NIH IC Directors. Furthermore, U.S. Senator Bill Cassidy, M.D. (R-LA), recently wrote a white paper titled "NIH in the 21st Century: Ensuring Transparency and American Biomedical Leadership."

With President Biden's withdrawal from the 2024 presidential election, a presidential transition will occur in 2025. The NIH Director is a political appointment that requires U.S. Senate confirmation. During a presidential transition, all political appointees customarily submit a letter of resignation that is either accepted or rejected by the incoming president. NIH will work with HHS to prepare presidential transition informational briefing documents across NIH research priorities. For NICHD, past examples included briefing documents on intellectual and developmental disabilities, reproductive health, maternal health, and rehabilitation research.

Women's Health Research (10:58)

NICHD conducts women's health research in each of the following "below the belt" areas:

- Gynecologic health and disease
- Contraception research
- Fertility and infertility
- Pregnancy and perinatology
- Maternal and pediatric infectious disease
- Obstetric and pediatric pharmacology and therapeutics
- Population dynamics

Dr. Bianchi provided updates on the White House Initiative on Women's Health Research, an endometriosis Rapid Acceleration of Diagnostics Technology (RADx® Tech) research challenge, and the IMPROVE initiative. She later noted that NICHD communications staff has created a new series of one-page summaries on women's health topics.

White House Initiative on Women's Health Research (11:23)

On March 18, 2024, President Biden issued an Executive Order on Advancing Women's Health Research and Innovation. This cross-government initiative is being championed by the first lady, Dr. Jill Biden. It was designed to promote collaborative, interdisciplinary research; to assess unmet needs in women's health research; and to develop a research agenda and common data elements related to menopause. Whether Congress will appropriate the funding that is proposed in the White House Initiative on Women's Health Research is unknown.

To date, NIH actions related to the executive order have included the following:

- Issuing a Notice of Special Interest on Women's Health Research
- Developing a list of all NIH grant opportunities related to women's health research
- Reviewing women's health research at NIH that has been submitted for publication
- Producing an NIH Women's Health Roundtable Series on the three following topics:
    - The Future of Menopause Research (May 16, 2024)
    - Endometriosis (August 19, 2024)
    - Maternal Mental Health Research (September 16, 2024)
- Forming an executive committee to discuss and further implement the directives in the Executive Order

RADx® Tech Advancing Cures and Therapies and ending ENDOmetriosis diagnostic delays (ACT ENDO) Challenge Launched (12:59)

To further address the White House Initiative on Women's Health Research executive order, NICHD recently launched a RADx® Tech challenge to develop reliable noninvasive tests that (1) enable early and accurate diagnosis of endometriosis and (2) facilitate the treatment of endometriosis. This partnership between NICHD and the National Institute of Biomedical Imaging and Bioengineering (NIBIB) is leveraging the RADx® Tech innovation funnel to accelerate the time to diagnosis, eliminate the invasiveness of current techniques, and/or improve accessibility, safety, convenience, and cost of diagnosis for endometriosis. The RADx® Tech ACT ENDO challenge was launched on August 12, 2024, with $3 million in cash prizes. Phase I submissions are due on October 11, 2024. Final winners are expected to be announced in March 2026.

IMPROVE Initiative (15:06)

IMPROVE is a major initiative designed to reduce maternal mortality and morbidity in the United States. With the addition of two new Maternal Health Research Centers of Excellence (at the University of Illinois–Chicago and the University of Pittsburgh), the IMPROVE initiative has now set up 12 Maternal Health Research Centers of Excellence. NICHD staff recently completed site visits at three of these centers of excellence.

Two IMPROVE initiative challenges will soon announce their final winners.

- The winners of the Connecting the Community for Maternal Health Challenge (which was designed to build research infrastructure in communities and teach community-based advocacy groups how to be competitive when applying for funding opportunities) will be announced on September 5, 2024.
- The final winners of the RADx® Tech for Maternal Health Challenge (a competition to develop diagnostics for postpartum monitoring in maternity care deserts) will be announced in October 2024.

The IMPROVE initiative's fifth anniversary meeting will be held in a webinar format on October 15–16, 2024. Geographically, the initiative's reach is from coast to coast, with locations in 22 U.S. states across the country.

Pediatric Research (18:50)

NICHD conducts pediatric research in:

- Developmental biology and congenital anomalies
- Child development and behavior
- Intellectual and developmental disabilities
- Pediatric growth and nutrition
- Pediatric trauma and critical illness
- Maternal and pediatric infectious disease
- Obstetric and pediatric pharmacology and therapeutics
- Pregnancy and perinatology
- Population dynamics

Dr. Bianchi provided research updates on drowning prevention, youth driving, childhood adversity, and reducing inappropriate computed tomography (CT) scans in children and youth.

Drowning Prevention Research (19:02)

Drowning is the foremost cause of injury or death in children ages 1 to 4 and a leading cause of injury or death for children ages 5 to 19. There are stark racial and socioeconomic disparities in drowning death rates. An NICHD-funded study identified disparities in adolescents' access to drowning-prevention strategies (such as swimming lessons and life jacket use) in the same demographic groups that experience higher drowning rates. See "Disparities in Adolescent Reported Drowning Prevention Strategies," by Erin R. Morgan et al., published in the *Journal of Adolescent Health* in December 2022. Now NICHD-funded principal investigators (PIs) are investigating the following drowning-prevention studies:

- A virtual reality lifeguard surveillance environment to identify points of failure and inform training (PI: Cathleen Moore)
- The effects of swim instruction on autistic children's swimming and water safety skills (PI: Lisa Lawson)

- The effectiveness of public policy interventions in reducing racial disparities in drowning (PI: Samuel Myers)

Youth Driving and Mood Disorders (20:40)

Youth with mood disorders are less likely to get their driver's licenses than peers who do not have mood disorders. Driving requires multiple neurocognitive skills (e.g., executive functioning, sensory perception, attention), but these skills are often impaired in individuals with mood disorders. Obtaining a license has been associated with higher self-reports of health and educational attainment in young adults, so lack of a license could be associated with adverse psychosocial outcomes. Recent NICHD-funded research revealed that youth with mood disorders who obtained licenses had a higher overall risk of crashing than other youth. In the NICHD science update, the authors commented, "Our findings point to the need to develop evidence-based training and education for adolescents and young adults with mood disorders who want to drive." See "Driver's Licensure and Driving Outcomes Among Youths With Mood Disorders," by Christopher E. Gaw et al., published in *JAMA Network Open* in April 2024.

Developmental Effects of Childhood Adversity (21:38)

NICHD intramural population health research conducted by Stephen Gilman, Sc.D., is showing that early childhood adversity may affect neurological and cognitive development. When exposed to combinations of parental divorce/separation, family loss and instability (e.g., foster care), and crowded housing, children (particularly children in households below the federal poverty threshold) had lower scores on tests of visual-motor and sensory-motor functioning and on intelligence and achievement tests. These findings have long-term implications for educational success, social and emotional well-being, and physical health in adulthood. See "Patterns of Adverse Childhood Experiences and Neurocognitive Development," by Jing Yu et al., in *JAMA Pediatrics* in May 2024.

Reducing Inappropriate CT Scans for Children and Youth (23:06)

Research conducted within the Pediatric Emergency Care Applied Research Network (PECARN) developed prediction rules for emergency departments to distinguish children with high versus low risk (CT scan versus no CT scan) for serious abdominal or brain injuries. The prediction rules were 100% accurate for severe abdominal injuries, 100% accurate for head trauma in children younger than age 2, and 98.8% accurate in children older than age 2. Validated prediction rules can be considered safe for minimizing inappropriate CT scans in children. See "PECARN prediction rules for CT imaging of children presenting to the emergency department with blunt abdominal or minor head trauma: a multicentre prospective validation study," by James F. Holmes et al., published in *The Lancet Child and Adolescent Health* in May 2024.

Rehabilitation Research (24:13)

Dr. Bianchi shared National Center for Medical Rehabilitation Research (NCMRR) updates on improving sleep for adolescent concussion patients and a new surgical procedure that enables below-knee amputees to achieve a more natural gait.

Aerobic Exercise May Improve Sleep for Adolescent Concussion Patients (24:22)

Many concussion patients experience sleep problems, which can worsen their concussion symptoms. Adolescent concussion patients who performed more than 150 minutes of aerobic exercise per week scored better on a sleep quality questionnaire than a group who exercised less. See "Exercising More Than 150 min/wk After Concussion Is Associated With Sleep Quality Improvements," by David R. Howell et al., published in the *Journal of Head Trauma Rehabilitation* in its July–August 2024 issue.

New Surgical Procedure Enables Below-Knee Amputees to Achieve More Natural Gait (24:50)

A new surgical procedure that allows continuous neural control via sensors in a neuroprosthetic interface has been shown to improve maneuverability of the robotic limb. In the study, patients walked faster with their prostheses and were better at climbing stairs and avoiding obstacles after undergoing the procedure. See "Continuous neural control of a bionic limb restores biomimetic gait after amputation," by Hyungeun Song et al., published in *Nature Medicine* in July 2024.

Extramural Training Update (25:40)

NICHD is committed to training the future scientific workforce. At the January 2024 Council meeting, the NICHD Extramural Training and Career Development (TCD) WG presented the following six recommendations:

- Rethink How We Talk About Outcomes
- Reinvigorate Institutional TCD Programs (T32 and K12)
- Create Community Among Trainees
- Use TCD to Diversify NICHD's Reach
- Reinvigorate the Loan Repayment Programs (LRPs)
- Use Training Programs to Support Strategic Research Priorities

To support implementation of the TCD WG's recommendations and action items, the TCD Implementation WG was formed, in February 2024, with 20 members and three co-chairs from both NICHD extramural divisions: the Division of Extramural Research (DER) and the Division of Extramural Activities (DEA). At the May 2024 Council meeting, each TCD Implementation WG subgroup presented a progress report. The following TCD goals have been accomplished since the last Council meeting:

- Funding for NICHD's LRP was increased, approximately 28%, from FY 2024 to FY 2023.
- Outreach for training opportunities has increased through the following activities:
    - Opening an Obstetric and Pediatric Pharmacology and Therapeutics Branch Clinical Pharmacology Training Network workshop to all NICHD-funded trainees (August 2024).
    - Having NICHD's Office of Health Equity (OHE) create new materials for extramural and intramural training opportunities to distribute at scientific conferences.
    - Having OHE submit abstracts for presentation at major national meetings (e.g., Society for the Advancement of Chicanos and Native Americans in Science, American Public Health Association, Annual Biomedical Research Conference for Minoritized Scientists [ABRCMS]).
    - Scheduling webinars about specific trainee funding opportunities (F99, K99, diversity supplements) that were led by OHE in collaboration with DER and DEA.
- New (Type 1) and renewal (Type 2) T32 applications are now being clustered separately for peer review.
- Competing T32 applications now require program official input on Diversity Recruitment and Retention Plans during funding plan development; NICHD has drafted language to encompass individual and institutional diversity for its T32s and K12s.
- A major cross-cutting theme on training has been added to NICHD's 2025 Strategic Plan.

Kudos (30:18)

Deb Henken, Ph.D., a program officer in the Developmental Biology and Congenital Anomalies Branch (DBCAB), was recognized by the 13th International Conference on Neural Tube Defects for her "unfailing enthusiasm, mentorship, guidance, and championing research into the causes and prevention of structural birth defects."

NIH and NICHD Staff Updates (31:08)

James Coulombe, Ph.D., branch chief of DBCAB since 2018, retired on August 31. He joined NICHD in 2006 and led the Gabriella Miller Kids First Research Program since 2017.

Mahua Mukhopadhyay, Ph.D., is now acting branch chief for DBCAB.

Henry Levin, Ph.D., has been selected as NICHD's Deputy Scientific Director. Previously a senior investigator and the head of the section of Eukaryotic Transposable Elements, he is currently the chair of DIR's Tenure & Promotions Committee and a program director for Early Career Awards and the Career Awards for Staff Scientists/Staff Clinicians. Dr. Levin has also received an NIH Outstanding Mentor Award.

National searches are currently underway for a DBCAB chief and a Fertility and Infertility Branch (FIB) chief. Those who are interested in either position, or who can suggest potential candidates for either position, should contact rohan.hazra@nih.gov.

NICHD currently has job openings for extramural branch chiefs, program officers, and policy officers, as well as openings for intramural laboratory postdoctoral fellows and trainees.

Discussion (34:37)

Patricia Dorn, Ph.D., said that Iceland requires all children to take swimming lessons; it is mandatory there. Dr. Bianchi said that drowning is a significant problem in the United States, and that there are significant disparities among different communities.

Genevieve S. Neal-Perry, M.D., Ph.D., asked for additional details about (1) the language that NICHD drafted to encompass individual and institutional diversity for T32 and K12 applications and (2) the policy stating that race and gender cannot be used as part of recruitment efforts. Dr. Bianchi said that it is important to diversify the workforce, so outreach is needed. In the past, NICHD has not included as many Historically Black Colleges and Universities (HBCUs) as it should have in its outreach efforts. NIH has recognized that all people must be made aware of opportunities. The race of the PI is not a factor in determining funding awards, but opportunities must be made available to all, and no one should be excluded.

Dr. Gyamfi-Bannerman asked how funding opportunity announcements (FOAs) might be affected by the upcoming presidential transition. Dr. Bianchi said that addressing significant health issues in the United States can be challenging when there is polarization around certain scientific issues, including women's health. She added that research will continue to be funded, but the language in FOAs may change over time to avoid polarization. Investigators are always encouraged to contact the branch chiefs or program officials to ask questions about the specific topics for any FOA. Dr. Gyamfi-Bannerman further asked whether any current women's health research funding could be cut because of a change in administration. Dr. Bianchi said that the White House Initiative for Women's Health Research is being championed by Dr. Jill Biden. NICHD and ORWH leadership have discussed the types of projects encompassed in women's health research (e.g., pregnancy was not included in the White House's initiative, because the focus was on diseases with a higher incidence in people born female, such as autoimmune diseases and cardiovascular diseases). Maternal health, however, is a nationwide initiative that has been championed by Vice President Harris. Although reproductive health is an issue that has been become a focus area in the upcoming election, it does not change NICHD's mission and vision or its focus on women's health "below the belt." Dr. Bianchi added that NICHD's 2025 Strategic Plan will outline its research priorities; NICHD staff will continue to frequently brief members of Congress and their staffs on its role within NIH; NICHD will continue to collaborate with ORWH and other ICs; NICHD will continue to take the lead on reproductive health, including the IMPROVE initiative.

David H. Rowitch, M.D., Ph.D., asked how decisions would be made if the NIH reorganization were to proceed forward and whether there might be an opportunity to combine age-appropriate research for women and children in the reorganization process. Dr. Bianchi said that several ICs were regrouped in the proposed plan, but NIH leadership was not consulted during that process about what would make the most scientific or medical sense in a reorganization of NIH. The congressional committee that posted the Request for Information (RFI) about NIH reorganization received comments from several pediatric chairs about what would be best for children. Marcelle Ivonne Cedars, M.D., said that women's health was completely left out of the proposed reorganization plan. Dr. Bianchi said that children were also left out of (not mentioned) in the plan. Laura Berkson, J.D., director of NICHD's Office of Legislation, Public Policy, and Ethics, said that ORWH remained in the Office of the Director (OD) in the proposed plan, which did not specifically mention women or children. The proposed plan contains a lot of unknowns, and any proposed changes would have to be approved by the U.S. House of Representatives, the U.S. Senate, and the President of the United States to be enacted.

Ms. Berkson added that there has been a lot of discussion on Capitol Hill about reorganizing NIH and providing additional oversight of it. Dr. Bianchi asked whether the discussions were related to congressional reauthorization of NIH. Ms. Berkson said that NIH was indeed due for reauthorization. Dr. Cedars asked what the time frame would be for an NIH reorganization. Ms. Berkson said that the House Committee on Energy and Commerce was the authorizing committee for NIH. That is the committee that organized the RFI as a way to gather input. The House Appropriations Bill included similar language about NIH, so the timeline may follow the budget approval process. Continuing resolutions are common in election years. There are many issues to work through. Dr. Bianchi said that there are a lot of congressional activities related to the restructuring of NIH, including a new Cures Act. In the meantime, NIH will continue its work.

Gayle Vaday, Ph.D., asked for clarification on the timing of the phases for the RADx® Tech ACT ENDO prizes. Dr. Bianchi said that the prizes would be given during each phase, and the program will wrap up in 2026. Dr. Vaday said that the U.S. Department of Defense's Congressionally Directed Medical Research Programs planned to fund endometriosis, menopause, and maternal mental health research in FY 2025, so the program's leadership looked forward to collaborating with NICHD leadership to ensure that the research gaps in these areas would be filled.

Dr. Bianchi acknowledged all of the NICHD staff who are working to brief members of congress on NICHD research and initiatives. She said that this is an important part of translating research knowledge into appropriations language.

José L. Contreras-Vidal, Ph.D., asked whether NICHD had plans to expand its training programs to children in kindergarten through grade 12 or to their teachers. Dr. Bianchi said that Chris J. McBain, Ph.D., planned to discuss training in his presentation later in the day, but that early training makes a huge difference. That is why NIH's intramural program currently has such an extensive summer internship experience for high school and college students.

Later in the meeting, Dr. Bianchi said that she was asked whether an NIH Director can remain in that position after a presidential transition. The answer is yes: The incoming President of the United States would reject the NIH Director's letter of resignation to keep that Director in place. This happened several times when Francis S. Collins, M.D., Ph.D., was the Director of NIH.

III. Tour of NIH Clinical Center and Intramural Research Laboratories (56:49)

Dr. Bianchi introduced Veronica Gomez-Lobo, M.D., director and fellowship director of Pediatric and Adolescent Gynecology at NICHD, who took Council members on a tour of the NIH Clinical Center ("America's Research Hospital") and several of NICHD's intramural research laboratories during the morning break.

IV. Annual Division of Intramural Research (DIR) Report (1:01:00)

Dr. McBain, scientific director of NICHD's DIR, provided a brief program overview followed by updates on budget and personnel, DIR Office of Education activities, and competitive funding opportunities.

Program Overview (1:02:54)

NICHD's DIR has seven divisions with a broad portfolio of basic, translational, clinical, and population research:

- Developmental Biology
- Translational Medicine
- Molecular and Cellular Biology
- Neurosciences and Cellular and Structural Biology
- Basic and Translational Biophysics
- Translational Imaging and Genomic Integrity
- Population Health Research (DiPHR)

DIR employs about 850 people, including 68 PIs, 64 staff scientists, and 254 trainees (i.e., graduate students, postbaccalaureate students, postdoctoral fellows, and clinical fellows). The basic and clinical programs are divided into 12 scientifically based affinity groups. DiPHR's epidemiologic programs are divided into three branches and one program. There are currently 63 clinical protocols being investigated by DIR faculty. Its two accredited medical training programs are on (1) reproductive endocrinology and infertility and (2) pediatric and adolescent gynecology. For the first time in several years, all four of DIR's top leadership positions are now filled. DIR's 12 scientific affinity groups foster communication around a scientific area or theme.

Budget and Personnel Updates (1:07:53)

DIR currently receives 12.8% of the NICHD budget, or slightly less than $220 million.

In August 2024, DIR trainees included 137 postdoctoral researchers, 9 clinical fellows, 17 graduate students (from more than 12 graduate partnership programs), 91 postbaccalaureate students, and 51 summer interns (with most of them doing in-person projects). NICHD held an exciting in-person intramural scientific retreat on September 26, 2023. The 2024 retreat is planned for later in the month.

The following staff changes were announced over the past year:

- Bizu Gelaye, Ph.D., M.P.H., was recruited to become a senior investigator and chief of the DiPHR's Epidemiology Branch (effective September 8, 2024).
- Vivek Mahadevan, Ph.D., became the functional director of NICHD's intramural Molecular Genomic Core on April 7, 2024.
- Leonid Margolis, Ph.D., senior investigator in the Section on Intercellular Interactions, retired on September 30, 2023.
- Melvin DePamphilis, Ph.D., senior investigator in the Section on Eukaryotic DNA Regulation, retired on January 7, 2024.
- Alan DeCherney, M.D., senior investigator and deputy director of the Reproductive Endocrinology and Infertility Fellowship Program, retired on July 31, 2024.
- Karel Pacak, M.D., Ph.D., D.Sc., a senior investigator in the Section on Medical Neuroendocrinology, will retire in September 2024.
- Andres Buonanno, Ph.D., a senior investigator in the Section on Molecular Neurobiology, will retire on September 30, 2024.

DIR is currently recruiting for the following positions:

- Tenure-track investigator in neural development
- Tenure-track investigator in the Social and Behavioral Sciences Branch
- Pediatric endocrinologist staff clinician

Stadtman Investigator. This annual NIH-wide search is open each August and September to all doctoral-level biomedical and behavioral researchers interested in NIH intramural tenure-track positions. Researchers who are interested in studying important problems in innovative ways can learn more at https://irp.nih.gov (under the Careers/Trans-NIH Scientific Recruitments tab).

The Lasker Clinical Research Scholar program, which provides a unique bridge for early-stage clinical investigators, is currently accepting applications. Individuals who are interested in this program can learn more at https://irp.nih.gov/careers/trans-nih-scientific-recruitments/lasker-clinical-research-scholars.

The following investigators and programs received honors and awards over the past year:

- Edwina Yeung, Ph.D., has been elected president of the Society for Pediatric and Perinatal Epidemiologic Research for the 2024–2025 term.
- Gisela "Gigi" Storz, Ph.D., an NIH Distinguished Investigator at NICHD, has been elected as a fellow of the American Association for the Advancement of Science.
- Jack Yanovski, M.D., Ph.D., who conducts research on pediatric obesity, was featured on CNN's *Chasing Life* podcast, which is hosted by Dr. Sanjay Gupta.
- Doreen Matthies, Ph.D., an Earl Stadtman tenure-track investigator and the head of the Unit on Structural Biology in the Division of Basic and Translational Biophysics, will receive an award from the Biophysical Society.
- DIR now has 27 laboratories participating in NIH's Green Labs Program (GLP)—up from six in 2022—with an aim to increase the awareness and participation of laboratory personnel in sustainable laboratory practices and a goal of protecting the environment and human health. Practices include conserving energy and water, reducing waste and recycling, and collaborating with other NIH researchers to develop and share innovations. GLP was recently nominated for the 2024 International Institute for Sustainable Laboratories Phil Wirdzek Leadership Award in recognition of the efforts made across many NIH ICs to implement innovative strategies, overcome challenges, and increase participation in GLP.

Office of Education Updates (1:18:04)

The NICHD DIR is expanding its education and training efforts. Erin Walsh, Ph.D., the division's former Office of Education director, has been promoted to deputy science director for science management and now oversees all DIR training programs. The new director of the Office of Education is Megan S. Bohn, Ph.D.

Sally Chang, Ph.D., has been named the bioinformatics training program manager. Leading the newly formed Bioinformatics Training Core, Dr. Chang will regularly assess DIR bioinformatics and data science training needs, design short courses and other training content, manage feedback, develop evaluative systems for informing future content, and grow and maintain a community of learners by providing support throughout their NICHD career and beyond.

The Office of Education will continue to develop activities, programs, and professional development opportunities for career advancement, including public speaking, teaching, grantsmanship, publishing, interviewing, and networking. The office's ongoing key activities include:

- An annual postbaccalaureate seminar series on career exploration, professional development, and graduate or medical school application preparation
- Two K99 grant-writing courses and a K99 preparation series (in collaboration with DER)
- Ad hoc industry job consulting sessions and a monthly industry careers webinar series

- An exit survey that was implemented in summer 2022 and continues to actively collect data
- An IDP and annual progress report system for NICHD postbaccalaureate and postdoctoral trainees
- A new science writing skills workshop
- One-day grant-writing workshops
- Academic job application and interview process assistance
- An annual fellows retreat
- Quarterly group postdoctoral orientations
- Preparation assistance for giving three-minute talks

DIR trainees also participate in NIH-wide activities, including the annual postbac poster day.

Trainee recruitment initiatives for 2024 and 2025 have included hiring an outreach and a recruitment training specialist, collaborating with NICHD's OHE for outreach, and enhancing Office of Education web content to showcase resources, facilities, and trainee programming and to feature social media videos made by the fellows and investigators. NICHD is also participating in the Biophysics Fellows Research Conference to be held in May 2025, where 25 predoctoral candidates and postdoctoral biophysics researchers—from the United States and abroad who are not already members of an intramural fellowship program at NIH—will be given the opportunity to explore the rich environment, unique resources, and research opportunities offered by five ICs.

DIR Diversity Initiatives (1:29:52)

DIR's initiatives to recruit, train, support, and sustain a diverse group of talented young scientists, including those from groups traditionally underrepresented in science, remain strong. The following programs are contributing to these efforts:

Developing Talent Scholars Program. Three postbaccalaureate scholars, including one returning scholar, were selected for FY 2024. The alumni group now includes more than 30 scholars, many of whom are currently in professional school, medical school, or doctoral programs.

Summer Internship Program. This program funds 25 positions each year. Five new projects in health equity research were added in 2024.

Fellows Recruitment Incentive Award. One new postdoctoral student was selected for FY 2024, bringing the total to seven funded trainees since 2018.

Summer Research in Health Equity. This new summer student program to promote health equity and health disparities research is a collaborative effort between OHE and the Office of Education. In addition to conducting research, the five students selected for summer 2024 also participated in a 5-week-long seminar series. This program will be expanded to 15 students for 2025.

Virtual Student Summer Opportunities to Advance Research (V-SOAR). V-SOAR began during the COVID-19 pandemic to encourage undergraduate students who cannot join an in-person summer internship to virtually participate in basic and

bioinformatics research. The online curriculum covers research techniques (e.g., sequencing short-form RNA) along with the development of professional skills.

Summer Program Poster Day. A total of 51 intern posters were displayed during the summer program poster days held August 1–2, 2024.

Competitive Funding Opportunities (1:33:45)

DIR has created the following opportunities for trainees to compete for funding:

Intramural Research Fellowships. Postdoctoral and clinical fellows in their second or third year of training write grant applications for a $25,000 award for one year that can be used for equipment, reagents, training, or a stipend. In 2023, a committee of NICHD investigators, postdoctoral grantees, and tenure-track alumni reviewed 13 applications; the review, scoring, and study section procedures mirrored NIH's F series extramural scoring system. The eighth application cycle for 2024 started in June.

Early Career Awards. This internal funding opportunity is aimed at promoting the research careers of early-stage intramural researchers in the basic, clinical, and translational sciences. Now in its fourth cycle, early career awards were launched in FY 2021 as an NICHD OD, Office of the Scientific Director, and Office of Education initiative. The program is modeled after Tufts University School of Medicine's Zucker Grant Program. Individual awards up to $25,000 are given for outstanding, original, 1-year research proposals. Up to $10,000 can be awarded for proposed scientific meeting participation or training that supports scientific or professional development. In FY 2024, NICHD received 57 applications and provided 19 awards for a total of $425,622.

Staff Scientist/Staff Clinician Career Development Awards. This new career training and development award opportunity was launched in 2024. Individual awards up to $20,000 are given for outstanding, original research proposals that support 1-year research projects for current staff scientists or clinicians. Up to $10,000 can also be awarded individually to applications for proposed scientific meeting participation or training that supports scientific or professional development. In 2024, DIR received 23 applications and provided 11 awards for $156,125.

Discussion (1:37:45)

Dr. Lang said that it was a pleasure to hear about DIR's progress over the course of her time on the Council. She asked about the process for reviewing and revising DIR's scientific affinity group structure. Dr. McBain said that the investigators and trainees regularly drop in and out of the affinity groups. Some of the groups were established for historical reasons; others come together for a time and then dissolve. Two of the smaller groups have clinical and translational researchers working together, and might soon reorganize or join together. Group revision is generally at the discretion of the investigators, and it is based on their needs for intellectual interaction.

Dr. Lang asked for clarification on how the intramural and external Offices of Education and Health Equity differ in focus and how they collaborate. Dr. McBain said that the OHE is

in the OD, so it serves both the intramural and extramural divisions and has been quite successful.

Ignatia Barbara Van den Veyver, M.D., asked for additional details on how the graduate partnership program works. Dr. McBain said that instead of pursuing academic credentialing, NIH forms partnerships with academic institutions around the world to share graduate students. The partnerships are usually forged with individual researchers, and the students are subject to the rules and requirements of their institution, because the academic institution is the entity that is awarding the degree. Each academic institution establishes logistical parameters for its own students. Dr. McBain has worked to decrease the complexity of the program, remove impediments, and increase participation. He aims to continue to grow the number of students who participate, because it is such a valuable program for all parties. Dr. Neal-Perry agreed and thanked Dr. McBain for his infectious enthusiasm for this program and all the others that he manages. She said that he is incredibly invested in the next generation.

Dr. Neal-Perry said that she was excited to hear that NICHD is working with ABRCMS. Dr. McBain credited Anirban Banerjee, Ph.D., from the Section on Structural and Chemical Biology for his efforts in encouraging NICHD trainees to attend ABRCMS. It has been a great organization for educating young scientists about the opportunities available at NICHD.

Ethylin Wang Jabs, M.D., asked Dr. McBain to comment on postdoctoral outcomes for the fellows who complete their training at NICHD. She asked whether NICHD trainees were going on to conduct further research in academia or industry. Dr. McBain said that the national and international trends for trainees leaving research were similar at NICHD. He added that a larger problem is that the number of people applying for postdoctoral positions is "dramatically and dangerously" low. The main goal is to not expect every researcher to become a PI; it would be better to change the outcomes expectations. For example, NICHD is now encouraging trainees to consider working in the biotechnology industry. It is increasing salaries for postdoctoral researchers and thinking about how to redefine what is expected from people who take these positions (e.g., no more long hours and low pay). Imagination, inclusivity, supportiveness, and mindfulness are all needed to create meaningful change.

V. Scientific Presentation: Genomics, Models, and Therapeutic Targets of Genetic Skeletal Disorders (1:52:07)

Carlos Ferreira, M.D., staff clinician in the Metabolic Medicine Branch and head of the Skeletal Genomics Unit at NIH's National Human Genome Research Institute (NHGRI), presented his work using genomics and modeling to develop new therapies for patients who have skeletal disorders of a genetic origin.

Background (1:54:11)

The mission of NHGRI's Skeletal Genomics Unit is to conduct natural history studies to uncover the clinical spectrum of selected skeletal dysplasias, identify new gene-disease associations, understand their pathomechanisms via cell and animal models, and develop targeted treatment approaches.

In 2021, NHGRI launched a dedicated natural history study titled "Clinical and Laboratory Study of Rare Skeletal Disorders" (NCT05031507) to collect data on disorders that affect skeletal development and gain more information about their causes and how they progress over time.

Dr. Ferreira's primary interests are (1) disorders that affect skeletal development with an unknown molecular basis and (2) disorders caused by phosphate deficiency related to the fibroblast growth factor 23 (FGF23)–phosphate axis.

Disorders of Skeletal Development of Unknown Cause (1:55: 57)

The 34 known skeletal development disorders with unknown etiology are described in the most recent (2023) nosology classification publication (see "Nosology of genetic skeletal disorders: 2023 revision" by Sheil Unger et al., published in the *American Journal of Medical Genetics, Part A*). The previous nosology classification, published in 2019, did not include the majority of newly documented gene-disease associations. Furthermore, recent studies have shown that as many as 40% of patients in large skeletal study cohorts have no confirmed diagnosis. So there is still much work to be done to gain new insights into skeletal biology and physiology.

Disorders of the FGF23 Phosphate Axis (Biomineralization) (1:57:28)

FGF23, the hormone in the body that regulates phosphate biology, is made by bone cells. The FGF23–phosphate axis, which regulates serum phosphate levels, includes the kidney for phosphate excretion and the intestines for phosphate absorption.

Trevor Disease. Dr. Ferreira recently discovered the genetic cause of Trevor disease, a skeletal disorder that causes overgrowth at the ends of the long bones near joints. The overgrowth restricts the range of motion of the joints, which leads to contractures, deformity, pain, and decreased quality of life. Studying the natural history of Trevor disease revealed a mosaic disorder with mostly unilateral, localized lesions and no familial cases; therefore, the genetic cause of Trevor disease occurs after conception. Histological evaluation revealed overgrowth in both the bone and cartilage of the joint. After performing deep sequencing to identify the somatic variant, quantifying the rare candidate variant, and using immunohistochemistry to detect the mutant protein in patient bone biopsies, Dr. Ferreira's lab confirmed its discovery in a mouse model of Trevor disease. The next step is to develop therapeutic targets.

ENPP1 Enzyme Deficiency. ENPP1 helps regulate skeletal and soft tissue mineralization by generating circulating and extracellular pyrophosphate (PPi) from adenosine triphosphate. PPi is toxic to hydroxyapatite, the mineral that creates 70% of a bone's weight. The presence of PPi, even in small amounts, is a potent inhibitor of bone mineralization, while its deficiency causes pathological arterial calcification.

Generalized Arterial Calcification of Infancy (GACI). GACI is one of the most severe phenotypes of ENPP1 deficiency. It presents with calcification along the internal elastic lamina of the arteries along with intimal proliferation. It has a high overall mortality rate of 40.5% in babies. As many as 4.7% of fetuses with GACI die *in utero* or are stillborn; those that are born have a mortality rate of 36.8% before 6 months (the critical period). Patients who survive the critical period develop FGF23-mediated hypophosphatemic rickets, short stature, and bone pain.

Autosomal recessive hypophosphatemic rickets type 2 (ARHR2). Patients with milder forms of ENPP1 deficiency can develop ARHR2, which is mediated by the presence of excessive levels of FGF23. It is not yet understood how ENPP1 deficiency leads to an excess of FGF23. In a cohort of patients with hypophosphatemic rickets, the average age of onset of hypophosphatemia was 1.6 years. The probability of developing rickets was 20% by age 2 and 50% by age 7, and the vast majority developed rickets by adolescence. Standard rickets treatment (e.g., phosphate supplementation) leads to complications such as kidney calcification.

Pseudoxanthoma elasticum (PXE). PXE is another presentation of ENPP1 deficiency. Patients with PXE have skin changes (e.g., rashes) and retinal bleeding that leads to scarring and blindness.

Enthesopathy. Major morbidity can occur in adults with enthesopathy, which is enthesis calcification of the connective tissues between bones and tendons or ligaments. It can be found in the Achilles tendon, elbow, or even the cervical spine and presents with pain that is not relieved by medication and impaired function.

Therapies for ENPP1 deficiency are in development.

- In a natural history study, bisphosphonates therapy trended toward providing a benefit, but the trend did not reach a level of statistical significance.
- Preclinical studies are investigating the use of enzyme replacement therapy (ERT) for ENPP1 deficiency. Experiments have shown that ERT prevents vascular calcification, mortality, and nephrocalcinosis in ENPP1-deficient mice. ERT has also been shown to increase bone mass, improve skeletal mineralization and bone strength, and partially prevent enthesopathies.
- Clinical trials investigating ERT in adults and children with ENPP1 deficiency are now underway.
- Future directions for research include moving from soluble ERT to gene therapy.

In summary, ENPP1 deficiency is a systemic disease with multiple presentations and phenotypes. The age in which it develops can be related to its severity and presentation.

Discussion (2:19:38)

Dr. Van den Veyver asked whether the mosaic presentation of Trevor disease could be transmitted from a parent to a child. Dr. Ferreira said that mosaic genetic changes happen after conception, so they are not transmitted from parent to child. He added that mosaicism is also the reason that not all joints are affected by Trevor disease. Dr. Van den Veyver clarified that her question was whether a child who developed mosaic disease could then pass on that genetic issue to their child. Dr. Ferreira said that that relationship has not yet been studied for Trevor disease, but there are researchers studying such relationships for other mosaic diseases.

Dr. Neal-Perry asked about the difference between chimerism and mosaicism. Dr. Ferreira said that in mosaicism, different genetic sequences arise from your own cells. In chimerism, different genetic sequences arise from two different individuals (e.g., parent and child or twin to twin *in utero*). Essentially, the origin of the different genetic sequences is what differs.

VI. Voice of the Participant: A Family Living With GACI (2:23:03)

Natalie is an 11-year-old girl with an ENPP1 deficiency that presents as GACI. She and her parents, Anne and Jerry, attended the Council meeting to share their experiences living with a genetic disorder and participating in multiple clinical trials at the NIH Clinical Center. Natalie was only 4 months old when she was first enrolled in an NIH clinical trial. Anne shared that the family lives in northern Texas and have had six children, three of whom developed GACI. Their 20-year-old son, Drew, and 14-year-old twins, Julie and Graham, do not have GACI.

When they had their first son, 23 years ago, the pregnancy went well, and Reed Christopher was born about 4 weeks early. When he was about a week old, Reed was taking a nap when Anne noticed that his breathing was slightly unusual. After calling a clinic and then taking Reed there, Anne and Jerry were quickly referred to the emergency room, then transferred by helicopter to a children's hospital in another city. The treating physicians were puzzled by the unusual calcifications they found in Reed's body but eventually diagnosed him with idiopathic infantile arterial calcification (IIAC) of unknown etiology.

Told that the baby's chance of survival was low, Anne and Jerry felt hopeless. They returned home without any parental support. Five weeks later, the breathing symptoms reoccurred and they went back to the hospital. A week later, Reed passed away in their arms. He was only 7 weeks old but had had multiple heart attacks before he passed away. The autopsy confirmed the diagnosis of IIAC, and the family elected to send some of Reed's

tissues to a researcher in Germany. They wanted to help others learn more about this horrible disease.

During the next few years, Anne had a couple of miscarriages. But in 2004, she became pregnant with their son Drew. During the pregnancy, Anne and Jerry received a letter from researchers who had found the genetic mutation that causes IIAC, now called GACI. Although it was overwhelming to learn this news when Drew was due in just a few weeks, Anne and Jerry both got tested for the gene. After Drew was born, his cord blood was also tested. Anne, Jerry, and Drew did not have GACI, but all three carried the genetic mutation for GACI.

In 2010, after Anne had experienced more miscarriages, twins Graham and Julia were born. The twins were tested for GACI and were also carriers but were not affected. When Graham and Julia were 5 months old, Anne unexpectedly became pregnant again. The 20-week ultrasound looked good, but the 32-week ultrasound revealed a small amount of fluid around the baby's heart. Further ultrasounds confirmed significant arterial calcifications. Anne and Jerry reached out to Frank Rutsch, M.D., a physician in Münster, Germany, to inquire about new treatment options. The medical team suggested delivering the baby at 36 weeks for potential treatment with bisphosphonates. Ian James was born in January 2011 and began treatment with bisphosphonates. At 5 weeks old, scans revealed that the bisphosphonates seemed to be having an effect, but the treating physicians could not obtain good imaging views of his coronary arteries. Two days later, Ian was rushed to the emergency room. Sadly, Ian passed away from cardiac arrest, in March 2012. It was another devastating loss.

After several months of consideration and difficult conversations, Anne and Jerry took a leap of faith and decided to have another child. During the pregnancy, the 20-week ultrasound showed arterial calcifications. Amniocentesis testing confirmed a diagnosis of GACI. Anne and Jerry were devastated—especially because further ultrasounds indicated that the calcifications were rapidly progressing; they wondered whether the baby would survive the pregnancy. They again reached out to Dr. Rutsch about new research or treatment developments. Dr. Rutsch sent an article that had been co-written by a Dr. Levine at Children's Hospital of Philadelphia (CHOP). CHOP treated children with rare genetic disorders, so Anne and Jerry were able to schedule a consultation there.

Michael A. Levine, M.D., FAAP, FACP, MACE, FACE, is a pediatric endocrinologist at CHOP. During their consultation with him, Anne and Jerry were thrilled to meet a doctor who was an expert in GACI and who had treated other children and babies with GACI. They asked Dr. Levine about the possibility of beginning treatment during pregnancy. Although it had not been done before, he prescribed etidronate (a bisphosphonate medication that was used to treat and prevent osteoporosis) for Anne, because it had safely been given to pregnant women with other conditions. Anne moved to Philadelphia at 30 weeks of pregnancy, started taking etidronate, and underwent weekly ultrasounds and doctor appointments while Jerry stayed home with the three children. Amazingly, the arterial calcifications did not continue to spread or worsen.

Natalie Grace was born at 39 weeks. She was admitted to the neonatal intensive care unit (NICU) and started on another new medication that was given 5 days a week via intravenous infusion through a central line. Anne and Jerry cautiously prayed and continued the treatment until Natalie was 13 months old; thankfully, the calcifications did not worsen or progress. They threw a big party for Natalie's first birthday.

Natalie has done well over the past 10 years. When she was 3 years old, she was started on a course of phosphorus and cholecalciferol to help prevent rickets, because physicians detected changes in her bones and knees. She also was fitted for hearing aids when she was 3 years old because of hearing loss.

When asked what it was like to participate in NIH clinical trials, Jerry said that this visit was the family's 11th trip to the NIH Clinical Center. Before the first visit, he said that he "had no idea what the National Institutes of Health was or what an amazingly rich resource it could be for a family like ours." The journey to NIH began with Dr. Levine at CHOP. During the family's last appointment before leaving CHOP with Natalie in 2013, Dr. Levine told Anne and Jerry that they might be getting a call from someone at NIH. That call came the same year, in August 2013, when William A. Gahl, M.D., Ph.D., a senior investigator in NHGRI's Medical Genetics Branch, called to introduce himself. It was a great conversation that meant a lot to Jerry.

Jerry said that it was hard to express how it felt as a parent to lose two children to GACI, and to have a third child with it as well. The 12-year journey he and Anne undertook to have a family felt like climbing an insurmountable hill. Until they met Dr. Levine, none of their physicians had even heard of their genetic disorder. In fact, when Reed was diagnosed with AAIC in 2001, they were told that only 100 cases of AAIC had ever been recorded anywhere.

Jerry said that receiving the call from Dr. Gahl and being invited to NIH to participate in research did not require a second thought: "Absolutely," he said. "What can we do immediately?" He said they did not know at that time how amazing everyone at NIH would be in terms of their hearts, their interests, and their expertise. After years of feeling alone in the medical community, Jerry said, it felt mindblowing to find a place like NIH where everyone they met was interested in their family's ultrarare disorder. Jerry said that participating in clinical trials at NIH has been an absolute privilege, and having NIH on their side, fighting for them and learning about this genetic disorder, put the wind in their sails for the first time in 12 years. He said that it was hard to put such admiration, respect, and appreciation into words.

Natalie was 4 months old on the family's first visit and stay at The Children's Inn at NIH. After he arrived the first time—graciously welcomed by Dr. Gahl, Dr. Ferreira, and the entire team of doctors (who continued to collaborate with Dr. Levine and Natalie's other doctors)—Jerry asked Dr. Gahl why a research organization would be interested in studying an ultrarare disorder when it might not be profitable to do so. Dr. Gahl replied that studying rare disorders provides clues for understanding more common disorders.

Anne said that they were grateful to learn more about GACI at NIH. The family was "all in" despite having to provide skin biopsies and endure needle sticks for bloodwork.

Speaking for herself, Natalie shared that she is now 11 years old and just started fifth grade. She said that having GACI is hard, because she has to take care of a lot of things, such as her hearing aids, medicines, and doctor appointments. She thanked the Council members for helping her and for doing research on GACI.

When asked about what had changed most over the course of their 23-year journey with GACI, Anne said that in 2018, she and Jerry joined together with three other families (from the United States, Ireland, and Australia) to start a nonprofit patient advocacy organization called GACI Global. This group provides support and resources for families through its website and an active Facebook group. Last year, GACI Global hosted two conferences: one in Manchester, England, and the other in Baltimore, Maryland. For many families, these conferences were the first time they had ever met another family living with GACI, heard others' stories, built community, and learned directly from medical experts in the field. The conferences were also special because they allowed the kids to get together, meet each other, and play—to have fun and connect in a special way. Natalie met many new friends in the United States and other nations at these conferences.

Jerry said that NIH and Dr. Ferreira have been incredibly helpful in building the worldwide GACI community by connecting GACI families that come to NIH from around the world. Jerry and Anne congratulated Dr. Ferreira for his work on GACI and shared that they had never met a medical professional with a heart for his patients like that of Dr. Ferreira. They added that Dr. Ferreira works so diligently to connect medical researchers with doctors and doctors with patients that he is saving lives all over the world. The GACI Global community recently awarded Dr. Ferreira with its Hope Award, which is given to individuals who continuously give hope to the GACI community.

Discussion (2:47:00)

Dr. Bianchi asked Natalie if there were any restrictions on her activities and whether she could do everything at school that everyone else can do. Natalie indicated that she does not have any restrictions on her activities.

Dr. Bianchi then asked Natalie to share something about her experiences at The Children's Inn. Natalie said that she liked The Children's Inn a lot, especially playing with the children there and seeing little kids playing outside. Anne added that Natalie was so young during their visits that she does not remember a lot about The Children's Inn, but in the past year, she had asked about the place they stayed when they went to Washington, D.C., and said that she remembered it. Anne added that even years later, children remember the good things but not the needle pokes or blood draws. They remember The Children's Inn, and Natalie was excited to stay there on this visit.

Dr. Barkin asked Natalie and then her parents: "What does research mean to you?" Natalie said that research is finding out more about what other kids have and seeing what doctors

can see about you and what GACI does to you. Jerry said that his early understanding of research was that it was something that was done in a faraway place behind closed doors by smart people in white coats. After participating in research at NIH with Natalie and being treated like rock stars, he said, research now feels much more personal. He said that research is conducted by real people working very hard to understand the human body and what can be out of alignment to cause a particular disorder. Research at NIH also involves wonderful human interactions and human connection with all members of the staff. It is quite personal. Anne added that in the past 23 years, GACI research has gone from nonexistent to clinical trials. All that has happened or is now happening is amazing. Jerry said that if NIH were not involved in research, there would be no clinical trials and there would be no connection between GACI families all over the world. NIH has been at the center of all of this progress.

Dr. Bianchi said that this meeting was being broadcast online, so that NICHD staff and others could see this incredibly inspiring and motivating story. She read the following statement from an NICHD branch chief who was watching online: "Thank you so much for sharing Natalie and her parents. It is incredibly motivating to all of us who work here."

Dr. Bianchi said that hearing the science from Dr. Ferreira was important, but seeing Natalie, hearing this story, and feeling the family's losses made an indelible impression. Families that participate in research motivate NIH staff to get out of bed every day and solve medical mysteries—and the reason that the NIH Clinical Center is called "the House of Hope." Scientists know the gene variant that caused the heartbreak in this story because of the work that was done to sequence the human genome, and that work was largely conducted at NIH. Going from genome sequencing to understanding how a variant affects the human body and metabolism to treatment has occurred in such a short time, but it could not be done without families willing to sacrifice their time or without participants like Natalie.

Dr. Bianchi thanked Natalie, Anne, and Jerry on behalf of NICHD—"from the bottom of our hearts."

VII. Center for Scientific Review (CSR) Initiative to Strengthen Peer Review (2:55:05)

CSR Director Noni Byrnes, Ph.D., described upcoming changes in the first-level peer review of NIH Research Project Grants (RPGs) and Individual Fellowship (F) Awards. Dr. Byrnes leads a staff of about 600 scientific, support, and contract personnel and is responsible for overseeing NIH's peer review process.

Background (2:56:25)

CSR's mission is to ensure that NIH grant applications receive fair, independent, expert, and timely scientific reviews—free from inappropriate influences—so that NIH can fund the most promising research.

In FY 2024, CSR reviewed 67,039 (77%) of all grant applications submitted to NIH, including 35,739 (95%) R01 applications; 7,757 (95%) Small Business Innovation Research and Small Business Technology Transfer applications; and 5,525 (85%) fellowship applications. CSR also reviewed applications for 164 special initiatives (e.g., IMPROVE, Common Fund, trans-NIH programs). These reviews are completed with the assistance of about 19,000 reviewers and 255 scientific review officers (SROs) at roughly 1,200 review meetings each year.

CSR's strategic framework is centered on the quality of peer review. Its three domains are study sections, process, and reviewers. CSR staff members are central to driving its mission. The Center's core operating principles are transparency, data-driven decisions, stakeholder engagement, and staff training and development.

In terms of capacity building for the future of NIH peer review, CSR has taken several steps in recent years to establish a strong foundation in communications, training, and data analytics. For example, in 2020, CSR created an Office of Communications and Outreach to foster engagement, transparency, and easier access to review information for the scientific community. This office has been particularly focused on initiating targeted outreach to institutions and communities that have traditionally had less engagement with NIH. Then, in 2021, CSR's Division of Planning, Analysis, and Information Management was formed as a centralized data operation to provide analytics and tools to support data-driven decision making. Finally, in 2022, CSR launched its Office of Training and Development to centralize multimedia training resources for study section chairs, reviewers, and SROs. The addition of these resources has allowed CSR to continually develop and implement initiatives that promote fairness, integrity, and quality in the NIH peer review process.

Dr. Byrne asked Council members to share the following recent changes in NIH peer review with their networks:

- The pool of reviewers is being broadened in multiple dimensions of diversity (e.g., scientific, geographic, ethnic, racial, gender) to ensure fresh perspectives and reduce undue influence or scientific gatekeeping.
- All NIH reviewers must now attend mandatory trainings on bias awareness and mitigation as well as review integrity before participating in study sections.
- An avenue has been created for anyone to report concerns about the fairness of the NIH review process (email reportbias@csr.nih.gov). Every report is investigated, and the review is redone in the same cycle if bias has been introduced.
- A simplified review framework (SRF) is being implemented on January 25, 2025, for most NIH RPGs.
- The review criteria and application for F awards has been revised and will become effective on January 25, 2025.

The New SRF for Peer Review (3:04:00)

There are two main goals for simplifying the review framework. The first is to refocus first-level peer review on its singular role of providing advice to the agency on the scientific and

technical merit of grant applications. SRF reframes the review criteria to focus reviewer attention on three key questions related to merit and removes distractions of certain administrative compliance items. The second goal is to mitigate reputational bias (e.g., institutional reputation, investigator pedigree) in the peer review process. SRF refocuses evaluation of investigator and environment to be within the context of the proposed project and facilitates the overarching goal of peer review, which is the identification of the strongest, potentially highest-impact research.

Grant applications submitted before January 25, 2025, receive an overall impact score based on five criteria:

- Significance (scored 1–9)
- Investigator(s) (scored 1–9)
- Innovation (scored 1–9)
- Approach (scored 1–9)
- Environment (scored 1–9)

Grant applications submitted on or after January 25, 2025, will be given an overall impact score based on three factors:

- Factor 1: Importance of the research (should it be done?) (scored 1–9)
- Factor 2: Rigor and feasibility (can it be done well?) (scored 1–9)
- Factor 3: Expertise and resources (are the expertise and resources in place to do it?)
    - Evaluated as "appropriate" or "additional expertise/resources needed;" if additional needs are identified, comments are required
    - Gaps in expertise and/or resources should affect overall impact score

These RPG review changes are based on extensive input from the scientific community. The following timeline outlines the high-level steps in this process:

- January 2020 to April 2021: CSR Advisory Council WGs met to gather input and develop a new framework.
- July 2021 to September 2022: CSR gathered input from NIH leadership.
- December 2022 to March 2023: NIH posted a public RFI to gather public feedback on the proposed SRF.
- October 2023: NIH announced the launch of the SRF via NOT-OD-24-010.
- January 25, 2025: The SRF will go into effect.

Revised Review Criteria for F Awards (3:11:21)

The goal of NIH F Awards is to optimize the identification and training of the most promising scientists of the next generation.

The scientific community raised concerns that NIH is potentially leaving out very promising research scientists of the future because the review process for the *Ruth L. Kirschstein* National Research Service Awards, or "F awards," favors elite institutions and

senior, well-known sponsors. A CSR WG of council analyzed the data from more than 6,000 applications, and the results supported the concerns. The findings revealed that a small number of institutions submit a majority of the F applications, that applications from institutions that submit more Fs have better review outcomes, and that review outcomes for Fs improve as the rank of the sponsor increases.

Using a process similar to what was used to develop the SRF (i.e., a process of extensive community input and engagement), F application review also changed from five criteria to three.

F applications submitted before January 25, 2025, are given an overall impact score based on five criteria:

- Fellowship candidate
- Sponsors, collaborators, consultants
- Research training plan
- Training potential
- Institutional environment and commitment to training

F applications submitted on or after January 25, 2025, will be given an overall impact score based on three criteria:

- Candidate preparedness and potential (this criterion includes a wide range of indicators of scientific potential and preparedness)
- Research training plan
- Commitment to candidate (evaluations of the sponsor and environment will now be framed in terms of their contributions to the applicant's scientific training; the sponsor's extramural funding is not to be considered by peer reviewers)

Importantly, F applications are being revised to align with the new criteria, which places more emphasis on the quality of the training plan. Grades are not required or allowed, because they have been determined to be poor indicators of research potential. The applications will be shorter, more structured, and targeted to reduce the boilerplate language that has been used to mass produce F applications.

Implementing RPG and F Changes (3:17:31)

There is a lot of ongoing groundwork at CSR to implement these changes to the RPG and F review programs. Trans-NIH implementation committees with deep, multidimensional domain expertise in peer review, communications, policy, eRA systems, reviewer training, and staff training have been assembled to implement the changes. The major launch of reviewer and study section chair training will not occur until spring 2025.

NIH has published "one-stop shop" websites to learn more about the new RPG and F review processes. Interested parties can register for public webinars, view recorded webinars, access resources, read FAQs, and more. The following websites are now live:

- RPGs: https://grants.nih.gov/policy/peer/simplifying-review.htm
    - Questions can be sent via email to SimplifiedReview@nih.gov
- Fs: https://grants.nih.gov/policy/peer/revisions-nih-fellowship-application-review-process.htm
    - Questions can be sent via email to FellowshipReview@mail.nih.gov
    - Registration is now open for a webinar on September 19, 2024

To learn more about other CSR initiatives and priorities, visit CSR's website at https://public.csr.nih.gov/. The following topics (and more) are available:

- CSR's 2022–2027 Strategic Plan
- Data, full reports, and analyses behind the upcoming changes in the review of RPGs and Fs
- Actions to address bias in peer review
- CSR's Early Career Reviewer Program
- In-person versus Zoom meeting evaluation
- Reviewer demographics
- CSR Advisory Council and Council WG reports

Discussion (3:20:00)

Dr. Cedars asked whether the review panels would now meet remotely or in person, noting that remote panels could be a disservice to the candidates. Dr. Byrne said that the CSR website has several reports that analyze reviewer experience along with objective analyses of score distributions, diversity on Zoom calls versus in person, and more. CSR did not find a difference in outcomes, but most reviewers have a preference. To get the broadest range of reviewers with the right expertise, there will be one in-person study section meeting per year. Eventually, there will likely be three hybrid meetings each year, so CSR is working to develop hybrid technology and continuing to do more analyses.

Dr. Barkin asked which metrics would be used to determine whether SRF was successful. Dr. Byrne said that CSR will continue to analyze the data on its current initiatives to broaden the panels and incorporate many changes in peer review. One measured outcome will be to determine whether funded applications represent a broader range of investigators and institutions. However, because NIH and several ICs have initiatives to promote applications from a broad range of institutions, it may be difficult to tell whether the results are a direct result of the peer review changes. CSR's data operation will also measure outcomes by surveying reviewers, study section chairs, and applicants. Measuring the impact of the changes will take time.

Dr. Barkin said that she has been fortunate to serve on study sections and to also submit grant applications. She said that reliability can depend on the study section (e.g., you can respond to reviewer comments then receive a different answer for the revisions). She asked whether the new SRF would create more reliability. Dr. Byrne said that two problems with amended applications are (1) that the same peers do not attend every meeting and (2) that the study section changes. From the agency perspective, however,

different reviewers can also be a plus of peer review, because the goal is to identify the strongest science and give a score that makes sense within the group of applications in that review section. The data show that when the same reviewers score a revised application, the score is better than if only one previous reviewer provides a score. She added that review is not necessarily supposed to have inter-rater reliability, but if any unfairness exists in the process, CSR wants to know about it through the "report bias" email address mentioned in the presentation. Dr. Barkin said that it may not be an issue of unfairness but rather of consistency. Dr. Byrne said that submitting revised applications can sometimes create false expectations for applicants.

Dr. Gyamfi-Bannerman asked whether the changes to the F applications would also apply to Research Career Development Award (K) applications. Dr. Byrne said that CSR does not provide review for many Ks, because they are done internally. She said that CSR's website has answers to K award questions in its FAQ section.

VIII. NICHD Strategic Plan Refresh: Research Objectives and RFI (3:28:43)

G. Stéphane Philogène, Ph.D., director of NICHD's Office of Science Policy, Reporting, and Analysis (OSPRA), provided a progress update on the institute's 2025 Strategic Plan. NICHD's last 5-year Strategic Plan was published in 2020; OSPRA is leading the effort to update the plan for 2025.

Background (3:30:37)

The three sections of the 2020 Strategic Plan were **scientific research, scientific stewardship,** and **management and accountability.** The goals that communicate NICHD's priorities within each of these sections are now being updated for the 2025 Strategic Plan, which is expected to be released in the spring. Under scientific research (the first section), the goals and themes in the 2020 Strategic Plan included five points:

- Understanding the Molecular, Cellular, and Structural Basis of Development
- Promoting Gynecologic, Andrologic, and Reproductive Health
- Setting the Foundation for Healthy Pregnancies and Lifelong Wellness
- Improving Child and Adolescent Health and the Transition to Adulthood
- Advancing Safe and Effective Therapeutics and Devices for Pregnant and Lactating Women, Children, and People with Disabilities

The cross-cutting scientific research themes that were interwoven with the above goals in 2020 included global health, health disparities, infectious diseases, nutrition, and prevention.

The 2025 Strategic Plan will maintain the same overall structure as the 2020 plan. The structure of the plan uses the following hierarchy:

Focus Area → Goal → Objective → Initiative → Activity

The objective level is underlined because it is currently the primary focus of the OSPRA Strategic Plan refresh team. More specifically, the team is now working to update the objectives in the scientific research section.

The process for updating the scientific research objectives (and all objectives) is based on the core or guiding principles of transparency, stakeholder participation, and decisions informed by evidence. The goals of the process are to identify priorities, identify partnerships and collaborations, and inform future investments in research, training, and infrastructure.

- For transparency, the Strategic Plan is being led by NICHD staff, including branch chiefs, intramural and extramural leaders, and office directors, who are organized into WGs to generate ideas for each section of the plan.
- To help the WGs make decisions informed by evidence and to inform progress on key goals and objectives across the agency, the NIH Office of Evaluation, Performance, and Reporting created the Strategic Tracking and Reporting Tool (START). START provided each Strategic Plan WG with data on the timelines of major programs or FOAs that support the implementation plan, funding trends on research initiatives and activities, and information on cross-cutting theme representation in the goal (including well-represented areas and areas of opportunity).
- Stakeholder input has been gathered through five external listening sessions that provided targeted feedback on draft objectives. Input is also being requested at this Council meeting and through the publication of an RFI.

For Review: Draft Scientific Research Objectives (3:36:44)

The following cross-cutting themes, goals, and objectives have been proposed for the scientific research section of the 2025 Strategic Plan:

Cross-Cutting Themes

- **Global Health:** Improve pre-pregnancy health globally using new interventions to benefit pregnancy outcomes; prevent prematurity, malnutrition, childhood stunting, disease, and developmental delays.
- **Health Disparities:** Understand how social, economic, structural, and regional factors are vital to the advancement of preventive, diagnostic, and intervention efforts.
- **Prevention:** Prevent adverse health outcomes, improve early detection, and understand the optimal timing of prevention efforts.
- **Nutrition:** Improve our understanding of the lifetime impact of nutrition on reproductive health, fertility, pregnancy, and fetal, child, and adolescent growth and development.
- **Infectious Disease:** Improve the basic understanding of how infectious pathogens affect NICHD populations, address their impact on overall health, and advance safe and effective treatments.

- **Research Training:** Train and develop the next generation of the scientific workforce.

Goal 1: Understanding the Molecular, Cellular, and Structural Basis of Development

A. Improve understanding of the mechanisms underlying developmental processes by elucidating the **intrinsic** factors (e.g., genetic, epigenetic, molecular, cellular, metabolic, biomechanical) that contribute to pre- and postnatal development.

B. Explore how **extrinsic** factors (e.g., prenatal and perinatal insults, metabolic and nutritional deficiencies, environmental factors, infection, early injury and disturbances) influence developmental and physiological processes—particularly in the context of addressing congenital anomalies, neurodevelopmental disorders, and intellectual and developmental disabilities.

C. Enhance collaborative developmental biology research by investing in **improved infrastructure**, along with **tools and technologies**, to analyze and validate large-scale data derived from model systems research and emerging scientific areas.

D. Use **single-cell genomics, proteomics, and metabolomics** to profile gene and protein expression and regulation and to characterize regulatory networks across tissues and time during development.

Goal 2: Promoting Gynecologic, Andrologic, and Reproductive Health

A. Improve **understanding of reproductive stages across the life cycle,** with particular emphasis on typical and atypical initiation, timing, and symptomatology of critical windows such as puberty, andropause, and perimenopause.

B. Characterize reproductive aging and **its impact on reproductive, andrologic, and gynecologic outcomes,** particularly infertility and the health of children born to older parents.

C. Identify biologic and environmental factors that can lead or contribute to **idiopathic infertility.** Apply this knowledge to expand technologies or methods for fertility stimulation, fertility preservation, and contraception.

D. Identify biologic mechanisms underlying how gynecologic conditions, including endometriosis, fibroids, and vulvodynia, result in **generalized and pelvic pain.**

E. Identify interventions for **treatment of gynecologic conditions,** such as endometriosis, fibroids, pelvic floor disorders, gynecologic pain, and polycystic

ovary syndrome. Assess the impact of new and existing treatment approaches on gynecologic health disparities.

F. Improve understanding of the **multilevel factors affecting contraceptive use** and non-use and preferences for specific methods. Apply this knowledge in developing new and improved contraceptive options for both men and women and designing interventions to improve access to and use of preferred methods. Advance knowledge about the **effects of contraceptives on human health,** including their effectiveness as treatments for health conditions.

Goal 3: Setting the Foundation for Healthy Pregnancies and Lifelong Wellness

A. Capitalize on **interdisciplinary collaborations** to advance knowledge of the mechanisms and potential causes of **preterm birth** and to develop prevention approaches.

B. Improve the long-term outcomes of infants born preterm or with aberrant fetal growth by understanding the **roles of maternal and paternal factors, social determinants of health (SDOH), environmental and nutritional factors,** and early interventions.

C. Integrate and analyze **diverse types of data** (such as genomic, social and behavioral, and/or exposure data) to inform interventions for adverse maternal conditions and complications of pregnancy. Support **community-informed research** to develop maternal health interventions that are widely applicable, with an emphasis on populations experiencing health disparities.

D. Use innovative **basic and translational science** approaches to further **understand the placenta,** including its role in pregnancy outcomes and in the long-term health of the mother and infant. Continue to develop technologies and methods for **human placental models** across gestation and test the ability of emerging technologies to assess placental health.

E. Develop prevention strategies for **labor and delivery complications** that contribute to maternal morbidity and mortality.

F. With an emphasis on populations that experience health disparities, identify new approaches to **mitigate maternal and paternal risk factors for conditions associated with pregnancy** with effects that extend through the postpartum period and beyond.

Goal 4: Improving Child and Adolescent Health and the Transition to Adulthood

A. Identify and assess **risk-reduction strategies** to address the systemic, as well as individual, causes of infant mortality domestically and globally. Identify potential approaches to **prevent stillbirth, SIDS, and SUID.**

B. Determine how **social and environmental factors** affect infant, child, and adolescent health and use this knowledge to develop new (and improve the effectiveness of) early intervention approaches.

C. Develop and assess prevention, treatment, and implementation strategies to address **trauma, injury (unintentional and intentional), and violence, along with disaster preparedness and response.** Advance research and research training across the continuum of care to optimize recovery of children and families who experience critical illness or traumatic injury.

D. Increase understanding of physical, cognitive, social, and emotional development across the **early lifespan** (infancy through adolescence) to **optimize timing of interventions** for healthy development.

E. Conduct research to support better **integration of pediatric and adult systems of care, especially for youth transitioning to adult health care.** Develop measures that help determine successful transition, at the individual, provider, or system level, to improve care for adolescents and emerging adults.

F. Enhance the evidence base for pediatric and adolescent primary care by **identifying practices and features of health care delivery associated with positive child health outcomes.** Support dissemination and implementation research for pediatric prevention strategies with demonstrated efficacy, including in health disparity populations.

Goal 5: Advancing Safe and Effective Therapeutics and Devices for Pregnant and Lactating People, Children, and People With Disabilities

A. Conduct and support foundational research on the development of interventions targeted to the specific needs of pregnant or lactating people, children, and/or people with disabilities informed by **pharmacokinetic, pharmacodynamic, pharmacogenomic, dosing, and formulation studies.**

B. Identify and validate **biomarkers,** modeling approaches, and outcome measures that can be used to support rigorous testing and/or regulatory approval of

pharmacotherapies and devices in pregnant and lactating people, children, and/or people with disabilities.

C. Support **clinical research and its dissemination and implementation** to evaluate scalable, accessible therapeutics, diagnostics and medical devices for pregnant and lactating people, children, and/or people with disabilities.

D. Use advanced data science techniques to **assess health outcomes, therapeutic safety or effectiveness, health care engagement, and health care delivery** in datasets that include pregnant and lactating people, children, and/or people with disabilities.

RFI Comment Period (3:46:20)

On August 28, 2024, NICHD published an RFI, NOT-HD-24-028, to solicit feedback on the scientific goals and opportunities under consideration for the refreshed NICHD strategic plan. Responses are being accepted through September 27, 2024.

Dr. Philogène asked Council members to provide their feedback on the scientific research priorities listed in the RFI, either now at this meeting or by responding to the RFI.

Discussion (3:47:30)

Dr. Rowitch said that one gap in the draft plan would be in the realm of child, adolescent, and teenage mental health. The rising rates of mental health problems can affect real-world outcomes, such as school attendance, and lead to more serious health crises (e.g., eating disorders, adolescent suicide). He suggested including mental health as another objective in the Strategic Plan. Dr. Bianchi said that one of the goals of the Strategic Plan development process was to identify potential partnerships. In the past, NICHD has partnered with the National Institute of Mental Health (NIMH). Although NIMH is currently undergoing a search for a new director, studying adolescent suicide could be an opportunity for collaboration.

Dr. Van den Veyver said that the objective that includes disaster response and preparedness made her think about the importance of understanding the effect of climate on health. She asked whether climate change as a health factor would be linked with disaster preparedness. Dr. Bianchi said that there is an NIH-wide initiative on climate change and health, with representation from NICHD, including Dr. Bianchi on the executive committee and two program officials on the steering committee. NICHD's populations and science are being included in that initiative.

Dr. Gyamfi-Bannerman asked whether maternal mortality could be more heavily emphasized in the Strategic Plan. She noted that the draft implies that maternal mortality and morbidity are related to labor and delivery events, but most are not; rather, they are usually cardiovascular complications. Dr. Philogène said that maternal morbidity and

mortality is called out in the objectives, but it can also be further emphasized in the implementation phase of the Strategic Plan process.

Dr. Barkin asked whether the cross-cutting themes should include the judicious use of artificial intelligence (AI), because the technology is currently exploding and may be part of the toolkit 5 years from now. Dr. Philogène said that he spoke with the director of the NICHD Office of Data Science and Sharing (ODSS), and she intends to include AI as part of the stewardship section of the Strategic Plan. ODSS plans to include aspects of AI that apply to the work of NICHD in the plan. Dr. Contreras-Vidal later agreed with the idea to include the responsible use of AI in the Strategic Plan.

Dr. Barkin recommended adding exposomics to the goal to understand molecular, cellular, and structural basis of development, because environmental exposures are driving a lot of diseases and conditions.

Because endometriosis has been understudied, Dr. Barkin recommended specifying it in Goal 2. Dr. Philogène noted the recommendation and said that endometriosis may be included in the section of the plan on aspirational goals (which has not yet been discussed).

Christina M. Bucci-Rechtweg, M.D., congratulated NICHD staff on the draft plan as an important move in the right direction. Regarding Goal 5, she suggested more broadly socializing the role of modeling, quantitative methodologies, and leveraging data for creating smarter, smaller, pragmatic trials that generate pharmacokinetic and pharmacodynamic data. Dr. Bucci-Rechtweg said that these studies can be more efficient than definitive clinical trials when developing therapeutics for use in different phases of pregnancy, but many researchers are unaware of the power of these types of inquiries in the clinical spectrum.

Anna Aizer, Ph.D., M.S., said that NICHD will need to prioritize the goals (and subsequent funding) in the Strategic Plan.

Dr. Aizer said that she supports the inclusion of economic and SDOH in the draft plan, adding that it is important for NIH to promote research that links maternal and child health with future economic and social outcomes. Dr. Aizer said that health is an incredibly important predictor of economic growth, which is something that all policymakers care about. Therefore, NIH should promote research that clarifies the link between good health and economic growth: It provides evidence for why it is important for the nation to invest in the health of mothers and children.

Dr. Aizer suggested clarifying whether the inclusion of data science techniques in the plan also included developing new, large datasets that could be used for machine learning (ML).

Beyond the development of new therapeutics, Dr. Aizer suggested emphasizing the use of known (and effective) therapeutics for mothers and children. She said that many families—especially disadvantaged ones—do not have access to basic care, so extending the availability of effective treatments could improve overall child health and well-being.

Dr. Neal-Perry said that the presentation was very comprehensive and quite thoughtful. She suggested adding the effects of SDOH on future fertility.

Dr. Neal-Perry said that urogynecology, and particularly pelvic health, was an important and understudied part of women's health and quality of life (e.g., dysfunction, loss of wages, mobility). She recommended broadening the pelvic pain section, beyond endometriosis and uterine fibroids, to include vulvodynia. Dr. Philogène said that this was great feedback for the team. He said that the implementation plan could specify what NICHD could do to achieve the objectives. Candace Tingen, Ph.D., chief of NICHD's Gynecologic Health and Disease Branch (GHDB), said that this is the first time that pelvic floor health has been prioritized for the Strategic Plan, so pelvic floor disorders and the work of the Pelvic Floor Disorders Network will now be included in the 2025 Strategic Plan.

When an attendee asked whether outcome measures would be collected for the goals and the subcomponents under each goal, Dr. Philogène said that the team would establish metrics for all activities at the activities level. These data are collected by the START system; they were used by the WG members over the past year, and will also be used in the new plan going forward.

Given what has been done in the older population with regard to lifelong learning, Dr. Contreras-Vidal suggested specifically including the arts in pediatrics to promote brain health and to help understand development through a different lens.

Dr. Jabs suggested including gene therapy, or therapy for genetic disorders, in the Strategic Plan as an important area of therapeutics that is poised to grow over the next 5 years. She added that NIH's intramural program could play a partnership role with its resources to study ultrarare diseases.

Dr. Jabs said that she agreed with including health disparities as a cross-cutting theme. She also suggested including the association between health care delivery and health outcomes, as well as trying to develop community outreach.

Dr. Philogène reminded Council members to continue to share feedback by responding to the RFI, which will remain open until September 27, 2024.

IX. Comments From Retiring Members (4:09:43)

The retiring members all expressed gratitude to their fellow Council members, Dr. Bianchi, and NICHD staff.

Dr. Barkin (4:10:21)

Dr. Barkin said that being on the Council has been a moment in life when she was in the right place with the right people at the right time. She called her cohort a special group of people who emerged from the COVID-19 pandemic together. Dr. Barkin learned that participation in providing second-level grant review is a systematic, thoughtful, thorough, and inspiring process. The Council also gave Dr. Barkin the opportunity to learn about the

latest and greatest science (including in many new areas), contribute to NIH's large impact, and become part of an incredible community. Dr. Barkin announced that she had just that day accepted a position to become chief and chair of pediatrics at Children's Healthcare of Atlanta—a position she learned about through Lucky Jain, M.D., a previous member of the Council.

Dr. Bucci-Rechtweg (4:14:28)

As a private-sector member of the Council, Dr. Bucci-Rechtweg said that her experience was important, because research and education companies cannot do what they do without the foundational scientific work of NIH, the clinical investigators who are well trained to perform trials in therapeutic development, and the highly skilled researchers who become employed in industry after completing training at NIH. She has been inspired by the work of NIH investigators and what they accomplish with a limited amount of funding. She quoted Natalie's father, Jerry: "NIH is an amazingly rich resource." The networks that are developed through NIH are incredibly valuable to Dr. Bucci-Rechtweg and her colleagues around the world. She will continue to work to increase funding and investment in NIH and NICHD. In a later comment, Dr. Bucci-Rechtweg expressed kudos and gratitude to NICHD's ethics and compliance team for working diligently to ensure her participation on the Council as an industry representative.

Dr. Lang (4:19:00)

Coming from the medical rehabilitation community, Dr. Lang said that serving on the Council has been valuable for learning how NCMRR fits into NICHD and about the organizations' shared values and shared scientific approaches. Dr. Lang has felt valued by NICHD leadership, and Council input "is not just for show." Dr. Lang said that she has gained new friends and better perspectives about life and science from being on the Council.

Dr. Neal-Perry (4:20:19)

Dr. Neal-Perry said that serving on the Council has truly been an honor and an uplifting experience. She said that she is reminded of the movie *The Wizard of Oz*, wherein visitors travel down a yellow brick road, meet Dr. Bianchi (the wizard), and learn about everything behind the curtain. Dr. Neal-Perry said that Council members learn amazing things about all the research at NIH and really do make a difference. "The work that we do matters," she said, and added that she felt valued and heard while serving on the Council. She expressed disappointment that the COVID-19 pandemic kept her cohort from meeting in person for several meetings, but said that she gained a lot from the relationships she developed, adding that she will always be a fan of the review process, and that she will continue to tell others that it is quite fair. In a later additional comment, Dr. Neal-Perry said that part of the culture at NICHD is that all staff have "infectious enthusiasm" for their work, which makes her think it must be a prerequisite to hiring.

Dr. Rowitch (4:23:12)

Dr. Rowitch said that he would echo the comments of the other Council members, particularly in that he values the interactions he has had with them and looks forward to continuing friendships. He added that Council meetings are fun to attend because they are well organized, have interesting scientific presentations, and include the voice of the participant, which drives home the message of NICHD. Dr. Rowitch said that he leaves Council meetings feeling energized, and that the concept clearance and strategic planning parts of each meeting show a thoughtful outlook of where the field should go in the future. He said that Dr. Bianchi is a skilled, determined, and committed champion for women's and children's health in the United States, and has been a wonderful mentor.

X. Concept Clearance (4:29:15)

Dr. Rasooly led the Council through the review of nine concepts.

Biological Testing Facility (4:30:02)

Min S. Lee, Ph.D., presented this concept from DiPHR's Contraceptive Development Program (CDP). Council members had no comments or questions. **Decision: Approve.**

Development of Novel or Improved Infertility Technologies (4:32:24)

Travis Kent, Ph.D., presented this concept from FIB. Dr. Cedars asked how funding this concept would affect FIB's National Centers for Translational Research in Reproduction and Infertility (NCTRIs). Dr. Kent said that three of the six NCTRIs would be closed, noting that NICHD is congressionally mandated to have two NCTRI sites that focus on infertility. The NCTRIs have been successful in many metrics, but unsuccessful in changing clinical practice and developing novel technologies, so this concept shifts the funding toward product development. Dr. Cedars expressed concerns for the high-risk/high-reward model of this concept and recently decreased funding for the Reproductive Medicine Network. Dr. Kent said that the overarching goal of this concept was to improve the product development pipeline and make it more robust. The future model will likely follow CDP's phased approach to getting projects into a competitive state before increasing funding of larger projects. Daniel S. Johnston, Ph.D., FIB's acting chief, said that using milestone- and phase-based (e.g., R61, R33) mechanisms has been valuable for driving innovation toward product development. Dr. Neal-Perry said that she shared some of the same concerns as Dr. Cedars, because the change could cut other important areas of research (e.g., initial hot-flash research was conducted at a NCTRI). Dr. Neal-Perry also recommended rewording the concept's title from "improved infertility technologies" to "improved *fertility* technologies." Dr. Kent said that product development was currently a gap area in fertility and infertility research and described several ideas for improving the pipeline. Dr. Neal-Perry noted that patients seeking treatment for infertility can be a fragile population that is averse to high-risk research and expressed additional concerns for decreasing funding to NCRTIs. Dr.

Johnston said that the concept is essentially a call for innovation in this area. **Decision: Approve.**

NICHD Program Project Grants for HIV Research (4:46:35)

Denise Russo, Ph.D., presented this concept from the Maternal and Pediatric Infectious Disease Branch (MPIDB). Dr. Lang thanked Dr. Russo for presenting the program's previous results. **Decision: Approve.**

Navigating Pediatric to Adult Health Care: Lost in Transition (4:49:20)

Sonia S. Lee, Ph.D., presented this concept from MPIDB. Dr. Cedars asked about previous programs that addressed this topic. Dr. Lee said that several ICs have created similar programs, and that one previous NICHD program focused on HIV/AIDS, so the model has proven to be successful. For this concept, nine ICs with similar programs will now be collaborating, because there are several core elements of health care transition that can be applied more broadly. Dr. Barkin expressed support for this concept and suggested including policy experts in the collaboration. **Decision: Approve.**

Natural History of Disorders Screenable in the Newborn Period (4:55:19)

Kathleen Huntzicker, Ph.D., presented this concept from the Intellectual and Developmental Disabilities Branch. Dr. Lang expressed support for it. Dr. Rowitch suggested highlighting the potential impact on families and noting the possible downsides of enrollment. Dr. Van den Veyver asked how often the list of screenable conditions is updated. Dr. Huntzicker said that the funding opportunity was open to conditions that are either on the list or that may eventually be added to the list. **Decision: Approve.**

Research on Drowning Prevention (4:58:36)

Cinnamon Dixon, D.O., M.P.H., presented this concept from the Pediatric Trauma and Critical Illness Branch. Dr. Barkin asked whether drowning in bathtubs was included in this concept. Dr. Dixon said yes, the concept included drowning in bathtubs, pools, and open water. **Decision: Approve.**

Child Health Research Career Development Award; K12 Mentoring for Pediatrician Scientists (5:01:14)

Karen Winer, M.D., presented this concept from the Pediatric Growth and Nutrition Branch. Council members had no comments or questions about this concept. **Decision: Approve.**

Effects of Contraception as Treatment for Gynecologic Disorders (5:03:08)

Leigh Allen, Ph.D., presented this concept from the Contraception Research Branch. Dr. Cedars asked what type of long-term study protocols would be used for these projects. Dr. Allen said that most of the projects would be short term, but that these would eventually lead to larger, longer-term projects. Dr. Van den Veyver asked whether the research would generate enough evidence to create new treatment guidelines. Dr. Johnston said that this concept included collaboration with the GHDB so that it could focus on treating gynecological pain. Dr. Neal-Perry suggested adding language to the concept to clarify that the treatment of pain was included. Dr. Allen said that concept included studying off-target effects of contraceptives. Dr. Gyamfi-Bannerman said that it was important to be able to do larger clinical trials to answer some of the clinical questions, and that collecting physiology data would also provide an economy of scale. Dr. Neal-Perry suggested adding language to the concept to clarify that it included noncontraceptive benefits of contraceptive medications. Dr. Barkin agreed with the suggestions to make further revisions to the concept's language. **Decision: Table until the next meeting.**

Learning Disabilities Hubs (5:13:00)

Brett Miller, Ph.D., presented this concept from the Child Development and Behavior Branch. Council members had no comments or questions. **Decision: Approve.**

XI. Closing Remarks (5:14:56)

Dr. Bianchi thanked all Council members, presenting staff, and attendees and announced the schedule, location, and agenda for Day 2.

XII. Day 1 Adjournment

Dr. Bianchi adjourned Day 1 at 5:12 p.m. A total of 217 people viewed the live Day 1 NIH VideoCast.

XIII. Day 2 Call to Order and Introductory Remarks (0:04)

Dr. Bianchi opened Day 2 of the 186th meeting of the NACHHD Council at 9:00 a.m. ET. In each section below, the number in parentheses after each heading refers to the timestamp on the Day 2 NIH VideoCast; please go to that point in the recording to listen to the full presentation.

XIV. Necrotizing Enterocolitis (NEC) in Premature Infants WG Report (0:27)

Dr. Bianchi introduced the NACHHD NEC in Premature Infants WG of Council co-chairs, Dr. Maldonado and Ravi M. Patel, M.D. M.Sc. This WG of Council was formed in August 2024 at the request of HHS Secretary Xavier Becerra. Dr. Maldonado is the Toby Professor of Global Health and Infectious Diseases at Stanford University, senior associate dean of faculty development and diversity, and a professor of pediatrics and infectious diseases and of epidemiology and population health. She directs Stanford's Global Child Health Program and serves as the medical director of infection prevention and control at the Lucile Packard Children's Hospital. Dr. Maldonado is also currently serving as the interim chair of the Department of Medicine at Stanford and conducts research on the epidemiologic aspects of viral vaccine development and the prevention of perinatal HIV transmission. Dr. Patel is a neonatologist at Children's Healthcare of Atlanta and a professor of pediatrics at the Emory School of Medicine, where he conducts research on NEC (including its relationship with neonatal transfusion practices) and caffeine therapy in preterm infants. Another Council member, Dr. Rowitch, is also serving on this WG.

WG Charge and Process (3:27)

The NEC in Premature Infants WG was given the following charge:

- Assess the scientific evidence regarding enteral feeding practices in premature infants and factors that may protect against or increase risk for NEC.
- Identify important research gaps.
- Make recommendations for potential future research directions.

The WG's process included recruiting bench-to-bedside NEC subject matter experts and advocacy leaders to serve on the WG. Members also included laboratory scientists, neonatologists, and clinical trials specialists. The WG has met three times: on August 15, 22, and 28, 2024.

The WG then conducted an NEC portfolio analysis for the 5 years from FY 2018–2023. The analysis revealed that more than $101 million in NIH funding was related to NEC (i.e., 342 unique projects, 100 unique PIs, and 61 unique institutions). Of the funding, 44% came from NICHD (including clinical trials) and 24% came from the National Institute of Diabetes and Digestive and Kidney Diseases (including many mechanistic studies). Of the studies, 40% were primarily focused on NEC (versus NEC as a secondary aim or outcome). Of the

types of awards, 73% were RPGs, 10% were Small Business Innovation Research or Small Business Technology Transfer grants, and 9% were cooperative agreements.

WG members then reviewed the state of the science for NEC, specifically examining risk factors for NEC, nutritional support for preterm infants, and associations between feeding practices and risk or severity of NEC.

After the review period, the WG developed recommendations to improve the evidence base.

Background on NEC (7:52)

NEC is a common, serious gastrointestinal illness in which the tissue lining of the intestines becomes inflamed, dies, and can slough off. Symptoms include bloating or swelling of the abdomen, bloody stool, bile in the stomach, and food not moving through the intestines.

NEC is one of the leading causes of illness and death in preterm infants born before 28 weeks gestational age. One infant dies almost every day from NEC in the United States, and there were 356 deaths in 2022, according to data from the U.S. Centers for Disease Control and Prevention. NEC can appear suddenly and progress quickly in infants who may otherwise seem to be getting healthier.

NEC is a multifactorial disease with many antenatal, perinatal, and postnatal risk factors, including:

- **Maternal/antenatal factors:** Preeclampsia and hypertension (increased risk); antenatal steroids and/or tocolysis (e.g., medications used to delay delivery) (protective)
- **Infant perinatal factors:** Very low birth weight infants (VLBWs) born with birth weight less than 1500 grams (increased risk); small for gestational age (increased risk)
- **Infant postnatal factors:** Antibiotics exposure (variable risk); human milk exposure (protective)

Scientific Evidence Assessment (9:32)

In terms of foundational starting points, the WG members acknowledged that all babies, including those in the NICU, must be fed as soon as is medically feasible, by whatever means are available. Nutrition is vital for brain and other organ development. It is important to note, however, that prolonged fasting increases risk factors for other serious conditions, and intravenous feeding increases risk of bloodstream infections. The American Academy of Pediatrics recommends that VLBWs receive human milk, preferably from their own parents. If the parent's milk is not available, pasteurized donor human milk is recommended. However, human milk often requires fortification to meet the nutritional needs of VLBWs.

The current state of the science, or evidence, for enteral (feeding tube) feeding practices and base diet for premature infants is listed below:

Initiation of enteral feeding:

- Early trophic feeding versus enteral fasting showed no significant effect on risk of NEC, with low certainty.
- Delayed feeding versus early progressive feeding showed no significant effect, with low certainty.

Advancement of enteral feeding:

- Slow versus faster feeding showed no significant effect on NEC, with moderate certainty.

Evidence for base diet:

- When a parent's own milk is insufficient or unavailable, donor human milk (versus preterm formula) showed lower risk of NEC, with moderate certainty.

Evidence for fortification of the base diet:

- Results have been mixed, with recent trials showing no significant differences in rates of NEC between bovine-based versus human-milk-based fortifiers. Trials have been too small with too few cases of definitive NEC to draw firm conclusions.

Research Gaps (12:17)

WG members identified the following limitations in the existing evidence about NEC:

- Other intestinal conditions may mimic NEC (e.g., focal/spontaneous intestinal perforation, cow's milk protein–induced enterocolitis syndrome).
- Much of the evidence shows associations, not direct or indirect causation linking biological pathways with risk factors for the development and/or progression of NEC.
- Some risk factors identified in observational data have not been confirmed in clinical trials (e.g., red cell transfusion, empiric antibiotics).
- Because NEC is not a common outcome, studies are often observational or are small clinical trials; generalizability of results may be limited as a result.

Research Recommendations (13:22)

The WG developed three overarching research recommendations followed by specific recommendations for studies on epidemiology, mechanisms, risk factors, nutritional support, and feeding practices. Each recommendation is listed below by category.

Overarching Recommendations

1. Expand research into prevention of premature birth, including ways to delay impending births beyond the window of higher NEC risk (approximately 34 weeks' gestation). The best way to prevent most NEC cases is to prevent preterm birth.

2. Develop a more specific definition of NEC and severity of NEC to improve epidemiologic studies and determine eligibility for trials and treatments.

3. Ensure that research on NEC incorporates the perspectives of affected families.

Epidemiology of NEC

1. Improve tracking and reporting of NEC cases (as well as deaths).

    - Expand epidemiologic data collection, using a common definition, to better quantify the total burden of disease.
    - Implement updated International Classification of Diseases, 10th revision, codes more specific to NEC and NEC severity; separate out spontaneous intestinal perforation and other conditions (e.g., meconium inspissation).
    - Track NEC cases by gestational age, as there may be differences between NEC that develop in early preterm infants versus late preterm or term infants. NEC in term infants may be associated with cardiac issues.

2. Expand support for neonatal biorepositories to facilitate research to identify diagnostic, prognostic, predictive, susceptibility and/or surrogate markers of NEC.

3. Explore innovative methods for collecting and analyzing data.

    - Expand data collection to improve estimations for attributable risk for NEC:
        - Disease rate attributable to exposures (e.g., gestational age, antibiotics)
        - Correct diagnosis rate attributable to a positive predictive result (e.g., Bell Stage III diagnosis)
        - Beneficial outcome rate attributable to a treatment (e.g., specific feeding strategy)
    - Consider whether open-ended AI or ML analyses of electronic health records (EHRs) of babies with and without NEC could aid in diagnostic criteria or prediction.
    - Consider the use of biomarkers to better study the disease, given its relatively low incidence (e.g., surrogate measures).

Mechanisms of NEC

1. Expand research support into the mechanisms of NEC development:

    - Improve early diagnosis of NEC (e.g., biomarkers) to expand the therapeutic window.

- Identify potential prevention and treatment targets (e.g., activated signaling pathways triggering intestinal cell death or gut barrier breakdown) that more clearly link biological pathways with development and progression of NEC.
- Explore genetic and epigenetic pathways for NEC.

2. Improve animal and laboratory models to better match the disease complexity of NEC.

    - Expand NEC-in-a-dish, NEC-on-a-chip, gastrointestinal organoid systems, animal models (e.g., stroma, vasculature, immune cell), and the complexity of the models.
    - Collect biospecimens and nutritional data for NEC research and encourage data and specimen sharing.

Factors Affecting Risk of NEC

1. Explore exposures that may be positively or negatively associated with risk of NEC development, severity, and mortality. Consider exposures to:

    - Nutrition components
    - Antibiotics
    - Bacterial dysbiosis and viruses

2. Expand research on feeding practices that may affect NEC risk. Consider these factors:

    - Timing of initiation/progression and the development of NEC
    - Components of human milk, fortifiers, and/or formula

Nutritional Support for Premature Infants and NEC

1. Support research to identify the optimal nutritional needs of premature infants and how these needs may vary by gestational age and nutritional needs of NEC survivors.

2. Increase research support to optimize parent's lactation performance for preterm and term infants.

3. Optimize and standardize procedures to collect, process, store, and dispense donor and/or maternal milk for safety and nutritional content (e.g., fresh, frozen, pasteurized).

    - Identify bioactive components of human milk that may be protective for NEC and how to preserve these factors while still protecting against infection.
    - Develop point-of-care diagnostics to measure milk components in NICUs and donor banks.

- Research potential standards for donor milk in terms of postpartum donation timing, milk composition, pooling practices, and optimization for specific populations (e.g., VLBWs).

Feeding Practices and NEC

1. Support large, independent, comparative effectiveness clinical trials of feeding practices and NEC risk, including timing of onset, severity, mortality, and long-term effects on survivors. Include the following in the clinical trials:

    - Fortification methods (human milk-derived fortifiers, bovine milk-derived fortifiers)
    - Timing and method of transiting from donor milk

2. Explore innovative clinical trials designs to test, via regulatory pathways when required, the safety and efficacy of promising nutritional additives to prevent and/or treat NEC. Include the following in the clinical trials:

    - Ways to manufacture probiotics consistently and test them safely in neonates
    - Ways to test multiple components working together, rather than individual components alone

3. Expand implementation science research to reduce disparities in availability of human milk. Include the following factors in the projects:

    - Barriers to access donor milk, especially for rural communities and underrepresented populations
    - Community support for breastfeeding and milk donation
    - Economic and workplace interventions for lactation support

4. Support research on parent education in the NICU about feeding practices and risk of specific conditions, including NEC.

Next Steps (20:35)

The next steps for this WG are to finalize a report of its findings and recommendations and submit it to Secretary Becerra by September 16, 2024.

Discussion (21:14)

Dr. Cedars asked whether any studies had identified the protective components of human milk. Dr. Patel said that the WG reviewed a number of studies that described protective factors, including human milk oligosaccharides, epidermal growth factor, and lactoferrin. These components may explain the beneficial effects of human milk on intestinal health and intestinal maturation. Dr. Maldonado added that a series of experts presented the milk components studies (both *in vitro* and *in vivo*). Taken together, there is a dearth of information about which factors promote gut health and nutrition. It is still unclear which

components are best in human milk and what is missing in formula. Dr. Cedars suggested adding those studies to the WG's recommendations, including studies on whether formula contains components that are detrimental. Dr. Maldonado said that this topic would fit under the recommendations to support research to identify the optimal nutritional needs of premature infants and to look at specific models (e.g., NEC on a chip, NEC organoid models) in order to analyze particular components.

Dr. Barkin suggested including microbiome studies in this work. She asked for clarification on the mortality incidence of NEC and asked whether the risk factor studies tracked and collected data on which infants get NEC versus those that do not progress to NEC. Dr. Patel said that new studies should definitely examine the true proportion of disease and the factors that can explain NEC. He said that studying why infants without risk factors develop NEC also provides an opportunity to better understand the disease. Dr. Patel added that studying the microbiome was included in the recommendations to study bacterial dysbiosis and viral infections, because they have been associated with an imbalance in and an abundance of specific types of intestinal bacteria (e.g., proteobacteria). Dr. Maldonado said that the recommendations also include epidemiologic studies. Among the almost 4 million births each year, almost 60,000 are premature births, and the highest risk group is the VLBWs. Studies should therefore examine whether the mortality is due to disease progression and whether NEC prophylaxis is effective. One of the WG recommendations is to study the overall prevalence of disease, endpoints, and EHR data to try to understand more about the children who have earlier versions of NEC and how they might be different from those who succumb to it. Dr. Barkin agreed that physicians may be underdiagnosing many different phenotypes of NEC. She encouraged the WG to also study children who have the same risk factors but do not go on to develop NEC to its recommendations.

Dr. Neal-Perry asked how steroids modified the gut microbiome and why that is protective. She also asked whether the WG had data on long-term health outcomes (e.g., health status through development, increased risk for other diseases) for children who were seriously ill but did not get full-blown NEC. Dr. Patel said that annual steroid administration, particularly in early preterm infants, improves survival, reduces bleeding, and assists with lung and gut maturation. Regarding long-term outcomes, Dr. Patel said that most studies only have 2-year outcomes and focus on infants with more significant disease, such as those who have required surgery; a substantial long-term burden of disease has been found in that group. Less is known about the milder cases and infants who recover, but families of survivors have reported that NEC has long-lasting effects.

Dr. Gyamfi-Bannerman said that she was particularly enthused to see that identifying strategies to prevent preterm birth was included as a way to prevent NEC. She noted that the primary therapeutic in maternal fetal medicine for preventing preterm labor was recently pulled from the market with nothing to replace it, so there is an urgent need to identify strategies to prevent preterm birth. Dr. Gyamfi-Bannerman suggested adding maternal–fetal medicine experts and obstetricians to the WG to assist with this recommendation if the WG continues to move forward.

Dr. Jabs asked how much of the current NIH funding for NEC research is addressing the WG's recommendations. Dr. Maldonado said that the WG had not yet had a chance to analyze the research portfolio, but that matching current NIH funding with the WG's recommendations was a good suggestion before submitting the final report. Dr. Jabs asked whether there were any premature cohorts that could be used for NEC research. Dr. Patel said that some groups have been discussing the creation of a multicenter biorepository, and that NICHD's Neonatal Research Network enrolls a number of cohorts of premature infants and routinely collects epidemiologic data across 15 participating centers. He added that it might be possible to enhance that cohort with more specific measures going forward.

Dr. Van den Veyver asked whether the treatment of other co-occurring morbidities that affect preterm infants would impact NEC and be integrated in the WG's recommendations. Dr. Maldonado said that the WG was interested in studying how attributable factors and underlying conditions affect the risk for NEC. Dr. Patel added that babies that require surgery for NEC have a high risk of cerebral palsy, and that risk might be increasing; therefore, additional work to understand the relationship between gut injury and brain health is important.

Dr. Bianchi said that maternal cells in breast milk play a role in educating the infant's immune system. She asked whether there could be consequences of giving foreign cells in donor breast milk. Dr. Patel said that the WG discussed human milk science in terms of specific variability and components of human milk versus donated human milk, but the WG did not specifically discuss cells and how they might differ between parents and donors. Dr. Maldonado said that NEC has a fairly limited period of risk, but evolving gut and infant gut immunity both may play a role in the critical early period in preterm infants (and also in some term infants). She noted that those areas were of interest to the WG.

Dr. Neal-Perry said she agreed with Dr. Cedars' earlier comment that it is important to study what is in maternal milk versus what is in formula to determine whether their differences can be used to identify the risk of developing NEC. She also said that the differences between parent milk versus donor milk and frozen milk versus fresh milk should be studied. Dr. Maldonado said that studies have demonstrated a statistically significant benefit to donor milk versus formula. Dr. Patel added that some of the WG presentations on the differences between parent's milk and donor milk described how pasteurization alters the milk but still has a protective effect (freezing milk may also alter it). Although there have not yet been any clinical comparative trials between donor milk and parent's milk, there have been some limited microbiome studies comparing them.

Dr. Rowitch said that some of the evidence that was presented to the WG showed that rates of NEC were half as high when human milk was given versus formula; therefore, this provides insight into the pathogenesis of NEC and also has practice implications. He added that what will hopefully come across in the WG report is that the parent's own milk is best, followed by donor milk, so the use of donor milk should be increased. Scientifically, the question is: "What is it about human milk that is protective?" Further research could then look for the specific cellular or biochemical factors in milk. Dr. Neal-Perry said that further

research should also investigate how best to preserve human milk for optimal effectiveness and benefit. Dr. Maldonado said that it was clear that standardizing protocols for handling, storing, banking, and distributing donor milk was an area of opportunity.

Dr. Van den Veyver asked whether the gestational age of milk donors and the gestational age of the parents at the time of delivery were considered in research studies. Dr. Patel said that the donors who provide milk vary in gestational age and that the nutritional content of milk – and its components – differ by gestational age. The WG discussed whether research in this area might help optimize the delivery of donor milk and maximize the beneficial content of specific components. It is an area where more data are needed. Dr. Maldonado added that another issue that arose was the lack of rapid, point-of-care diagnostics for determining the composition of milk at the time it is given (e.g., to match chronological and gestational age).

Given the number of studies in the NIH portfolio, Dr. Contreras-Vidal asked whether a concern would be dataset readiness for open-ended AI and ML, or whether any harmonization or infrastructure work would be needed before incorporating those tools. Dr. Maldonado said that the WG discussed the availability of EHR datasets, which are becoming increasingly available. Dr. Patel added that a challenge for ML models is training on a gold standard definition when the definition is unknown. He also said that NEC can be an acute disease with a sudden onset, so clinical symptomatology at the time of onset may be inconsistent: Some of the features that might be recorded on a daily note may not capture the granularity needed at the time of onset.

Dr. Contreras-Vidal asked how the WG members would prioritize their recommendations. Dr. Maldonado said that the WG had not yet done so, meaning that additional meetings might be needed.

Dr. Bianchi thanked the Council members for their interesting and relevant questions. She asked the Council members to vote on whether to approve the WG's report and endorse its future research recommendations. Dr. Cedars made a motion to approve the WG report and provide concept clearance. Dr. Van den Veyver seconded the motion. The Council then voted to approve the report and the concept. **Decision: Approve.**

XV. Closed Session (49:54)

Dr. Bianchi thanked all attendees and concluded the open session. The meeting was then closed to the public in accordance with the provisions set forth in Section 552b(c)(4) and 552b(c)(6), Title 5, U.S.C., and Section 10(d) of the Federal Advisory Committee Act, as amended (5 U.S.C. Appendix 2). NACHHD Council members provided second-level review of intramural and extramural applications.

XVI. XVII. 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 reviewed 652 applications, requesting $220,899,660 in Direct Costs and $311,710,918 in Total Costs.

XVII. Adjournment

There being no further business, Dr. Bianchi adjourned the meeting at 12:45p.m. on Thursday, September 5, 2024. The next Council meeting is a virtual meeting that is scheduled for January 13–14, 2025.

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

Diana W. Bianchi, M.D.
NACHHD Chair
NICHD Director

Date

Rebekah Rasooly, Ph.D.
NACHHD Executive Secretary
Director, NICHD Division of Extramural Activities

Date

[2] These minutes will be formally considered by the Council at its next meeting; any corrections or notations will be incorporated into the minutes of that meeting.