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

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

June 4-5, 2019

The National Advisory Environmental Health Sciences Council convened the open session of its one hundred fifty-seventh regular meeting on June 4-5, 2019 in the Rall Building, Rodbell Auditorium, National Institute of Environmental Health Sciences, Research Triangle Park, NC. The closed session of the meeting was held June 4, 2019.

The meeting was open to the public on June 4, 2019 from 2:00 p.m. to 4:45 p.m. and June 5, 2019 from 8:30 a.m. to 3:45 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 June 4, 2019 from 1:00 p.m. to 1:45 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

William Cibulas, Jr., PhD (*ex officio*) (by telephone)
José Cordero, MD, MPH
Irasema Coronado, PhD
Gary Ellison, PhD (*ex officio*)
Lynn Goldman, MD, MPH (telephone 6/4, in person, 6/5)
Della Hann, PhD (*ex officio*)
Shuk-Mei Ho, PhD
Terrance Kavanagh, PhD
Katrina Korfmacher, PhD
Maureen Lichtveld, MD
José Manautou, PhD
Donna Mendrick, PhD (*ex officio*)
Edith Parker, DrPH
Marla Perez-Lugo, PhD
Brad Racette, MD
Susan Schantz, PhD
Andy Shih, PhD
Michael Slimak, PhD (*ex officio*)
Patrick Sung, DPhil
Robert Tanguay, PhD
Robert Wright, MD, MPH

NIEHS Staff

Kathy Ahlmark
Janice Allen, PhD
Robin Arnette, PhD
John Balbus, MD, MPH
David Balshaw, PhD
Martha Barnes
Linda Bass, PhD
Sharon Beard, MS
Linda Birnbaum, PhD
Tiffany Bowen
Abee Boyles, PhD
Jed Bullock
Danielle Carlin, PhD
Jennifer Collins
Gwen Collman, PhD
Yuxia Cui, PhD
Sally Darney, PhD
Christie Drew, PhD
Chris Duncan, PhD
Anika Dzierlenga
Lisa Edwards
Sue Fenton, PhD
Symma Finn, PhD
Amanda Garton
Barbara Gittleman
Kimberly Gray, PhD
Jenny Greer
Janet Hall, MD, MS
Quaker Harmon, MD, PhD
Astrid Haugen
Michelle Heacock, PhD
Heather Henry, PhD
Jon Hollander, PhD
Mike Humble, PhD
Bonnie Joubert, PhD
Helena Kennedy
Steve Kleeberger, PhD
Alfonso Latoni, PhD
Cindy Lawler, PhD
Chris Long
Sarah Luginbuhl
David Malarkey, DVM, PhD
J. Patrick Mastin, PhD
Kim McAllister

Steven McCaw
Liz McNair
Carolina Medina
Aubrey Miller, MD, MPH
Rosemary Moody
Alison Motsinger-Reif, PhD
Sri Nadadur, PhD
Sheila Newton, PhD
Liam O'Fallon
Nicole Popovich
Tina Powell
Alicia Ramsaran
Carol Schreffler, PhD
Thad Schug, PhD
Sheena Scruggs, PhD
Dan Shaughnessy, PhD
Varsha Shukla, PhD
Kimberly Thigpen Tart, JD, MPH
Laura Thomas, PhD
Claudia Thompson, PhD
Brittany Trottier
Steven Tuyishime, PhD
Fred Tyson, PhD
Clarice Weinberg, PhD
James Williams
Mary Wolfe, PhD
Leroy Worth, PhD
Rick Woychik, PhD
Demia Wright, MPH
Dahea You
Darryl Zeldin, MD

Members of the Public Present

Lynn Albert, MDB Inc.
Sara Amolegbe, MDB Inc.
Megan Avakian, MDB Inc.
Larisa Bennett, MDB Inc.
Abigail Brewer, MDB Inc.
Kenda Freeman, MDB Inc.
Adeline Lopez, MDB Inc.
Matthew Cave, MD, University of Louisville
Ernie Hood, Bridport Services, LLC

I. Call To Order and Opening Remarks

Division of Extramural Research and Training (DERT) Director Gwen Collman, Ph.D., welcomed attendees and called the meeting to order. She asked attendees in the room to introduce themselves.

II. Consideration of February 2019 Meeting Minutes

Approval of the February 2019 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.

III. Report of the Director, DERT

Dr. Collman updated the Council on recent developments in the division.

She welcomed new DERT staff members Jenny Greer and Anika Dzierlenga.

She described recent NIH-level policy changes resulting from issues connected to the NIAAA MACH (Moderate Alcohol and Cardiovascular Health) study, which was discontinued. She mentioned that to maintain public trust in NIH, processes must support transparency, impartiality, and research integrity. That effort informs NIH engagement with the extramural community via program officer roles and responsibilities and funding opportunity development. She listed several newly defined general principles in those areas. She also discussed several elements designed to enhance workshop transparency, and described the process of sharing concepts with the Council going forward. As part of that process, she delineated several co-funded initiatives planned for FY2020.

Dr. Collman briefed the Council on a process of transitioning from non-parent Program Announcements to Notices of Special Interest (NOSIs). The goal is to increase efficiency in expressing interest in a scientific area and decrease efforts spent on writing, reviewing, and publishing non-parent PA for involved NIH staff. A number of ICs have already been using the approach.

She listed several DERT-sponsored meetings and workshops that have taken place since February, taking place from NIEHS and Raleigh to India, Canada, Italy, and Uganda. She also described several events and activities related to Autism Awareness Month, which was in April. Finally, she discussed a workshop she had attended May 26-27, Reducing the Cardiopulmonary Impact of Particulate Matter Air Pollution in High Risk Populations, which was co-sponsored by NIEHS, NHLBI, EPA, CDC, and CMS.

IV. Concept Clearance: Pregnancy as a Vulnerable Time Period for Women's Health

Dr. Abee Boyles from the Population Health Branch presented the concept to the Council. The project's aims are to accelerate research projects studying the effects of environmental exposures on maternal physiology, endocrine, and metabolic functions during and shortly after pregnancy, and potential long-term health effects in the mother. It will aid understanding of how environmental exposures affect women during and after pregnancy, and identification of modifiable factors for disease prevention.

Dr. Boyles described how the project aligns with the NIEHS Strategic Plan and the Trans-NIH Strategic Plan for Women's Health Research. She discussed the reasons for focusing on changes during pregnancy as an especially vulnerable window of susceptibility to environmental exposures. She provided several examples of NIEHS-supported studies supporting interest in the area, including more than 30 NIEHS-funded birth cohorts with banked samples that could be used to consider maternal outcomes. She listed active NIEHS studies in animal models and human populations.

She noted that the scope of the RFA would address the goal of spurring animal-based mechanistic and epidemiological research to investigate exposures during pregnancy and the post-partum period with impacts on maternal health and determine the life-long effects of exposures on a woman's health. Potential areas of investigation include:

- Environmental influences on maternal physiology during pregnancy and resolution after birth
- Modifiable factors that limit the physiological impact of exposures during this window
- Susceptible populations identified for targeted interventions in the future
- Long-term health effects in the mother from environmental exposures during pregnancy

The proposed initiative would be a one-time RFA for 6-8 R01s, with a total cost of approximately $4 million per year for up to 5 years. It is proposed to begin in 2020.

Dr. Schantz was the first Council discussant. She said that she very much liked the proposal, in that it highlighted the fact that the focus has always been on the children, with little attention to the mothers. She appreciated that it includes both mechanistic laboratory animal work and population health work. She hoped that the effort would include grants to address health disparities. She was concerned that existing cohorts may not have much data on the mothers.

Dr. Wright was the second Council discussant. He agreed that the concept addresses an important question, and is very cost-effective due to leveraging existing birth cohorts. He said he fully supports the concept.

Dr. Lichtveld asked Dr. Boyles to clarify the timeline involved. Dr. Boyles noted that there had been little focus beyond the term of one year post-birth, and the focus would be beyond that time as it would be appropriate for the outcome. Dr. Lichtveld mentioned that there are cohorts with sufficient biospecimens banked to feed and link and cross-fertilize with the HHEAR program as well. She suggested in addition to looking at glucose by itself, in terms of gestational diabetes and Type 2 diabetes, to look at it as an entity of cardiovascular disease as well.

Dr. Cordero added his endorsement of the project. He asked what would be considered the period prior to pregnancy. He discussed risks of preterm birth, particularly high risk associated with a short interval between pregnancies. Dr. Boyles replied that the period prior to pregnancy would depend on the exposures being studied and how persistent they might be. She said 3 months is typical, but not always appropriate. She said it would be interesting for someone to study the impact of a short pregnancy interval. Dr. Cordero noted that exposures tend to be continuous.

Dr. Ho asked if the proposal would cover maternal mortality, which is an increasing problem in the U.S., particularly in states with a significant immigrant population. Dr. Boyles said it had been considered, but it presented methodological issues, including likely insufficient sample size. Dr. Collman added that the Office of Research on Women's Health has identified maternal mortality as a priority, and is working on a variety of initiatives in that area, which NIEHS will no doubt want to be part of.

Dr. Hann said that NICHD welcomes having partners in this area. Regarding maternal mortality, she cited two recent meetings addressing the topic, with a workshop on morbidity coming soon. She said that the recent conference was looking more at societal factors. She said that learning more about the impact of pregnancy on the future of a woman's health, and child health, is incredibly important for NICHD, and that she was gratified to see this initiative.

Dr. Sung said that he loved the concept, but was surprised that more was not known about the impact of pregnancy and birth on a woman's health later in life. He noted that the gender of the child may have an influence. He said that prioritization will be important with so many potential subjects for study. "This could be a really impactful program," he observed. Dr. Boyles asked Dr. Sung if he thought that the prioritization he was recommending should be conducted now, to focus the scope.

Dr. Birnbaum noted that with interest from NICHD, NIMHD, and ORWH, it is likely more funding will be added to the RFA from those and other partners.

Dr. Coronado recommended that teen mothers be taken into account in the program, as well as elevated age pregnancies, as both represent instances of preventable deaths.

Dr. Manautou asked whether therapeutic interventions would be considered along with mechanisms and epidemiology studies. Dr. Collman said that there is not yet a good base of literature with which to predict outcomes, but interventions would come in a later phase once a good base of scientific knowledge is established.

Dr. Kavanagh said that the consideration of teen pregnancy is interesting in the context of endocrine disruption and earlier menarche in some populations, which brings the potential for disparities.

Dr. Perez-Lugo said that given the increase in natural disasters associated with climate change, research in that area should inform protocols in disaster management to prevent later health conditions. Dr. Korfmacher suggested developing a survey that would be used to collect baseline data on the social science associated with disasters. Dr. Boyles said that idea had not been considered previously, and noted that trying to find pregnant women during a disaster would be challenging. Dr. Birnbaum noted that there have been cohorts recruited during disasters, with samples taken in some cases, offering an opportunity to leverage existing data with follow-up studies.

Dr. Racette felt that the program may be restricted to health outcomes in a narrow window. Dr. Boyles said that that issue had been considered. Dr. Collman asked Dr. Racette if he was referring to a need for pilot data. He agreed, noting that there may be some interesting ideas in the proposal that are not quite ready for R01-level funding.

Dr. Ellison said he finds the statistic that black women are 3-4 times more likely to die from pregnancy-related causes than white women to be remarkable. He asked Dr. Boyles whether she was thinking of expanding or broadening the scope of the project to include contextual factors (such as neighborhood features) that may increase the risk for outcomes. Dr. Boyles said that it may be included when working with partners and their interests, expanding the lens beyond environmental health. Dr. Parker agreed that it would be important to include social stressors in the research.

Dr. Collman asked for and received a motion and second to approve the concept. The Council voted unanimously in favor.

V. Cell Line Models of Cytotoxic Response – Integration of Statistical Models Development and Genetic Association Mapping

NIEHS Scientific Director Darryl Zeldin, M.D., introduced the speaker, Dr. Alison Motsinger-Reif, who recently joined NIEHS to be Chief of the Biostatistics and Computational Biology Branch.

The investigation and discovery of genetic factors that determine differential drug response is the fundamental goal of pharmacogenomics. Lymphoblastoid cell lines (LCLs) have become a well-established model for understanding dose response, including exploring the genetic etiology of such drug response. Dr. Motsinger-Reif presented the results of genome-wide association mapping studies (GWAS) for a large number of commonly used anti-cancer drugs, along with the methods development studies behind the high-throughput mapping. This GWAS screen produced interesting potential candidate genes, and she presented initial results of functional/clinical follow-up of those candidates. She also presented the initial results of clinical validation results from top candidates. Additionally, she described topical challenges and new directions related to drug combinations. The results demonstrate an integrated approach to bioinformatics methods development and application.

Dr. Manautou asked Dr. Motsinger-Reif whether she was measuring viability to find a cytotoxicity or a cytostatic effect, and if it is one versus the other, the impact on the genetic association mapping outcomes that she had. Dr. Motsinger-Reif replied that it is cytotoxic, as a blunt measure of cytotoxicity. Dr. Manautou asked if she had looked at idiosyncratic drugs. She replied that she had considered it in a brainstorming way, but focused on the anti-cancer drugs first. She said it would be a good next direction for the work.

Responding to an observation by Dr. Sung, Dr. Motsinger-Reif said that her group had hypothesized that LCLs were a better representation of the host genome than the cancer genome.

Dr. Ho noted that there were currently a number of preclinical trials looking at issues of drug resistance. In that context, she asked Dr. Motsinger-Reif what advantages her system would have. She replied that the hope is that it would contribute to precision medicine. With the large number of samples available to the LCL model, she hoped to discover new genes that should be targeted in preclinical experiments.

Dr. Kavanagh asked about the issue of public versus private alleles, and the frequency of the SNPS, as well as the inverse relationship of effect size for discovery. He asked whether that had been built into the group's statistics. Dr. Motsinger-Reif said the system has the exact same limitations and advantages as a GWAS study does. She said her group is working on a pipeline to testing rare variants using the Thousand Genomes data. Dr. Kavanagh asked about concerns that LCLs not being metabolically competent, and noted that there is work showing that they can be de-differentiated to IPSCs and then re-differentiated. He asked if there had been any thought to doing that. Dr. Motsinger-Reif said it was a great suggestion; but had not been considered thus far.

VI. Report of the Director, NIEHS

Dr. Birnbaum briefed Council on Institute developments since the February 2019 Council meeting.

She updated the group on budget and appropriations matters. She said a budget for the next fiscal year is not yet in place. She anticipates a continued increase in the overall budget, although the President's proposed budget includes large cuts to NIH, which are unlikely to be adopted. The House mark for FY2020 shows a $2 billion increase for NIH, and a $38 million increase for NIEHS. "At this point, the budget looks relatively promising," she concluded.

Dr. Birnbaum summarized her recent Congressional testimony on PFAS, as well as recent Congressional in-person briefings to both Senate and House staffers. She also described recent Congressional hearings on environmental health.

Turning to science advances, she briefly summarized several recent publications by NIEHS/NTP personnel or grantees. She began with two One NIEHS papers, one on DNA methylation in mice, the other on human leiomyoma cell proliferation from bisphenol A. She cited four DIR studies: the first on endogenous glucocorticoids, the second on the cryo-EM structure of an essential ribosome assembly, the third on methylation-based biological age and breast cancer risk, and the fourth on the role of dietary phytoestrogens and the nuclear receptor PPARγ in adipogenesis. She described two papers from DNTP; one on use of Tox21 screening for evaluation of botanical and dietary supplements, the other on screening for neurotoxic potential of 15 flame retardants using freshwater planarians. Finally, she recognized five DERT publications: elevated serum chemokines associated with endometriosis and uranium exposure, the human gut bacterial genotoxin colibactin, somatic mutation involvement with chronic liver disease, an emergent illness severity model, and epigenetic marks of prenatal air pollution exposure.

Dr. Birnbaum updated the Council on developments at Environmental Health Perspectives, including recruitment of a new editor-in-chief. She summarized existing Children's Environmental Health research programs, as well as plans for renovation of the Rodbell Auditorium, where Council meetings are held. She recounted several relevant past events and looked ahead to upcoming events through September.

She summarized several recent awards and recognition given to NIEHS personnel and grantees, including the most recent Outstanding New Environmental Scientist (ONES) awardees. .

VII. Concept Clearance: Mechanism for Time-Sensitive Opportunities in Environmental Health Sciences (R21)

Martha Barnes from the Population Health Branch briefed the Council on the proposed reissue of an RFA related to the NIEHS Time-Sensitive Research Program, which originated in 2007, with the first NIEHS Program Announcement coming in 2010. She described the history of the program, the process itself, and an analysis of the portfolio involved.

The Time-Sensitive Program is designed to offer significantly faster review and funding turnaround than unsolicited R21s. The research has resulted in important findings that may have a positive impact on public health. In some instances, the program offers connections to longer-term research. Ms. Barnes provided specific examples of time-sensitive research projects that have added significantly to scientific knowledge or have connected to longer-term research.

The 2019 RFA is a reissue of RFA-ES-16-005, and includes Superfund Research Program interests, such as fate and transport and application of promising remediation methods. Eligibility requirements to include foreign institutions or components are being considered, and the language of the RFA has been strengthened to emphasize the uniqueness and importance of the proposed research. Although mechanism options have been revisited prior to each re-issuance of the program, in this instance the R21 mechanism is still considered to be the most appropriate.

Dr. Cordero was the first Council discussant. He said it is a very important program, citing the experience with Hurricane Maria in Puerto Rico. He said that the ability to make proposals with letters of intent with a short period of turnaround is crucial, and he supported the proposal.

Dr. Parker was the second Council discussant. She agreed that it is a wonderful program, and said she was impressed with the timeline involved. She endorsed the addition of the Superfund interests. She hoped that the approval timeline could be made even shorter, despite the constraints involved. She said she liked the flexibility involved, such as including policy research.

Dr. Lichtveld said the program is very much needed. She noted that she lives in an area where disasters occur frequently, and the program has been instrumental in getting research into the field as quick as possible. She observed that "disasters know no borders," and recommended inclusion of international components.

Dr. Parker asked about opportunities for sharing across agencies. Dr. Collman replied that some of the other NIH ICs have developed their own rapid response programs, and that sometimes there is coordination, sometimes there is room for improvement. It has been approached as individual situations occur. Dr. Manautou asked how different the NIEHS program is compared to those of other ICs. Dr. Collman said that they are in their own mission areas, with quite different science than that being sought by NIEHS.

Dr. Perez-Lugo said she had seen a negative bias toward the local universities related to the program, and asked whether that had been noted and addressed to allow the local universities to initiate research or add capacity. Ms. Barnes said there have not been programs specific to time-sensitive research to add capacity, but other programs have addressed the situation. She said she had not seen a negative bias, with the best applications funded regardless of where they came from. Dr. Collman added that through the Disaster Response Research (DR2) program, considerable capacity had been built in the grantee community. She said that the grants are not limited to the local, and that other subject matter experts are allowed to partner, with community engagement encouraged so that the research can be implemented appropriately.

Dr. Mastin said that the larger universities have more infrastructure to enable faster turnaround, while NIEHS has taken steps to mitigate that potential advantage.

Dr. Goldman said she was glad the program would be continued, and hoped that ways to process R21s more efficiently were being discovered. "What we really want is to be able to get out there right away," she observed. She presented an idea for a completely different mechanism that would allow for identification of potential grantees before disasters, allowing researchers to have pre-reviewed tests and methods ready to hit the ground. Dr. Collman noted that DERT did have a mechanism for fast-tracking administrative supplements. Dr. Birnbaum made the point that the time-sensitive awards are not just for disasters.

Dr. Hall noted that part of the DR2 program was working with the regulatory aspects, helping to get research out into the field sooner rather than later. She pointed out that DR2 has resources such as pre-approved questionnaires available on its website. Also, a package or template for IRBs on how to review time-sensitive research proposals should be forthcoming within the next six months or so.

Dr. Racette said that one way to accelerate the process would be to emulate what is being done in the clinical trials world, through use of central IRBs, with months of differences in approval times. Dr. Hall said that care must be taken that the approvals are well-informed, particularly in the case of vulnerable populations who may be present at or working in disaster sites.

Dr. Korfmacher said she was particularly interested in the non-disaster-related components of the mechanism covering predictable, man-made disasters such as fracking. She suggested re-wording some of the language in the proposal.

Dr. Collman asked for and received a motion and second to approve the concept. The council voted unanimously to approve the concept.

VIII. Concept Clearance: A Translational Lens for Children's Environmental Health: A New Vision for 2020

Concept Clearance: A Translational Lens for Children's Environmental Health: A New Vision for 2020

Dr. Kimberly Gray from the Population Health Branch presented a concept for a new children's environmental health (CEH) program that will facilitate translation of the research into tangible tools, methods, messages, and activities to protect and improve children's health from environmental threats.

Dr. Gray presented considerable background information about the legacy of NIEHS research in CEH, particularly the NIEHS and EPA CEH Research Centers. In the decade from 2008-2018, NIEHS funded a grant total of more than $1 billion in CEH research; more than $100 million in 2018 alone. There remains considerable investment in ongoing CEH research program by NIEHS and NIH.

Capitalizing on the strong base of fundamental knowledge established over many years, NIEHS is proposing the use of a center-like mechanism to create a collaborative network of CEH Translation Centers across the U.S. Each center will support a diverse base of subject matter expertise in CEH and health communications (e.g., health behavior, health education, risk communication, health policy) to accelerate the use of research findings into practice and policy to protect children's health. Centers will be encouraged to look outside their academic institutions to bring in the right balance of subject matter expertise and disciplines to support research translation efforts and activities.

Each center will be managed and directed by two Program Directors: an established CEH investigator and a health communication researcher. The center will be comprised of three components: a Research Translation Component, a Development Component, and an Administrative Component. The program's goals are to:

- Facilitate interaction among experts in CEH science, health, and risk communication, behavioral and social sciences, as well as engaging stakeholders to move the science into public health and clinical practice.
- Synthesize and translate extant CEH research into tangible communication tools, dissemination methods, health messages, and educational activities that can be used by stakeholders, including at-risk populations, affected communities, and the clinical or public health community to improve children's health.
- Stimulate pilot projects that address emerging environmental health concerns/exposures, as well as test new tools, methods, and/or intervention/prevention strategies.

A P2C or U2C center mechanism is proposed, with a December 2020 start date. The RFA would fund about five awards, with an estimated total of $5 million committed in FY2020.

Dr. Parker was the first Council discussant. She said that she found the proposal to be very exciting, "another example of the creativity and leadership of NIEHS in pushing not only NIEHS grantees but potentially all NIH grantees by presenting a model." She felt that it could address the challenge of translating research by devoting resources and emphasis to that effort. She anticipated that there would be concerns among some who are accustomed to the traditional children's centers model, particularly that there may be fewer resources committed to basic and exposure research. She noted that there are alternative mechanisms available to continue research efforts when a particular funding mechanism is discontinued. She endorsed the emphasis on health communications in the proposed centers, as well as the emphasis on reaching outside local center expertise. She said some areas would need clarification going forward, such as impacts and deliverables, and who the target audience is. She discussed the broader NIH activities in dissemination and implementation science that this could be linked to, and suggested that that area be included in the health communication section as a suggested team member or option. She liked the aspect of tapping international expertise, although most of the older centers were more focused on local issues.

Dr. Shih was the second Council discussant. He said he found several elements of the program to be exciting. He offered a community stakeholder perspective. He said that in his group, they spend much time trying to determine how to communicate scientific information to their constituency. He said they have funded research themselves on how to digest and present important scientific outcomes to advocacy communities. In that context, the translation centers program is very welcome, he noted. He said that although the work has been supported by community stakeholders and advocates, it has been largely ignored by mainstream practitioners, resulting in a disconnect between advocates and the researchers. He expressed concern that targeting professionals in this program could result in less attention to community advocates, raising the question about target audience. He said the primary audience of social media would be the community, not necessarily professionals. He hoped that there would be attention to how to use community advocacy to accelerate and enhance the impact of translational work.

Dr. Wright advocated the idea of moving toward translational science. He mentioned that he is a pediatrician, and said that a question he often receives when he is giving a community talk is, "How come my pediatrician doesn't know anything about this?" He said that one reason is that medical education does not include environment. He suggested an additional core (or component) for medical education that would require residency directors to be involved. By engaging them in the process, it might be a good

way to get environmental health science into the medical curriculum. He envisioned a snowball effect going forward, as more and more institutions would include environmental health in the medical curriculum. He added that similar contacts with nursing schools and family medicine programs could also be beneficial.

Dr. Cordero said he found the proposed program to be very thoughtful, particularly in that there is a different environment from when the children's centers were started. He supported the idea of medical training, as well as involving nurses, who are key to educating patients. He added that most health care professionals are required to pursue annual continuing education, which could be an important way to bring in new knowledge for those already in practice.

Dr. Korfmacher expressed concern that the program summary appeared to perpetuate the vision of translation as one-way, while NIEHS is a leader in acknowledging and developing the importance of two-way engagement. She encouraged bringing that principle more strongly into the proposal. She said that the development and support of partnerships, especially at the local level, has been far more effective than communication. Thus, focusing on communication should not be the key outcome for translation of environmental health research, while reducing exposures is. She questioned whether it is the role of NIEHS to be investing in development of educational theory. She suggested that the center co-lead be a translation and engagement professional, as opposed to restricting it to communication researcher. Regarding the developmental component, she said it consists of pilot projects for new research and development of translational approaches. She felt that those two elements are fundamentally different, requiring different prioritization strategies, review criteria, reviewers, allowable expenses, and even formats. She recommended separating the two functions within the developmental component. Regarding the translational endpoints and targets, she expressed concern that the term "children's environmental health research translation" tends to focus specifically on clinical aspects, which by its nature emphasizes individual action over community engagement or policy action. It should have a broader scope, perhaps changing the terminology.

Dr. Schantz said she was confused about what the pilot projects would cover. She noted that she was unfamiliar with the proposed mechanisms, and asked Dr. Gray to describe them in more detail. Dr. Gray discussed the background of how the mechanisms came to be chosen. She said that the program is a reframing one that has been in place for a long time, so that it could be seen through a lens broader than just community engagement. The components have a research base that is required for translation. The pilot project has been used to generate new ideas, but is based on what is needed for the translation. It could be the basis for external, interdisciplinary collaborations. She delineated the mechanisms from the more traditional P30. She said the P2C mechanism is not focused on research.

Dr. Lichtveld noted that there was an opportunity to build in enterprise evaluation up front. Regarding target audiences, she said there were a number of built-in partners that could be worked with, and named several potential professional organizations as potential partners. She said that in this case, performance evaluation becomes key to see whether there has been uptake, whether it is CME or another credentialing unit. Also, there is an opportunity to evaluate how to build and increase environmental health literacy.

Dr. Manautou noted that his university had just approved a mandate that there be environmental literacy in general education courses, so this program could even reach the undergraduate level. It could also enter the realm of accreditation.

Dr. Coronado discussed her work with a local community group of poor people and children. She noted that sometimes the only health care provider the children would see is the school nurse. School districts need to be part of the translation program, she said. "The more that we can do to also address the structural impediments to good health and good environment is critical," she observed.

Dr. Goldman said she was excited to see the translational science framework brought to life in a program. She said she was also a pediatrician who had long been involved in training pediatricians in environmental health, but that this program is not just about training clinicians. It is certainly about changing clinical practice, but that is perhaps the most obvious aspect. She noted that changing the behavior of industry should also be addressed. She recommended flexibility: "I think it's very, very important to provide the applicants with the ability to customize their approaches around what they know about the community." She agreed with the idea that the co-PI could be another type of behavioral scientist. She approved of the chosen mechanism, based on her experience.

Dr. Racette said he was concerned about an over-focus on medical education. He said the problem is not just about education, but also about practicality of implementation in practice. He felt that broader ideas for implementation would be likely to be effective.

Dr. Wright was concerned about the definitions of the possible pilot projects associated with the program. Dr. Collman agreed that more work was needed to define the pilot projects, to determine the best approach to them for this program.

Dr. Birnbaum said she had heard much excitement about the formation of the translation research centers, to take advantage of the $1 billion in research over the past decade, and the $100 million funded last year, to "really move it out into the field."

Dr. Slimak said that NIEHS is moving in the right direction, and that EPA likes the approach. He noted that the heart of EPA's research planning is translational work.

"The relationship that EPA has had with NIEHS in the Children's Health Centers for 20 years has been fantastic," he observed, but given current budget realities, EPA could no longer commit to supporting the partnership. He noted that EPA has its own internal children's health research program, and on that basis, EPA "would love to work with you as you implement this concept."

Dr. Ho recommended integration with small business and entrepreneurship, representing another level of translation that would be outside both the public health and clinical sides.

Dr. Collman asked for and received a motion and second for the Council to approve the concept. The vote was unanimous in favor.

IX. Concept Clearance: Research to Action Program Renewal

Dr. Symma Finn and Liam O'Fallon from the Population Health Branch briefed the Council on the concept regarding renewal of the Research to Action (R2A) program.

The R2A program promotes and advances academic-community partnerships to address environmental health concerns of diverse communities and to ensure authentic community participation in research leading to public health actions. The existing projects and completed ones have addressed many critical environmental health risks plaguing communities nationwide and many different populations most at risk from environmental factors. However, gaps exist in the issues addressed and which communities are served. The vision is for a program that is nimble enough to incorporate research on new environmental health threats or the increasing environmental problems associated with a changing climate.

Dr. Finn provided background information about the R2A program, including the scientific justification for renewing the program, the NIEHS Strategic Plan goals addressed, the goals of the program, past investment in the program, and some R2A project highlights and success stories.

R2A programmatic requirements reflect the program's deep commitment to authentic community engagement:

- Communities have a role in identifying the environmental health risks that are of greatest importance to them.
- Community partners receive financial support to conduct the research project in partnership with investigators.
- Investigators collaborate with their community partners in developing effective strategies to mitigate exposures and/or improve health outcomes.

- Community partners provide oversight and input throughout the research process, which ensures that strategies/education are developed in accessible, culturally sensitive formats and at a literacy level and language appropriate for members of that community.

The new solicitation will retain the goals of the current program announcement, including the requirement of an established community-university partnership. The new solicitation would highlight the eligibility of disease advocacy groups as community partners.

The proposal is to renew R2A as an R01 program using the RFA mechanism that would be issued for the next two years. Each year, 4-5 awards at a cost of $400,000 per award are anticipated. Given approval, new awards would begin in late fall, 2020.

Dr. Ho was the first Council discussant. She said R2A is a very important area of research that NIEHS should continue to support. She felt that the research should not be restricted to just population-based or more traditional community-based research, but should be expanded to include basic and mechanistic research. She noted that economic developments are creating emerging population groups, such as new populations at risk due to 5G technology. Regarding action, she felt that it should not be limited to public health action, but could also include working with industries as a target for action, or local areas and local community groups. She emphasized the importance of assessing the program, measuring its impact. She said that some of the projects may not take five years or spend $400,000, so the funding should be nimble, allowing more projects to be funded in a broader base. She added that well-trained community participants should be part of the review process.

Dr. Lichtveld was the second Council discussant. She noted that in the concept statement, there was language about causal relationships. She said that one of the frustrating aspects for communities is that causal relationships cannot always be established; sometime associations must suffice. Thus, flexibility is required for communities to be full partners. She said the focus and emphasis on mixtures is important, because in communities, that is often the nature of exposures. She added that there should be attention to both chemical and non-chemical stressors. She recommended referring to "climate and health" as opposed to "climate change." She was glad that environmental health literacy was included.

Responding to Dr. Ho's comments about involving industry, Dr. Finn cited a project involving a local small business that is changing its practices because of its involvement in the project. Dr. Collman mentioned that the $400,000 figure is the maximum, and grants do not have to come in at that level.

Dr. Perez-Lugo asked whether grantees would be required to publish their results in non-peer-reviewed publications. With the communities involved in the research itself, they should also be involved in how the research is published, she said. She asked if the program considers funding basic research on interventions that go beyond individual behavioral changes, as political influence in the community is a key to reducing exposures. Dr. Finn said the community plays a major role in how the information is disseminated. She added that some of the interventions are intended to go beyond individual responsibility for reducing or eliminating an exposure, with many incorporating a policy goal, and that is very much what the program is all about.

Dr. Goldman asked if the grantees are asked to formally connect with public health, citing lead standards as an example.

Dr. Korfmacher said the program is critically important and the proposal needs to be moved forward. She felt that the move to in-house review is critical. She suggested that the funding cap should be higher, not lower, than a typical R01, and so was curious about the rationale for the $400,000 figure.

Dr. Finn said that there is involvement with public health in some instances, and it is encouraged, but it cannot be required. She agreed with the in-house review being a critical development. However, in response to a Council comment about having the dissemination of findings implemented as a follow up study, she said she would prefer not to peel off the dissemination into a separate project, because it starts from the inception of the project.

Dr. Collman asked for and received a motion and second to approve the concept. The Council voted unanimously in favor.

X. Environmental Liver Disease

Dr. Birnbaum introduced NIEHS grantee Dr. Matt Cave from the University of Louisville, who presented an overview of his research on environmental liver disease to the Council.

Over the past 20 years, deaths due to liver cirrhosis have increased by 65% in the U.S., while liver cancer-related deaths have doubled, and nonalcoholic fatty liver disease along affects more than 25% of the global population. The liver is known to be the most common target for chemical toxicity, but chronic liver diseases remain understudied in the environmental health sciences.

Dr. Cave described his career path, beginning as a clinical gastroenterology fellow in 2007 to today, when he is an associate professor and NIEHS R35 awardee. He serendipitously discovered toxicant associated steatohepatitis occurring in polyvinyl

chloride production workers at the Rubbertown chemical manufacturing complex near Louisville.

His laboratory currently takes a reverse translational approach consistent with the NIEHS translational research framework to explore fundamental questions related to environmental liver disease. He has recently collaborated with investigators from multiple major cohort studies such as the Anniston Community Health Surveys, the GuLF Study, and the C8 Health Study to add or enhance liver assessments to the research.

Dr. Kavanagh asked if Dr. Cave had seen any changes in phosphatases. Dr. Cave said no differences had been seen. Dr. Kavanagh asked about the ketogenic diet, and the potential mobilization of liver fat with sudden weight loss. Dr. Cave said it was a real and reasonable concern, but that there is little data on that at present.

Dr. Manautou asked Dr. Cave about clinical cases with individuals exposed to PCBs or vinyl chloride, and whether overweight is a requirement for developing NASH (nonalcoholic steatohepatitis) or NAFLD (nonalcoholic fatty liver disease), or whether he has seen cases of individuals with environmental exposures developing NASH or NAFLD. Dr. Cave replied that there appears to be a dose response with vinyl chloride, and in the older workers cases he had looked at, many were overweight but not necessarily obese, and they were highly exposed. He said he did not necessarily believe that the chemicals caused the disease, but that they make the diet-induced disease worse. Dr. Manautou asked Dr. Cave to discuss the role of exposures to environmental toxicants and changes in adipose tissue. Dr. Cave said that his lab had not done a lot of measurement in that area, although they have saved adipose tissues and would be happy to share the samples with other researchers.

XI. Studying the clinical effects of environmental exposures on disease sequelae

The balance of the Council meeting was taken up by a general discussion among Council members. First, Council members Dr. Wright and Dr. Racette delivered a brief presentation setting the stage for the discussion on environmental precision medicine research.

Dr. Wright provided a definition of precision medicine; and referred to the difference in the precision medicine perspective which deals with treatment and individual people vs public health which deals with populations and prevention/causation. There are well known differences between the public health community and the medical community that need to be considered when moving from epidemiology/toxicology to precision

medicine. The most relevant difference with regards to precision medicine is that the probability of illness is very different in the two fields. In medicine the probability of illness is "1" in public health/toxicology it is a number <1, often much less than 1. He said that the most important backgrounds to consider in precision medicine are not genes or environment, but disease and treatment. From the medical perspective, the physician is looking for help in diagnosing a patient, and in treating a patient. Epidemiology and toxicology research focus on causal risk factors may help with diagnosis; but play little or no role in treatment decisions. "If we want to do environmental precision medicine research, we have to ask the right questions, and the questions are whether the research we do will impact treatment decision and disease progression," he noted. For this reason, most precision medicine studies should start after disease onset and move forward in time, he averred. He described barriers and opportunities facing environmental precision medicine:

- Clinical diseases may be relatively rare
    - Networks may be required to identify sufficient patients
- Environment may be "place based"
    - Air pollution, pesticides, lead, etc.
    - Networks may increase geospatial variability
- Few physicians are trained in environmental health or epidemiology
    - Occupational medicine and pediatric environmental health specialty units are exceptions
    - Most know little about environmental health or toxicology
    - Most think genetics is more important than environment
- Few environmental epidemiologists conduct clinical research
    - No easy access to patients
    - May know a lot of risk factors and little about treatment or disease progression after onset
    - Partnerships between epidemiologist and physicians are complementary

To illustrate the points Dr. Wright had made, Dr. Racette provided neurodegeneration as an example. "I think that this concept of environmental precision medicine works particularly well with neurodegenerative diseases," he said. They are the ideal paradigm for precision medicine because of:

- Dramatic differences in disease progression, nearly completely unexplained
- Measuring exposure during disease course is highly feasible
- Can easily build on existing disease cohorts
- New disease-based cohorts are easy to assemble
- Responsive to patient and support organization interests

- The current genomic precision medicine paradigm is not well suited to neurodegeneration due to low heritability

But –

- It requires multi-disciplinary teams that do not typically work together
- Biological plausibility may be difficult to establish

Beginning the general discussion, Dr. Goldman said that traditional medical science "often used this kind of method to try to help people get better," citing spas, TB sanatoriums, and so on. Thus, precision medicine is not a new idea, but hasn't been thought of as a scientific idea. She noted other concepts such as midwifery that came out of practice but turned out to have an empirical basis. Thus, she said, it is an intriguing idea. She felt that as a pediatrician, an obvious example would be childhood asthma, where environmental interventions "absolutely can improve the course of the disease." She said it has been important to connect the environmental intervention to the actual pathophysiology of what triggers the symptoms. Regarding the neurodegenerative diseases, she mentioned the variability of the conditions, and said that some have not been convinced that there is one single diagnosis. The variability could result from having different pathologies involved, she noted. That would need to be taken into account in research studies. Dr. Racette said that there has not been an ability to split the neurological diagnoses in a logical way to reflect Dr. Goldman's point. Dr. Wright noted the enormous advances in exposure science over the last 10 or 15 years, with panels that can measure hundreds of chemicals. He said he would argue that just as genomics has reached a point where precision medicine is possible, environmental health and exposomics is getting closer to that point every day, and much can be done currently that was not possible even five years ago.

Dr. Ho said that precision medicine is actually getting closer and closer. She noted the progress in artificial intelligence as a contributing factor, possibly allowing integration of data points from birth to facilitate predictability.

Dr. Korfmacher said she supports the idea, while wondering how it progresses. She said she would encourage the participation of all affected populations, certainly the disease interest groups, but also those who would be involved in exposure reduction and development of the research agenda. She expressed concern that at first blush the term "precision medicine" has the ring of treatments available to the privileged few. She said it would be important to develop systems for exposure assessment, management, payment, and policy at the same time as developing clinical knowledge. She noted that environmental treatments and preventative measures are not typically covered by insurance, so it would be necessary to take that challenge into account as new interventions are developed. A totally different way to think about clinical translation is

required. She stressed that it will be very important to have a very inclusive process for developing the research agenda.

Dr. Lichtveld said she was also aware of the ethical constraints inherent in the new direction. She asked, "Ethically, from a patient perspective, can we do something about what we find clinically?" She wished to include precision public health in the discussion, because some of the individual exposures are actually community-driven and community-based, and contextually influenced by community. Dr. Wright said that because the thrust is not to describe what caused a particular disease but looking at something that will affect its progression, he would argue that there is something to be offered. An intervention may not treat a disease; but could keep its progression from worsening. He felt that that type of contribution was much more likely in this paradigm than disease causation research. He felt that precision medicine and precision public health are not mutually exclusive. But that precision medicine, because it deals with treatment is, easier to implement. It doesn't matter if phthalates caused a person's diabetes. But once someone already has diabetes, phthalates may affect their glucose levels regardless of the cause of their diabetes. The problem of multiple phenotype/disease subtypes that plagues environmental causal studies of complex diseases may be much less important in studies of environmental impact on treatment effects/progression of complex disease.

Dr. Racette noted that currently there is no disease-modifying therapy that affects disease course for Alzheimer's, Parkinson's, or ALS. He said it would be a great service to patients if environmental factors that could be modifiable could be identified. Regarding Dr. Korfmacher' s comment regarding equity, he observed that her concern about precision medicine only being available to a privileged few is actually the current situation. However, he felt that the disease model being discussed is more inclusive than the model currently being used, as the poorest of the poor would be included.

Dr. Cave suggested that it would be useful to involve industry-sponsored clinical trials in the effort. He said it would be relatively inexpensive to add exposomics to some of the placebo-controlled clinical trials. Regarding community, he pointed out that one important community would be the community of people who have a particular disease, who are advocates.

Dr. Goldman noted that there are established patient cohorts, allowing longitudinal study of people with particular diagnoses. Natural experiments would also be available in that scenario. She also said that there are chronic diseases where the exposures that caused the disease can continue to make it worse, such as liver disease or diabetes. She felt that that might be another path to take. She suggested that research to improve conditions in medical settings might also be a fruitful pursuit.

NIEHS Clinical Director Dr. Janet Hall said that she felt it is a very important area with an opportunity "to get a lot of traction." She said it would not be possible to underestimate the ignorance of the physician community about environmental health. She felt that part of the problem is that so much of the data in the field comes from animal models or epidemiologic studies. Physicians view aspects of policy and public health as not being directly relevant to their care for patients. Bringing the physician community into a role where they feel they have an ability to have an impact is going to be "an incredibly powerful thing to do." So, she applauded the effort to bring those aspects to the floor. She described the All of Us cohort, which has enrolled as many as 200,000 participants currently. She noted that a lot of resources are going into it, and that it will collect a great deal of data. Many NIH ICs are considering how to integrate their missions with it, and NIEHS should begin thinking about that effort, despite the fact that there is not much environmental content in the study at present.

Dr. Ellison from NCI drew attention to survivor cohorts that NCI supports. He said he was not aware of any studies looking at environmental exposures, cancer progression, and impact on treatment, and that that constitutes a real opportunity. He cautioned that with some of the cohorts, the relevant exposure period may have passed when measuring exposures at baseline. Thus, are risk or progression actually being measured in that situation, he wondered. His main point was that NCI does support cohorts that would be amenable to the type of research being discussed.

Dr. Racette said that the All of Us cohort had been discussed, but it may not be useful for less common diseases. However, there are ways to reach those populations, he noted, but there are artificial and unnecessary barriers in some studies.

Dr. Cave mentioned that the Million Veteran Program, which is genotyping one million veterans, would be a great resource, particularly if exposure assessment could be added.

Dr. Ho noted that the VA has a registry for burn pit exposures, which now numbers more than 20,000. She added that consumer forces should also be looked at, such as the many people doing DNA testing, by asking for them to volunteer. The AARP could also be recruited. The important thing is to think outside the box, with tremendous amounts of data available from a variety of sources.

Dr. Birnbaum said that one of the major barriers facing the environmental health community is the lack of recognition that environment impacts our health. That is the overwhelming message from the medical community, she added. A communications campaign should be considered, she said. Moreover, communication must be not only message delivered, but message received. It must be known how to deliver a message that people will accept and respond to. She agreed that advocacy groups, disease

cohorts, and people in clinical trials represent groups that could be accessed to ask questions about exposures and long-term outcomes. Citing the example of Dr. Cave's entrance into environmental sciences, she said that more mentors need to be developed.

Dr. Collman said the perhaps one way to better reach clinical audiences would be to develop proof of principle cases. Dr. Birnbaum added that that effort could be started by compiling information that is already known, in asthma for example. Dr. Collman said there were some isolated cases in the portfolio over the years where that was done, citing examples from breast cancer and autism. She noted that today there are more ways to use technologies to be able to characterize both exposure and phenotypes, so perhaps it is time to try that approach again.

Dr. Wright said that it is difficult when thinking in a public health perspective to not think about cause. Almost all environmental research deals with the causes of disease. Studying environment after disease occurs requires a reorientation on what is being studied and we must avoid falling back into discussions of causation as that may confuse the audience about the goals. Causation may not even be relevant in this type of research. The goal is to look at environment's concurrent impact on disease and not how past environment may or may not have caused the disease.

Dr. Birnbaum said that along with exposures in the external sense, the microbiome should be considered as well, since its key role in many health conditions is starting to be appreciated.

Dr. Goldman said that in the clinical context, it is important to determine how to convey positive messages. For example, there could be focus on a good microbiome, as opposed to a bad microbiome; a positive environment with better nutrition. Dr. Birnbaum agreed, adding that the question should be, "What's the good news?" Dr. Collman noted several potential positive statements and said that case studies could be found that would support positive messages. Dr. Birnbaum said there would be a tremendous benefit to the population if the progression of chronic diseases such as Alzheimer's could be slowed by controlling exposures that accelerate them.

Dr. Schantz said that the discussion had been "a really useful conversation on a really important topic."

XII. Adjournment

Dr. Collman thanked the staff members who had contributed to a very successful meeting. Dr. Birnbaum adjourned the meeting at 3:00 pm, June 5, 2019.

CERTIFICATION:

/s/

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

/s/

Gwen W. Collman, PhD
Executive Secretary
National Advisory Environmental
Health Sciences Council

Attachment:
Council Roster