

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
NATIONAL INSTITUTES OF HEALTH
NATIONAL INSTITUTE OF ENVIRONMENTAL HEALTH SCIENCES**

**MINUTES OF THE ONE HUNDRED FIFTY-THIRD MEETING OF THE
NATIONAL ADVISORY ENVIRONMENTAL HEALTH SCIENCES COUNCIL**

February 12, 2018

The National Advisory Environmental Health Sciences Council convened the open session of its one hundred fifty-third regular meeting on February 12, 2018 in the Rall Building, Rodbell Auditorium, National Institute of Environmental Health Sciences, Research Triangle Park, NC. The closed session of the meeting was held February 7, 2018.

The meeting was open to the public on February 12, 2018 from 8:30 a.m. to 5:00 p.m. In accordance with the provisions set forth in Section 552b(c)(4) and 552b(c)(6), Title 5, U.S. Code and Section 10(d) of the Federal Advisory Committee Act, as amended (5 U.S.C. Appendix 2), the meeting was closed to the public on February 7, 2018 from 2:00 p.m. to 4:00 p.m. for consideration of grant applications. Notice of the meeting was published in the *Federal Register*.

Dr. Linda Birnbaum presided as Chair.

Participating Council Members

Habibul Ahsan, MD (via WebEx)
Philip Brown, PhD
William Cibulas, Jr., PhD (*ex officio*) (via WebEx)
Jeanne Conry, MD, PhD (via WebEx)
José Cordero, MD, MPH
Irasema Coronado, PhD (via WebEx)
Kevin Elliott, PhD (via WebEx)
Brenda Eskenazi, PhD
Kenneth Fasman, PhD
Andrew Feinberg, MD
Shuk-Mei Ho, PhD
Maureen Lichtveld, MD
José Manautou, PhD
Donna Mendrick, PhD (*ex officio*) (via WebEx)
Susan Schantz, PhD
Andy Shih, PhD (via WebEx)
Patrick Sung
Deborah Winn, PhD (*ex officio*)

NIEHS Staff

Kathy Ahlmark
Robin Arnette, PhD
John Balbus, MD, MPH
David Balshaw, PhD
Sharon Beard, MS
Bryann Benton (via WebEx)
Brian Berridge, DVM, PhD
Linda Birnbaum, PhD
Tiffany Bowen
Abee Boyles, PhD
Jed Bullock
Danielle Carlin, PhD
Trisha Castranio
Lisa Chadwick, PhD
Jennifer Collins
Gwen Collman, PhD
Brennan Davis
Christie Drew, PhD
Chris Duncan, PhD
Lisa Edwards
Benny Encarnacion
Symma Finn, PhD
Christine Flowers
Amanda Garton
Barbara Gittleman
Kimberly Gray, PhD
Janet Hall, MD
Astrid Haugen
Michelle Heacock, PhD
Heather Henry, PhD
Jon Hollander, PhD
Michael Humble, PhD
Bonnie Joubert, PhD
Helena Kennedy
Alfonso Latoni, PhD
Cindy Lawler, PhD
Kelly Lenox
Robbie Majors
J. Patrick Mastin, PhD
Kim McAllister, PhD
Steven McCaw
Liz McNair
Aubrey Miller, MD, MPH
Sri Nadadur, PhD

Aaron Nicholas
Sheila Newton, PhD
Liam O'Fallon
Kristi Pettibone, PhD
Molly Puente, PhD
Lingamanaidu Ravichandran
Scott Redman
Les Reinlib, PhD
Cynthia Rider, PhD
Thad Schug, PhD
Dan Shaughnessy, PhD
Ashley Singh
William A. Suk, PhD, MPH
Laura Thomas, PhD
Claudia Thompson, PhD
Brittany Trottier
George Tucker
Steven Tuyishime, PhD
Michelle Victalino
James Williams
Mitch Williams
Leroy Worth, PhD
Rick Woychik, PhD
Demia Wright, MPH
Wei Wu
Xian Wu, PhD
Darryl Zeldin, MD

Members of the Public Present

Manish Arora, PhD, MPH, Mt. Sinai
Maureen Avakian, MDB, Inc.
Megan Avakian, NIEHS Contractor, MDB, Inc.
Nathan Blouin, UNC-Chapel Hill
Eric Dishman, All of Us Research Program (via WebEx)
Jack Griffith, PhD, UNC-Chapel Hill
Ernie Hood, Bridport Services, LLC
Alexia Kelley, PhD, UNC-Chapel Hill
Perry Kirkham, PhD, Purdue University
Cindy Nakatsu, PhD, Purdue University
Carlos Pérez-Torres, PhD, Purdue University
Michael Phillips, RTI International
Jonathan Shannahan, PhD, Purdue University
Joyce Tan, PhD, UNC-Chapel Hill

I. Call To Order and Opening Remarks

NIEHS/NTP Director and Council Chair Linda Birnbaum, Ph.D., welcomed attendees and called the meeting to order. She asked the Council Members attending via WebEx to introduce themselves, followed by the attendees in the room. Following the introductions, NIEHS Division of Extramural Research and Training (DERT) Director and Council Executive Secretary Dr. Gwen Collman reviewed meeting logistics, including votes to be taken through the Electronic Council Book.

II. Review of Confidentiality and Conflict of Interest

Designated Federal Official Dr. Collman reviewed the Conflict of Interest and Confidentiality procedures, which had been provided earlier to Council members in written form, and reviewed various other administrative matters.

III. Consideration of October 2017 Meeting Minutes

Approval of the October 2017 meeting minutes was moved and seconded, and Council voted to approve the minutes, with all in favor. Dr. Collman noted the dates of the upcoming Council meetings for members to put on their calendars.

IV. Report of the Director, NIEHS

Dr. Birnbaum briefed Council on Institute developments since the October 2017 Council meeting.

She presented the retiring members of Council, Ken Fasman and Andrew Feinberg (who will represent NIEHS on the Council of Councils), with certificates of appreciation for their dedicated service. She recognized the retiring Council members who were attending via WebEx, Jeanne Conry and Kevin Elliott, as well as Marie Lynn Miranda, who was unable to attend.

She began her presentation with a report updating appropriations. She described the gradual budget increases in the past three fiscal years under omnibus appropriations. For Fiscal Year 2018, the President's Request for the NIEHS budget represents a substantial budget cut. The House has passed its appropriation bill, which would give NIH an increase of \$1.1 billion, which would give NIEHS approximately \$11 million more than in 2017. The Senate Appropriations Committee approved a \$2 billion increase for NIH, reflecting a \$23 million increase for NIEHS. She expressed hope that the next omnibus appropriation would be completed soon. She noted that more than half of the increase in the House bill was earmarked for various initiatives, whereas in the Senate measure, only roughly one-third was earmarked.

She went over the five continuing resolutions that have been enacted in the 2018 fiscal year, including the two government shutdowns that have taken place. She noted that the most recent continuing resolution raised budget caps, negating the possibility of renewed sequestration. The hope is that there will be a budget as of the end of the current continuing resolution on March 23.

Turning to science advances, Dr. Birnbaum briefly summarized several recent publications by NIEHS/NTP personnel or grantees. She recounted four papers published by DIR scientists, three publications from DNTP researchers, and six papers from DERT grantees.

In staff updates, she noted the hiring of Dr. Paul Doetsch to be the DIR Deputy Scientific Director. In the NTP, Dr. Brian Berridge has assumed his position as Associate Director of NTP and Scientific Director of DNTP, with Dr. John Bucher moving into a role as NTP Senior Scientists. Dr. Nigel Walker is now Acting Branch Chief of the NTP Toxicology Branch. Dr. Birnbaum also noted several other staff updates.

She described several recent and upcoming activities by NTP, and the recent opening of the NIEHS Net-Zero Energy Warehouse.

She discussed the progress of the initiative to Reimagine HHS, and described its various elements, one of which is to Optimize NIH. She provided further details about that effort.

She noted that the initial draft of the new NIEHS Strategic Plan has been released, and went over the timeline remaining until its anticipated completion and publication in September 2018.

Dr. Birnbaum related NIEHS Worker Training Program activities related to the 2017 hurricanes, as well as the NIEHS personnel who had been selected for the surge capacity force.

She described several past events since the last Council meeting, as well as many events coming in the next few months.

In her summary of awards and recognition, she listed NIEHS personnel and grantees who have been named AAAS Fellows, and others included in the CHE 20 Pioneers Under 40 in Environmental Public Health. She also noted several additional individual awards and recognitions, including those from SOT, APHA, and other organizations.

In his final Council meeting, Dr. Feinberg took the opportunity to thank NIEHS: "It's an incredible privilege to advise and help this remarkable group of public servants. This is government at its best. You can just see the science core of what NIEHS does, but also its incredible engagement in so many communities and the practical things that matter

in real time too. ... It's really an amazing enterprise we have that's unique in the world, and this is one of its real crown jewels."

Dr. Lichtveld asked Dr. Birnbaum to elaborate on the timing of the glyphosate studies, as there are global implications. Dr. Birnbaum said the studies are now in progress, and the hope within NTP is to be able to release its data in short order. She added that the hope is to release some of the glyphosate data by late summer. She said that one of the main issues to be addressed is the variability in formulations.

V. Report of the Director, DERT

Dr. Collman briefed the Council on recent developments within DERT.

She recognized the recent departure from DERT by long-time employee Pamela Clark and the impending retirement of RoseAnne McGee.

She presented a list of twelve Council Delegated Staff Actions, which include continued authorization of the CHEAR and ECHO supplements, new FOAs for Diversity and Re-entry supplements, and the addition of applications greater than \$500,000 to the Electronic Council Concurrence process. Council voted unanimously to approve the measure.

Dr. Collman went over the NIH Clinical Trial Initiative, which recently took effect. She reviewed the updated definition of a clinical trial, as well as the questions to ask to determine if one's research is considered to be a clinical trial. She provided details about the NIEHS FOA Clinical Trial categories, in which some FOAs require clinical trials, some are optional, and in some, clinical trials are prohibited. She described a new NIH resource for clinical trial research methods.

She listed several upcoming NIEHS-sponsored meetings and workshops from March to September, 2018, and described the Parent NIH Support for Conferences and Scientific Meetings FOA (R13), in which NIEHS participates. She noted that in FY 2017, NIEHS supported 31 investigator-initiated meetings, and supported large, recurring meetings such as SOT, ISEE, and ISES.

Dr. Collman summarized NIEHS FY 2017 extramural funding and grant distribution. 1,487 applications were received across all categories. 276 competing awards were made, with the average cost of a competing research project grant (RPG) of \$369,000. The payline was at the 10th percentile, and the NIEHS success rate was 14.9% for all RPGs and 14.3% for R01s.

She described several initiatives anticipated in FY 2018, with \$31.4 million set aside for environmental sciences RFAs.

Regarding the R13 funding mechanism, Dr. Manautou noted that some of the conferences and meetings listed by Dr. Collman were quite technical in content, with an expectation of community engagement and participation. He asked her to provide some examples of creative approaches taken in highly technical meetings to meet that expectation. Dr. Collman said that many of the meetings revolve around policy, and in those cases community engagement is a natural element. She added that some of the meetings include educating clinicians about technical and scientific advances.

Dr. Birnbaum asked Dr. Collman to describe NIEHS funding of early-stage investigators. Last year, she said, up to the 25th percentile, all but four of the early-stage investigators were funded. Dr. Mastin confirmed that the figure was 14 of 18 applicants. Regarding investigators who may be at the critical career stage and may face funding gaps, Dr. Collman observed, "We have always looked for investigators who are at these critical stages of their career, and looked at how much funding they have, and whether they are going to lose funding. Is this their only grant, is an investment we've made in it for a long time, and if we have a lapse, what's the consequence to the entire effort?"

Dr. Brown asked about how successful the R35 RIVER program and the R25 undergraduate training program have been. Dr. Collman replied that the RIVER program was the first time NIEHS had used the R35 mechanism. She noted that there had been 19 applications, and that 8 awards had been made thus far. She felt that so far the R25 program had been a success, but the decision has not been made yet as to whether to renew it.

Dr. Lichtveld asked Dr. Collman to provide an update on the ViCTER program, and a general update on the NIEHS vision for oceans and human health. Dr. Collman said that ViCTER was originally a 3-year RFA, but the decision was made to not release the last year, since the program was slated to be revamped. The new RFA is being developed and finalized, but is not on the street yet. Regarding oceans and human health, she said that a funding plan is being developed.

Dr. Eskenazi asked Dr. Collman to comment on the success of the R24 maintenance grants, and whether supplements to the grant have been considered. Dr. Collman said that it is still early and premature to assess how well the investigators are doing. The program is still being evaluated, and that supplements have not yet been considered.

Dr. Coronado mentioned the importance of undergraduate research and undergraduates being given the ability to go to conferences. She urged continuation of the program.

VI. Concept Clearance: Environmental Risks for Psychiatric Disorders

Dr. Jonathan Hollander from the NIEHS Genes, Environment and Health Branch briefed the Council on a proposed new funding opportunity to stimulate research efforts exploring the role of the environment in the development of psychiatric disorders.

He provided background information about the nature and prevalence of psychiatric disorders, and went over the current NIEHS investment in the area, which totals \$38 million. He described NIEHS-relevant exposures linked with potential psychiatric disorders, including examples such as chlorpyrifos and fine airborne particulate matter. He summarized a 2017 expert panel workshop on the subject held at NIEHS, which helped to identify the most promising scientific opportunities and data gaps related to understanding the environmental risks for mental health disorders. A key challenge moving forward is that there seems to be little interaction between the psychiatric and environmental health research communities.

The goal of the FOA proposal is build a new NIEHS program designed to support innovative basic, epidemiological, and interdisciplinary research to understand mechanisms by which environmental exposures disrupt normal brain and behavioral functioning to increase risk for psychiatric disorders.

The proposed program is in three phases. Step 1 is a PAR to stimulate interest and signal to the psychiatric and environmental health science communities of NIEHS interest in the field. As interest and awareness generated from the PAR builds in years 1-2, the second phase of the program, R21 set-aside funding, will commence — \$1.4 million to fund 4-5 awards. Step 3 is an R01 program in years 3-5. During the time frame, capacity-building activities will also be undertaken. Dr. Hollander also provided several examples of potential projects falling within the scope of the initiative.

Dr. Schantz was the first Council reviewer. She said that she was “very, very supportive” of the initiative. She noted that up to now the research focus has been on early life conditions such as autism and ADHD and late-life disorders such as Alzheimer's, which has left adolescence as a life stage understudied in terms of neuropsychiatric disorders, such as anxiety disorders.

Dr. Manautou was the second Council reviewer. He also expressed support. “I think this is a space where we need to be,” he noted. He cited the importance of getting the two communities together, and said the program would be a strong catalyst to accomplish that goal. He noted the availability of \$6-8 billion in funding related to opioid addiction. He said he had recently hired a researcher to look at epigenetic signatures related to addiction, and that it would be interesting to discover the impact of environmental exposures on those signatures. He fully endorsed the initiative Dr. Hollander had presented.

Dr. Feinberg agreed. He said that there is a bit of a paradox in the field in that NIMH has been discouraging use of whole organism mouse models. He asked Dr. Hollander whether his impression was correct. Dr. Hollander said that NIMH is involved in providing input to the initiative. He noted that there is certainly controversy about the use of whole animal models, but that they can be important for modeling various aspects of the disorders. He said he would continue to engage with NIMH staff to ensure that the program announcement aligns with their vision. Dr. Birnbaum added that the NIMH director is open to environmental issues as they relate to mental health.

Dr. Eskenazi said it was “a fantastic proposal, and something that we really need to do.” She cautioned that there was much less funding going toward ADD/ADHD research (compared with autism), although the condition is an important precursor to later behavioral disorders. Also, she said it would be important to look at very early predictors of behaviors, perhaps even *in utero*. She hoped there would be some focus on that in the RFA. She added that it would be important to look at both chemical and non-chemical stressors, and how they might interact in the development of neuropsychiatric disorders.

Dr. Brown added his support. He approved of the added contact with more NIH ICs, raising NIEHS visibility. He recommended that Dr. Hollander consider the impact of disasters, which can lead to issues such as social isolation, disruption or lack of networks, etc., which are not DSM-V categories.

Dr. Shih commented that he was very enthusiastic about the initiative, and that the return on investment would likely be multi-fold.

Dr. Ho said that the role of NIEHS should focus on prevention, not just treatment. She felt that it would be important to find and develop relevant human models. She recommended linking to some of the other current NIH initiatives.

Dr. Lichtveld noted that she was delighted that the initiative would look at both chemical and non-chemical stressors. She concurred with Dr. Brown’s comments on the psychosocial impacts of disasters. She felt that supporting existing *in utero* cohorts would help accelerate research in adolescents.

Dr. Manautou was also supportive. He was impressed with the graph Dr. Hollander had shown depicting \$2 billion in spending on mental health at NIH, but that a small portion of these funds were spent on research that considered environmental factors. Dr. Hollander said that imbalance was one of the inspirations for the development of the program.

Dr. Collman called for the Council to vote to approve the concept. There was a motion and second to that effect. The Council voted unanimously in favor, including those in attendance via WebEx.

VII. Telomeres as Sentinels for Environmental Exposures, Psychosocial Stress, and Disease Susceptibility

Dr. Michelle Heacock presented the concept to support a research consortium and methods initiative, with an NIEHS-specific research component that will build upon the recommendations from a highly successful and current state-of-the-science telomere biology workshop held in September 2017 collaboration with colleagues at the National Institute on Aging (NIA).

She provided background about current knowledge regarding telomeres and disease risk. She noted that the field of exposure science and telomeres has been contentious due to a range of disparate findings in the literature. Thus, the workshop was organized in partnership with NIA, which brought together experts from basic telomere biology, medicine, biopsychology, epidemiology and related fields for the first time. Two distinct sets of recommendations emerged from the workshop: methods and standards development, and the need for a coordinating effort to foster interdisciplinary collaborations to move the field forward.

A staged approach is proposed. The first stage, in years 1 and 2, involves basic methods validation. Stage 2, in years 2-3, involves measurement considerations. In Stage 3, in years 4 and 5, research questions will be pursued along with tool development. In Stage 1, a consortium of 3-4 labs with a network hub coordination center is to be established. Stage 3 involves two phases, with the release of an R01 planned at the end of year 3. The first phase involves U24 and U01 grant mechanisms.

Dr. Eskenazi was the first Council reviewer. She said she was supportive of the concept, in that it is time to figure out what telomere length means. She approved of the integrative approach, utilizing lab scientists and other scientists to confer. She said her only concern was that even after the first few years of the program, it would remain uncertain what telomere length technology should be, or what it might mean, with the possibility that the R01 would not go forward. She added that if it does go forward, two years is a short period of time for an R01. Dr. Heacock replied that the R01 should not be dependent on a final decision regarding the technology.

Dr. Feinberg was the second Council reviewer. He said he had found the telomere workshop very impressive. He alluded to the scientific paradox with telomeres, in that there is still confusion about the impact of telomere length. He noted that the community needs help with determining the best methodology, and the proposed initiative would contribute. He said it might be necessary to include single-cell analysis.

He recommended that chromosome health measures such as DNA damage response and gene expression be included, to help make the epidemiology easier later in the process. He agreed with Dr. Eskenazi's assertion that there should be a checkpoint to assess the success and promise of the program prior to committing to R01 funding.

Dr. Winn recommended that Dr. Heacock be specific in the announcement about the kinds of epidemiology studies wanted in the program.

Dr. Ho noted that many toxicants impacting telomere length work in opposite directions, so it would be important to use the proper statistical methods to tease out how to give weight to the different pollutants or chemicals. She supported the use of a single-cell approach, because telomere length is very cell-type-specific.

Dr. Sung supported standardization of the technology. He said that the field is quite broad. He felt that in order to maximize the impact of the money being spent, it would be advisable to focus on one or two key issues based on feedback from the community.

Dr. Lichtveld said that her group has been collecting telomere biospecimens, and has been seeing associations between telomere length and socioeconomic status and community violence. She agreed that the program should be focused, particularly because there are so many exposures to mixtures. She said it would be important to see the agreement or disagreement, or variation, among the various methods being employed. She stressed that there are in fact existing cohorts to that can be used.

Dr. Manautou asked Dr. Heacock whether she anticipated that once the consortium of four labs was assembled, those labs would transition into the R01 funding stage. She replied that it would be open and not restricted to just those labs. Dr. Manautou asked her to confirm that the methodologies determined to be best in the first phase would be required to be used in the R01 phase. She said that that would be part of the objective of the U01s and the network — to establish standards that all would agree upon. Dr. Manautou observed that such an approach would curtail creativity and innovation in an R01 mechanism. Dr. Heacock said that there is an ability within the network to refine existing methods or develop new ones. Dr. Collman added that the network could be comprised of hundreds of laboratory scientists who would meet together and form the community of practice in telomere biology and the interface with environmental health. The group would provide data to look at the various measurement methods, so it is not NIEHS and/or NIA deciding which methods would be required, it would be the community coming up with standards and arriving at a consensus.

Dr. Collman called for a motion and vote on the concept. Approval was moved and seconded, and the Council voted unanimously in favor of the proposal, including the WebEx attendees.

VIII. Early Life Environmental Determinants of Health and Disease

Dr. Manish Arora from the Icahn School of Medicine at Mt. Sinai delivered the meeting's science presentation.

Dr. Arora and his colleagues have been working to identify environmental and metabolic signatures that predict the risk of later-life neurological disorders. Central to the work is the development of technologies that use human teeth to reconstruct prenatal and early childhood environmental exposures and the biological responses to those exposures. He shared recent findings from his laboratory on autism spectrum disorder and amyotrophic lateral sclerosis (ALS, Lou Gehrig's disease). He showed data suggesting that early life environmental stressors, such as exposures to certain metals at critical developmental stages, can alter developmental trajectories by disrupting the homeostasis of one or more systems, and in doing so produce identifiable biochemical signatures characteristic of the disease process or outcome.

Dr. Birnbaum observed that the methods described by Dr. Arora using baby teeth would be very useful to assess early life exposures, as many parents save their children's baby teeth. She asked if the data had been published yet. Dr. Arora said the findings were in the process of publication, but that it was difficult in some cases to get the studies reviewed. Dr. Birnbaum encouraged him to persevere in his efforts. Dr. Feinberg added that Dr. Arora should not be discouraged about going to topical journals, which may be more likely to publish new methodologies and observations.

Dr. Eskenazi said the ALS paper "truly is an amazing study." She asked if the teeth Dr. Arora had acquired were molars. He said they had acquired multiple teeth, typically taking the back teeth more than the front, upon autopsy, to preserve cosmetic integrity. He noted that it took three years to collect the first 40 teeth for the study. Dr. Eskenazi asked him to elaborate on the findings, particularly regarding the mixture that had been used. He further described the findings, stressing that it was difficult to make large claims with such a small sample size. Although not a full-blown epidemiologic study, he noted, it does constitute proof of concept.

Dr. Lichtveld said that her group has cohort studies where biological samples are being collected. She asked Dr. Arora to discuss his study that included hair samples. He noted that the baby teeth classifier for autism may be of limited use, since by the age of tooth shedding, clinically the disease is typically obvious. He said that his team had developed an assay using a single strand of hair, which would be accessible from any baby by the age of six months.

Dr. Manautou asked whether Dr. Arora had thought more broadly about pharmacokinetic parameters regarding metals homeostasis. Dr. Arora described his work with a colleague who has developed a mouse model for ALS, allowing a metalomics approach, using analysis of teeth and hair. "At the end of the day, if this is a true signal, it will be system-wide, existing in teeth, hair, blood and everywhere," he observed. He noted that he has applied for a new grant to disseminate the technology.

Dr. Coronado asked about the racial composition of the Texas cohort Dr. Arora had accessed in one of the ASD studies. He said that the Swedish cohort was not ethnically diverse, but there was extreme diversity in the New York cohort. In the UK, there was some diversity, but he was unsure about the composition of the Texas cohort.

IX. 2018-2023 Strategic Plan Follow-up

Dr. Sheila Newton, director of the NIEHS Office of Policy, Planning, and Evaluation, briefed the Council on the progress and current status of the updated NIEHS Strategic Plan.

She noted that input from the online survey, *Trends & Insights*, had been analyzed. A framework for the new Strategic Plan has emerged from careful consideration of the online input, the role of continuing priorities from the 2012-2017 plan, review of NIEHS's mission, vision, and statutory language, and alignment with the NIH Strategic Plan, which is now a requirement per the 21st Century Cures Act.

The survey had shown that it was felt that many of the goals and priorities in the existing strategic plan would be important to continue. Also, it was seen as important to continue research priorities: "A large-scale piece of bottom-line input that we got from the survey is, 'As you're going forward with all of this great science, try to keep an eye on what the ultimate goal is.'" Dr. Newton reviewed the applicable statutory language in the Public Health Service Act related to the NIEHS mission.

She went over the NIH-Wide Strategic Plan 2016: Turning Discovery into Health. It begins with an overview, including the mission of the NIH. It continues with a large section called Advance Opportunities in Biomedical Research, which includes language related to Fundamental Science, Health Promotion/Disease Prevention, and Treatments/ Cures. It includes a section called Set Priorities, Enhance Stewardship, as well as a call for NIH to Excel as a Federal Science Agency by Managing for Results, which includes references to building the NIH biomedical workforce, enhancing workforce diversity, rigor and reproducibility, and impact evaluation.

The new NIEHS Strategic Plan incorporates three new, interdependent Strategic Objectives:

- Advancing environmental health sciences
- Promoting the translation of data to knowledge to action
- Enhancing scientific stewardship and support

She illustrated a new cloud graphic depicting the three Strategic Objectives.

She provided details about each of the strategic objectives. The first, Advancing Environmental Health Sciences, incorporates research in the field and how factors in the environment affect biological systems and health and disease. It encompasses:

- All levels of biological organization from molecular to population
- Basic biological research
- Individual susceptibility
- The microbiome
- The exposome
- Co-exposures
- Predictive toxicology
- Data science and Big Data

The second strategic objective, Data to Knowledge to Action, addresses moving research results along translational lines to inform and support public health action and other contributions to health. It encompasses:

- Data to Knowledge
- Outreach, communications, and engagement
- Evidence-based prevention and intervention
- Environmental health disparities and environmental justice
- Emerging environmental health issues
- Partnerships for action

The third strategic objective, Enhancing Stewardship and Support, encompasses:

- The EHS professional pipeline
- Greater workforce diversity
- Promotion of collaborative science
- Training and capacity-building in global health
- Rigor and reproducibility
- Ethical conduct of EHS research
- Scientific research and data infrastructure
- Impact evaluation

"We are very excited about the new plan going forward," said Dr. Newton. The most recent draft has been posted, and comments from the public will be accepted until

March 30. The final plan will be presented at the June Council meeting, with publication anticipated in September.

Dr. Fasman said, "I've always been very impressed by how the Institute has used the current strategic plan — how you have constantly indicated which programs, which grants, which papers fell under each of the different strategic priorities." He felt that the plan had been so successful because each of the strategic priorities was relatively homogeneous and well-defined. He said he was a bit nervous about the revised plan and its much broader, much more heterogeneous, and less well-defined strategic objectives. He was concerned that over the next five years there would be less interaction among the strategic objectives, with almost every activity falling into only a limited number of categories. He asked Dr. Newton if from her perspective she felt that it would be a more useful tool. Dr. Birnbaum said that the three strategic objectives were like themes, whereas in the past plan, the links were most often with individual goals and sub-goals. She said that it had not yet been worked out what to call the sub-objectives under the three strategic objectives, and noted that suggestions are welcome. Dr. Winn observed that data sharing would fall under all three strategic objectives.

Dr. Lichtveld offered a solution for the terminology, emerging from her work in enterprise evaluation. She suggested that rather than "strategic objectives," they be called "strategic imperatives," which would lead to approaches, to benchmarks, and then to action. She thanked Dr. Newton for including much of the feedback Council had offered at its last meeting, particularly the provision for impact evaluation.

Regarding impact evaluation, Dr. Manautou asked what had been learned from the previous strategic plan regarding what metrics actually work, which should continue to be used, and which new metrics might be used. Dr. Collman said it was a great question, and something that had been thought about while crafting the new segments. She said one impact element to be considered would be the growth of an idea or concept.

Dr. Feinberg suggested that under Strategic Objective 1, genetic and epigenetic susceptibility should be listed together.

Dr. Elliott suggested moving impact evaluation from Strategic Objective 3 to Strategic Objective 2, since it is an element of moving knowledge to action. Dr. Newton said it was originally in Strategic Objective 2, but was moved to #3 to facilitate alignment with the NIH plan. Dr. Birnbaum emphasized the importance of understanding that many of the elements included in the new cloud diagram work together, so where something is specifically listed is not as important as where it "has tendrils that reach."

Dr. Lichtveld noted that in some models, evaluation is part of the overarching umbrella.

Dr. Coronado asked how many public comments were received, whether there was any geographical breakdown, and the major themes that emerged. Dr. Newton said there had been a breakdown of the types of affiliations, but not geographical. She discussed several of the main ideas that emerged from the comments. She said there were more than 200 responders. People had the opportunity to respond individually to the 11 goals in the previous plan, along with a box for general comments. Thus, with some respondents commenting in all of the boxes, some in those of particular interest, and some only in the general comments box, overall there were hundreds of comments.

X. Accelerating Precision Health for All of Us: The All of Us Research Program

Eric Dishman, Director of the All of Us (AOU) Research Program, provided the Council an overview of the All of Us Research Program.

He began his presentation with a moving recollection of his 23 years as a cancer patient and survivor. Trained as a social scientist and a long-time healthcare executive with Intel, his cancer is now cured thanks to precision medicine. He had his whole genome sequenced, and is now part of longitudinal study researching the role of chemical exposures in cancer. He was named Director of the All of Us Research Program in 2016, when it was known as the Precision Medicine Initiative.

He noted that environmental data has been a priority for AOU, stemming from a very broad definition of environment.

He described the mission and objectives of the AOU program. The mission is “to accelerate health research and medical breakthroughs, enabling individualized prevention, treatment, and care for all of us.” The objectives are to nurture relationships with one million or more participants, to deliver the largest, richest biomedical dataset ever, and to catalyze the robust ecosystem of researchers and funders hungry to use and support it. He summarized the program’s approach and protocol, involving a rich, longitudinal resource of deep clinical, environmental, lifestyle, and genetic data from one million participants over a long period of time. It will encompass a broad diversity of participants and researchers. He said that recruiting would concentrate on health care provider organizations with which the AOU will partner, as well as direct volunteers. He anticipated that new protocols would be issued every 3-to-3-1/2 years. The strategy is to provide diverse data types for participants as a national resource, including environmental, biological/clinical, social, and behavioral data. He summarized the approved initial version of the protocol, which involves enrollment, surveys, physical measurements, and collection of biosamples. The major building blocks of the program will be a data and research center, a biobank, a participant center, a participant

technology systems center, health care provider organizations, and communications and engagement efforts.

He showed the lineup of current consortium members, including many large organizations with national reach. He summarized the program's progress over the past 18 months.

Mr. Dishman described how the AOU is engaging the environmental research community. He listed the members of the Liaisons Coordinating Team, including Dr. Janet Hall from NIEHS, which is planning the AOU Scientific Research Priorities Workshop, which is scheduled for March 21-23, 2018 in Bethesda, Maryland. The workshop will focus on planning research priorities for the near-, mid-, and long terms. He listed the NIEHS invitees (Dr. Hall, Dr. Birnbaum, Dr. Stephanie London, and Dr. Dale Sandler) and several NIEHS-related external stakeholder invitees.

He listed the assays selected for initial use, which broke down into "Yes", "Maybe", and "No" categories, with some planned to be used in all one million participants (and/or a subset), a subset only, or not at all, respectively. He noted that genomics research is not part of the initial program. He described other environmental data investments, including a survey module devoted to environmental exposures and occupational health. He said that an environmental working group within the consortium would be announced soon.

He described efforts to ensure exposome and geographic diversity, with assistance from Council member Dr. Marie Lynn Miranda.

Mr. Dishman listed the specific ways that members of the EHS community can help the AOU, including submitting use cases on the AOU website, assistance in identifying the best tools, advice on issues such as future data linkages, biospecimens, assays and mHealth devices for future AOU protocol iterations, and help in refining exposome segmentation.

In conclusion, he asked "What new questions can we ask, and data types can we collect, with a diverse cohort of a million or more people to understand the impact of a broad definition of environment?"

Dr. Eskenazi said she was "super-excited" about the AOU, and that "in some ways, it is the National Children's Study made good." She noted that there would be a number of pregnancies during the program, and hoped that the ECHO (Environmental Influences on Child Health Outcomes) protocols would be integrated. She asked Mr. Dishman about the planned biological samples to be collected. She felt that the planned sample sizes would be too small to effectively measure pesticide exposures, and implored Mr.

Dishman to collect more urine. He thanked Dr. Eskenazi for the input, and pledged to pass it on.

Dr. Feinberg endorsed the population-based approach being taken by the AOU. He recommended careful preservation of samples for later study, and said that Dr. Dishman may want to interface with investigators from the NASA Twins Study for advice on preservation and working with small sample sizes. Dr. Birnbaum noted that several federal agencies other than those depicted by Dr. Dishman would be rich sources of data and information for AOU.

Dr. Brown said he appreciated the initial section of Dr. Dishman's presentation, as evidence of "a deep humanism and wonderful sensitivity" in the project. He encouraged inclusion of a team of ethnographers in the AOU program, including selection of a subset of participants for in-depth follow-up at the ethnographic level, as well as a subset to be interviewed regarding individual report-back about how they understood and used their results. Dr. Dishman said that the latter suggestion is "very much part of our plan." He said there has been some ethnographic work already, helping to define what is a participant, and what is a researcher.

Dr. Lichtveld thanked Dr. Dishman for sharing his personal story, which reminded her of her Gulf Coast community. She asked him about the program's commitment to intergenerational work. He noted some of the information that came out of post-mortem assessments of the National Children's Study, including the caution against "trying to be all things to all people." He said that there is a commitment to including children in the AOU, although the details of their involvement have not yet been worked out. He said that the program is looking at intergenerational aspects, including working to determine the appropriate number of children to be useful to people doing children's research or aging research, while not losing the focus on involving people at different life stages so that the factors that led to the emergence of health conditions over time can be better understood.

Dr. Ho said that "we should learn from China," such as its facial recognition technologies and other real-time data collection tools. She also recommended use of ZIP codes to aid health disparities research. Mr. Dishman replied that he had spent much time in China during his business career, and noted that there are interesting ethical challenges brought out by some of the technologies Dr. Ho described. "I know the potential of using those additional data types that could be really helpful for health research," he said, "but obviously the privacy and [other] implications of them are quite large."

Dr. Birnbaum reiterated Mr. Dishman's call for people to go to the AOU website and provide case studies and suggestions to the initiative. Dr. Hall added her

encouragement for environmental health scientists to provide their input, to help get in on the ground floor of EHS information being included in the AOU protocols. Dr. Collman suggested that researchers encourage their postdocs to add their input on topics they wished to pursue in their careers, so that future researchers would be represented and provided with the resources they will need to do their work. Dr. Hall noted that the general public is also allowed to provide input.

XI. Tackling Complex Problems: Combined Exposures and Mixtures Research at the National Toxicology Program

Dr. Cynthia Rider from the DNTP Toxicology Branch updated the Council on NTP mixtures research.

She provided background information on mixtures research, including definitions of terms such as defined, complex, and whole mixtures. She described the philosophy of mixtures study, broken down simply as “top down” and “bottom up” approaches, as well as the applicable concepts of additivity involved.

She reviewed the 2011 NIEHS Mixtures Workshop, which was intended to identify and focus on key issues presenting challenges in mixtures research. She discussed the key issues that emerged in detail, and noted that NIEHS has a Combined Exposures Mixtures (CEM) Working Group that helps coordinate mixtures research throughout NIEHS.

She detailed the three main approaches to mixtures research at NTP:

- Component-based approaches, which focus on individual chemicals in a mixture
- Whole mixture approaches for estimating the toxicity of complex mixtures
- Systems biology approaches to evaluate mixtures based on how exposures affect human health outcomes

Based on conclusions from the 2011 workshop and in response to Goal 4 of the NIEHS Strategic Plan, NTP has developed multiple mixtures-based projects, which are directed at three major challenges:

- Decreasing uncertainty in component-based risk assessments that utilize individual chemical data to estimate health effects from mixtures
- Developing approaches to evaluate the health effects of whole, complex mixtures
- Using knowledge of systems biology to inform understanding of health effects from exposure to mixtures

Research programs aimed at addressing those focus areas included polycyclic aromatic compounds, botanical dietary supplements, and environmental mixtures that contribute to cancer development.

Dr. Schantz asked Dr. Rider about the mixtures research grant portfolio, and whether the animal toxicology community is moving more toward using the whole mixtures approach, beyond the individual chemicals approach. Dr. Rider replied that there were very few examples of that, and that there is a need for more investigators to use whole mixtures in animal models.

Dr. Manautou asked Dr. Rider to provide more explanation of her data graphic depicting the determination of sufficient similarity. She noted that only in the *in vivo* section of the graphic did the size of the circles matter. She added that in the *in vitro* section, hierarchical clustering was employed for the entire dataset, without looking at the magnitude of effect in each endpoint.

XII. Building the 4D Nucleome

Dr. Lisa Chadwick briefed the Council on the NIH 4D Nucleome (4DN) Program, which is funded as part of the NIH Common Fund, and is led by NCI, NIDDK, and NIBIB. Dr. Chadwick is involved as the Program Director.

She said that past efforts in genomics and epigenomics thought about DNA in a linear fashion, but that in reality the genome is jumbled up in the nucleus, interacting with various structures in the nucleus and with itself, forming what is called the nucleome. The fourth dimension being taken into account is time, as the nucleome changes over time. The 4D Nucleome Program seeks to advance understanding of:

- The principles underlying nuclear organization of mammalian genomes in space and time
- The role that nuclear organization plays in gene expression and cellular function
- How changes in nuclear organization affect normal development and disease

The program has a major focus on delivering tools and resources to the broader scientific community to help catalyze the field. There has been a number of funding announcements focused on different aspects of the field, along with a data coordination center and an organizational hub. To help achieve the goals of the program, 4D Nucleome awardees have organized themselves into a 4DN Network.

Dr. Chadwick provided details about one of the new technologies under development by the 4DN program, genome architecture mapping, which combines ultrathin section of

nuclei with next-generation sequencing of DNA or RNA to measure several 3D nucleome parameters.

She directed Council members to the 4DN data portal, where the program's data is available: 4dnucleome.org. She noted the program's publication policy that relies on preprint servers, in an effort to disseminate the information as soon as possible.

To explain the relevance of the project to NIEHS, she noted that "in the future, we'll start to see our investigator community looking at how environmental chemicals impact this process of nuclear organization."

XIII. Adjournment

Dr. Collman thanked everyone involved in the meeting for a stimulating discussion, and thanked the staff who contributed their efforts to the meeting, particularly those of Liz McNair and Dr. Mastin, who were able to adjust to the last-minute changes in light of developments at the Federal government level. Dr. Birnbaum added her thanks, saying that it was "an especially great day." She reiterated the call for all to read through the draft NIEHS Strategic Plan and to contribute to the All of Us cohort. .

The meeting was adjourned at 5:00 p.m., February 12, 2018.

CERTIFICATION:

/s/
Linda S. Birnbaum, PhD, DABT, ATS
Chairperson
National Advisory Environmental
Health Sciences Council

/s/
Gwen W. Collman, PhD
Executive Secretary
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Attachment:
Council Roster