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

MEETING SUMMARY OF THE NATIONAL ADVISORY ENVIRONMENTAL HEALTH SCIENCES COUNCIL

September 11-12, 2024

The 173rd meeting of the National Advisory Environmental Health Sciences Council convened on September 11-12, 2024. Open session convened at 9:03 a.m. and ended at 5:00 p.m. on September 11. Open session convened at 10:00 a.m. and adjourned at 2:58 p.m. on September 12. A closed session took place from 3:00 p.m. to 4:30 p.m. on September 12. Dr. Rick Woychik, Director, NIEHS, presided as chair. The meeting was virtual; all participants attended via Zoom.

Participating Council Members

Yulia Iossifova Carroll, MD, PhD (*ex officio*)
Stephania Cormier, PhD
Bevin Engelward, ScD (*ad hoc*)
Suzanne Fitzpatrick, PhD (*ex officio*)
J. Timothy Greenamyre, MD, PhD
Annette Guiseppe-Elie, PhD (*ex officio)*
Andrij Holian, PhD
Darryl Hood, PhD
Keri Hornbuckle, PhD
Cathrine Hoyo, PhD
Jani Ingram, PhD
Thomas LaVeist, PhD
Gary Miller, PhD
Gökhan Mutlu, MD
Patricia Nez Henderson, MD (*ad hoc*)
Maria Savasta-Kennedy, JD
Cheryl Walker, PhD (*ad hoc*)

NIEHS Staff

Kathy Ahlmark
Irina Alva
Trevor Archer, PhD
Camilo Asuncion
David Balshaw, PhD
Jennifer Baker
Valerie Bartlett

Linda Bass, PhD
Kris Battle
April Bennett
Abee Boyles, PhD
Danielle Carlin, PhD
Toccara Chamberlain
Jennifer Collins
Gwen Collman, PhD
Yuxia Cui, PhD
Christie Drew, PhD
Beverly Duncan, PhD
Chris Duncan, PhD
Anika Dzierlenga, PhD
Benny Encarnacion
Michael Fessler, MD
Murali Ganesan, PhD
Nicole Garbarini, PhD
Amanda Garton
Kimberly Gray, PhD
Jenny Greer
Arshya Gurbani
Janet Hall, MD
Astrid Haugen
Michelle Heacock, PhD
Heather Henry, PhD
Jon Hollander, PhD
Mike Humble, PhD
Gary Johnson
Bonnie Joubert, PhD
Nicole Kleinstreuer, PhD
Cindy Lawler, PhD
Gerald Lilly, MD, MPH
Mbeja Lomotey, Dr.P.H.
John Maruca
Jacqui Marzec
Kimberly McAllister, PhD
Tracie McGraw
Carolina Medina
Latavia Miller
Parris Milly
Nathan Mitchiner
Srikanth Nadadur, PhD
Liam O'Fallon
Suzanne Osborne
Heather Patisaul, PhD
Amelia Pearson

Eric Persaud, DrPH
Kristi Pettibone, PhD
Nicole Popovich
Ashlinn Quinn, PhD
Lingamanaidu Ravichandran, PhD
Lisa Rider, MD
Thaddeus Schug
Chris Schnur
Dan Shaughnessy, PhD
Carol Shreffler, PhD
Varsha Shukla, PhD
Sadichha Sitaula, PhD
Claudia Thompson, PhD
Brittany Trottier
Tierra Tucker
Fred Tyson, PhD
Ashley Vargas, PhD
Leroy Worth, PhD
Rick Woychik, PhD
Darryl Zeldin, MD
Alicia Zorn

Members of the Public Present

David Conti PhD, University of Southern California
Nancy Cox, PhD, Vanderbilt University
Eric Green, MD, PhD, NHGRI
Ernie Hood, Bridport Services, LLC
Peter Kraft, PhD, NCI
Charmaine Royal, PhD, Duke University
Dan Tagle, PhD, NCATS

OPEN SESSION

The meeting was open to the public on September 11, 2024 from 9:03 a.m. to 5:00 p.m. and on September 12, 2024 from 10:00 to 2:58 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 September 12, 2024 from 3:00 p.m. to 4:30 p.m. for consideration of grant applications. Notice of the meeting was published in the *Federal Register*. Dr. Rick Woychik presided as Chair.

I. Call To Order and Opening Remarks, Review of Confidentiality and Conflict of Interest

NIEHS and NTP Director Rick Woychik, Ph.D., welcomed attendees and called the meeting to order. He read the Government in the Sunshine Act. DERT Director David Balshaw, Ph.D., asked Council members to introduce themselves. Members of the NIEHS senior leadership team introduced themselves. Dr. Balshaw went over some of the logistics for the meeting, and read the conflict of interest statement. Council members Philip Bourne, Ph.D., and Olivier Deschenes, PhD, were unable to attend.

II. Consideration of June 2024 Meeting Minutes

Approval of the June 2024 meeting minutes was moved by Dr. Cormier and seconded by Dr. Savasta-Kennedy. Council voted to approve the minutes, with all in favor. Dr. Balshaw mentioned the future Council meeting dates. The February 2025 meeting will be virtual.

III. NIH Director's Presentation

Dr. Woychik introduced Dr. Monica Bertagnolli, the 17th NIH Director, who began her tenure on November 9, 2023. She was previously Director of the National Cancer Institute. Dr. Bertagnolli was unable to attend the meeting via Zoom, but instead sent a video presentation.

Dr. Bertagnolli said that the mission of NIH is to seek fundamental knowledge about living systems, and to apply that knowledge to enhance health for everyone. She noted that as NIH Director, she is concerned about disturbing trends in the overall health of the American people. She cited two major challenges to improving the health of the American people that NIH must respond to. First, many communities are underrepresented in research, with data being especially lacking for populations who are older, uninsured, belong to minority groups, or live in rural locations. Second, research knowledge is not being effectively harnessed.

She described her guiding principles as Director of NIH. First, the work is not finished when scientific discoveries are delivered, but is only finished when all people are living long and healthy lives. As the rush of information from basic science comes in, NIH must become more effective in connecting what is learned, understanding the interplay between the genes we inherit and the environmental and societal factors that surround us, beginning even before birth, connecting that knowledge to everyday life and clinical practice. It is important to move as quickly as possible from biological insights to improvement in the lives of real people.

NIH research encompasses the laboratory, the clinic, and all communities. The public must be partners in discovery. The hope for NIH is that in the coming years it will better connect research to efforts that have real world impact. For example, it will be important

to deliver truly evidence-based health care by integrating all forms of relevant data and giving patients across the country the option to participate in clinical research. NIH should also make advanced methods such as new data analytics more widely available to help deliver data-driven health care. To harness the full power of artificial intelligence to improve health, it will be necessary to invest in a secure and sustainable data sharing infrastructure, with inclusion of data that represents the true diversity of the nation.

Dr. Bertagnolli described a new, recently launched pilot program to better connect research to primary care called Communities Advancing Research Equity, or CARE. The program will soon announce its first grants, which will focus on engaging communities in areas underrepresented in research, with the first grants to be awarded in rural communities.

She noted that NIEHS has long emphasized community-engaged research and advancing health equity. That long-standing commitment "resonates deeply with my priorities as NIH Director." She congratulated Dr. Woychik and everyone at NIEHS for the new NIEHS Strategic Plan, which she had read recently. She felt that it was very well aligned with the overall hopes for NIH, including the desire to see more collaborations among the NIH Institutes and Centers.

She recognized the importance of the environment, with its impacts on every organ system and every stage of life, playing a part in both chronic and acute diseases. She said it would be important to bring awareness of environmental impacts to all areas of health research across NIH. She discussed the fact that data on the exposome could well be the next step forward for precision approaches to preventing and treating diseases and making impactful public health interventions. It will be important for NIEHS to continue to lead in exposome research.

She said she was sorry she had been unable to join for this meeting due to her official travels, and passed along her best wishes for a productive meeting.

Dr. Woychik noted that Dr. Bertagnolli is very excited about the work being done at NIEHS, and has been very supportive. He said he looks forward to her having the opportunity to visit the Institute in person soon.

In recognition of the anniversary of 9/11, Dr. Woychik read a statement from President Biden, and then called for a moment of silence from meeting participants. He then introduced the next speaker, Dr. Eric Green, Director of the National Human Genome Research Institute (NHGRI).

IV. *At the Forefront of Genomics:* Making Genomic Medicine a Reality

Dr. Green provided an extensive background and history of genetics, genomics, and NHGRI itself. 2023 marked the 20th anniversary of the completion of the Human Genome Project, the most significant achievement in the field. It was the beginning of the field known as genomic medicine, also known by the related terms personalized, individualized, or precision medicine. Genomic medicine is an emerging medical discipline that involves using genomic information about an individual as part of their clinical care (e.g., for diagnostic or therapeutic decision-making) and other implications of that clinical use.

The milestone accomplishments en route to the realization of genomic medicine were:

- Human genome sequenced for the first time by the Human Genome Project
- Cost of sequencing a human genome reduced >1 million-fold
- Millions of human genomes sequenced
- Profound advances in understanding how the human genome functions
- Significant advances in unraveling the genomic bases of human disease

Dr. Green detailed the major advances in genomic medicine implementation:

- Cancer genomics
- Rare genetic disease diagnostics
- Noninvasive prenatal genomic testing
- Pharmacogenomic testing
- Genomics-based prevention

He described several vivid examples of genomic medicine that are now emerging, along with the many challenges still facing the field.

He went over the current state of genome sequencing. There are three major steps involved in analyzing a person's genome sequence. All of the genomic variants must be detected. Then they are filtered and prioritized to determine which ones are most likely to be clinically relevant. Then, the clinical relevance of prioritized genomic variants must be established.

To detect the variants, there must be a reference sequence. A reference sequence must be "super high-quality," meticulously generated, requiring multiple DNA sequencing technologies. It must be virtually complete, with no or very few missing sequences. The current cost to generate a reference human genome sequence is approximately $10,000. When a patient or research participant gets their genome sequenced, they are getting what is known as a routine genome sequence. Its goal is not to be meticulous and perfect, but to identify genomic variants. It is generated in a high-throughput way, using a single DNA sequencing technology. There are always missing sequences, and the cost is less than $1,000. The resulting sequence is

compared repeatedly to an existing reference sequence, which reveals differences that convey the desired diagnostic information.

It is critically important that the reference sequence reflect human diversity. No single reference genome sequence is ideal. The Human Pangenome Reference puts together a series of reference genomes to be used as a tool to be better than a single reference sequence. It is a composite of multiple human reference genome sequences that captures the breadth of human genomic variation much better than any single reference sequence, allowing more accurate and complete detection of genomic variants across diverse human populations.

Dr. Green listed what is required for accurate and equitable analyses of a person's genome sequences:

1. Appropriately matched human genome reference sequence, or a human pangenome reference
2. Reference population database (with aggregated genomic variant information) for matched ancestral population(s) Example: gnomAD
3. Robust knowledgebase of curated information about the likely pathogenicity of genomic variants (developed by expert panels) Example: ClinGen

He concluded by alluding to a series of "Bold Predictions for Human Genomics by 2030" that were part of NHGRI's 2020 Strategic Vision. They were:

#1: Generating and analyzing a complete human genome sequence will be routine for any research laboratory, becoming as straightforward as carrying out a DNA purification.

#2: The biological function(s) of every human gene will be known; for non-coding elements in the human genome, such knowledge will be the rule rather than the exception.

#3: The general features of the epigenetic landscape and transcriptional output will be routinely incorporated into predictive models of the impact of genotype on phenotype.

#4: Research in human genomics will have moved beyond population descriptors based on historic social constructs such as race.

#5: Studies involving analyses of genome sequences and associated phenotypic information for millions of human participants will be featured at school science fairs.

#6: The regular use of genomic information will have transitioned from boutique to mainstream in all clinical settings, making genomic testing as routine as complete blood counts (CBCs).

#7: The clinical relevance of all encountered genomic variants will be readily predictable, rendering the diagnostic designation “variant of uncertain significance (VUS)” obsolete.

#8: An individual’s complete genome sequence along with informative annotations will, if desired, be securely and readily available on their smartphone.

#9: Individuals from ancestrally diverse backgrounds will benefit equitably from advances in human genomics.

#10: Breakthrough discoveries will lead to curative therapies involving genomic modifications for dozens of genetic diseases.

Following his presentation, Dr. Green opened the floor for questions from Council members. Regarding the ten bold predictions, Dr. Hood asked Dr. Green for his thoughts on how the models and programs will reconcile the underrepresentation of equity input into some of the models. Dr. Green agreed that the idea of race in genomics has influenced thinking about diversity. It is also becoming relevant related to population descriptors, which the National Academies has been analyzing. He added that the pangenome is actually an equity story, and that there is a clear need to provide equitable access to genomic testing.

Dr. Archer asked Dr. Green to comment on the importance of epigenetic modifications. Dr. Green said that he had undersold the more basic side of the story, and that he had not meant to imply that the variation of sequence should be thought of exclusively. He noted that the new DNA sequencing technologies are readily adaptable to studying the epigenomic language of DNA. There is also the whole world of RNA to consider. It is a whole other story, and there is still a long way to go, he said.

Dr. Hoyo asked a question regarding computational space. She praised the NHGRI progress on sequencing, but felt there was less investment in computational space. Dr. Green said that his institute is investing hugely in data science, including the creation of an Office of Genomic Data Science. He noted that genomics is a not the only big data institution right now, but is certainly a huge one, and that situation is unlikely to slow down. The problem will not be solved by the NHGRI alone, he said. He and Dr. Woychik and the other NIH leaders are working hard to bring NIH where it needs to be in the data science arena. Dr. Hoyo mentioned that personnel in the area is lagging, which Dr. Green agreed with the need for more training and improved pay scale.

Dr. Miller said he was concerned about the development of the various omics sciences all running in parallel, and how to get the different groups in different agencies to come together in a common data structure. Dr. Green agreed with the concern, and felt that the point is getting some attention currently. As a first step, he mentioned the launch a

year ago of a new clinical program called Multi-omics of Health and Disease, which mandates integration of omic data. The All of Us program is another example of a situation bringing in environmental data. He felt that the right conversations are taking place, but they need to be turned into the right actionable programs.

Dr. Woychik applauded Dr. Green's leadership in bringing genetics and genomics into the fore of how the etiology of human disease is studied across the biomedical spectrum. He said he is interested in doing the same thing at NIEHS, bringing in greater awareness of the environment—how environmental triggers may be responsible for someone with a genetic predisposition developing a phenotype, and whether there are elements in the environment that could mitigate development of disease. Dr. Green agreed, and mentioned that we are just scraping the surface in that area. He noted that interactions between NHGRI and NIEHS are at an all-time high, and looked forward to increasing partnership between the institutes.

Dr. Woychik said that the Human Genome Project had been the catalyst for much of what has developed in genomic medicine. He asked how important it would be for the environmental health sciences community to create an equivalent, perhaps the Human Exposome Project. Dr. Green said that other major projects had been proposed along the lines of the Human Genome Project, but each should be looked at very carefully, because there were important lesson learned from the Human Genome Project, including having very well-defined quantitative goals. Any such project should have a defined beginning and end. If a proposed project seems too overwhelming on that basis, its framing should be reconsidered. Discrete goals should be defined.

V. Genetic and Environmental Risk Factors for Myositis Phenotypes Across the Life Span

Dr. Lisa Rider, head of the Environmental Immunity Group in the Clinical Research Branch of the NIEHS Division of Intramural Research, briefed the Council on progress in understanding of autoimmune diseases, with a focus on myositis.

Autoimmune diseases are a large and growing public health burden, affecting approximately 8% of the population, encompassing over 140 acquired disorders, with up to 25 million persons affected in the U.S. They have been recognized by the National Academies of Sciences as understudies, with the recent formation of the NIH Office of Autoimmune Disease Research to coordinate NIH research.

The Environmental Autoimmunity Group (EAG) is the only NIEHS scientific group in Bethesda, established to use the unique resources in the NIH Clinical Center. Spearheaded by the pioneering work of Dr. Fred Miller, it is focused on understanding the role of environment and genes and mechanisms in autoimmune diseases, with the aim of disease prevention. The group has developed the largest myositis databases and

biorepository in the world, with more than 3500 clinically well-characterized patients. They conduct myositis natural history studies, genetic and environmental risk factor studies, and therapeutic trials.

Dr. Rider provided background information about myositis, which is an autoimmune muscle disease, the most common acquired chronic muscle disease in the U.S. She described the similarities and differences between adult and juvenile idiopathic inflammatory myopathies (IIMs). Myositis specific autoantibodies define distinct subgroups of myositis. They are present in 50-70% of myositis patient sera, and occur exclusively in myositis patients. The autoantibodies define distinct phenotypes and are prognostic biomarkers.

Dr. Rider discussed possible gene-environment interactions resulting in myositis phenotypes, and described several reasons why it is important to identify genetic risk factors for myositis. She presented data illustrating that autoimmune diseases are increased in first degree relatives of myositis patients, which speaks to the heritability of IIMs.

Evidence for environmental influences in autoimmune diseases includes:

- Low to moderate disease concordance in monozygotic twins
- Major genetic risk factors are environmental response genes
- Biologic plausibility from in vitro and animal studies
- Strong temporal associations with some exposures and disease onset
- Seasonal and geographic clusterings in time and space with disease onset
- Changes in incidence over time
- Examples of dechallenge and rechallenge, especially for drugs, biologic therapies
- Epidemiologic associations between exposures and certain diseases

Dr. Rider described the four possible stages of disease development and environmental influences during the evolution of autoimmune diseases. She noted that geospatial distribution of myositis in the U.S. suggests clustering by phenotype, and provided several examples of environmental risk factors for myositis and subphenotypes. Season of disease onset has also been shown to vary among myositis phenotypes. Ultraviolet radiation exposure and stressful life events have also been associated with the disorders, particularly dermatomyositis for UV radiation, along with occupational or hobby exposure to silica, heavy metals, and solvents, particularly in patients with lung disease and an anti-synthetase syndrome phenotype.

Dr. Rider presented data on microbiome composition related to IIMs, as well as the roles of viral exposures, tobacco smoking, and statins. The interactions of tobacco

smoking and statins (E) with specific HLA alleles (G) have also now been determined to increase risk of certain phenotypes (GXE), including for anti-synthetase syndrome and immune-mediated necrotizing myopathy.

In summary, she discussed what we have learned about genetic and environmental risk factors for myositis:

- Genetic risk for autoimmune disease is important, but the rapid rise in autoimmunity/autoimmune diseases and other data implicate a strong role for environmental factors in myositis and other autoimmune diseases.
- HLA 8.1 haplotype genes and alleles are major risk factors for many myositis and autoantibody subgroups.
- Environmental risk factors for myositis phenotypes include UV radiation, stress, certain infections/commensal bacteria, medications, and in adults, tobacco use and occupational exposure to silica, heavy metals, and solvents.
- Certain exposures that are risk factors for development of myositis and specific phenotypes may influence disease course and disease flares.

Dr. Rider detailed the potential future directions of myositis research, including genetic and environmental risk factors and pathogenic pathways.

Dr. Cormier asked whether the increases in incidence may be due to better diagnostics. Dr. Rider said she believed that the rapid rise is due to more than improved diagnostics. Dr. Cormier asked whether there are areas where there appears to be less testing for autoimmune diseases such as rural areas. Dr. Rider replied that rural areas are underrepresented in the national registry.

Dr. Miller commented on efforts to integrate various types of data, such as geospatial, the environmental, and the genetics. He asked Dr. Rider for her thoughts about challenging data integration. She said that her group studies a very rare disease, and has interesting data on portions of the cohort, but not on everyone, such as transcriptomic, exposomic, or genomic data. She said that different cohorts are needed to be able to integrate some of the data, perhaps All of Us, for example.

Dr. Holian asked about the contribution of inflammation to the development and progression of autoimmune diseases. He asked if blocking chronic inflammation may be able to resolve autoimmune disease. Dr. Rider said that current medications focus on blocking inflammation, and that her hypothesis is that blocking environmental triggers would fit into the process. She described her experience with some patients who are quite sensitive to UV radiation, and how blocking such exposure has helped them. Blocking inflammation could in fact be a very important pathway, she said.

Dr. Zeldin asked Dr. Rider to what extent she is using pharmacogenomic data to customize therapy. She replied that there are currently only a few examples of using that data. Dr. Zeldin asked Dr. Rider for her two or three bold predictions about where her field might be going in the next five years. She said that one would be that it will be important to start to intervene on some of the environmental factors to see if patients' illnesses can be improved. She said the next study will be to intervene on diet and giving patients omega-3 fatty acids. Also, a better understanding of gene-environment phenotype interactions and the mechanisms involved will be an area of growth for the field, she predicted. Also, the pre-autoimmune area will be another focus of research, as will exposomic work and the role of environmental risk factors in autoimmune diseases.

VI. Overview of NIEHS Extramural Research Efforts in Gene-Environment Interaction (GxE) Studies

Dr. Balshaw introduced Dr. Kimberly McAllister, a Program Officer in the NIEHS Genes, Environment, and Health Branch, to set the stage for the mini-symposium covering the NIEHS portfolio in Gene-Environment Interaction (GxE) research.

Dr. McAllister defined GxE interactions, and outlined why it is important to study them:

- Understanding biological mechanisms and pathways
- Risk prediction for complex disease
- Identifying the most genetically susceptible individuals to exposures to ultimately adapt prevention/intervention strategies to protect (precision environmental health)

She depicted a timeline from 2005 to the present to illustrate the many NIEHS investments in GxE research in partnership with other NIH institutes, especially NHGRI and NCI. She provided several examples of those partnerships.

She outlined the challenges involved in identifying new GxE findings in human populations studies or validating existing ones:

- Underpowered studies
- Complexity of measuring environmental exposures
- Limited range of genetic and/or environmental variation
- Most genetic variants are in non-coding regions
- Secondary epidemiology studies with comparable G and E to validate may not exist

In recent years, NIEHS has explored alternative approaches for GxE discovery and/or validation, such as the Collaborative Cross and Diversity Outbred mouse models, along with several others.

Dr. McAllister described multi-omics initiatives, including MOHD, the Multi-Omics for Health and Disease initiative involving NIEHS, NHGRI, and NCI. She discussed the Mendelian Diseases and Environmental Risk Factors symposium from 2021, the 2022 workshop on Ethical, Legal, and Social Implications (ELSI) of GxE Research, and the Report Back Study for environmental exposures and GxE initiative published in 2024.

Dr. McAllister introduced the speakers for the mini-symposium: Dr. Peter Kraft from NCI, Dr. Charmaine Royal from Duke University, Dr. David Conti from the University of Southern California, and Dr. Nancy Cox from the Vanderbilt University Medical Center. She moderated the mini-symposium.

VII. Genetic Environmental Factors in Cancer Epidemiology Cohorts and Consortia: Opportunities and Challenges

Dr. Peter Kraft from NCI addressed Council on opportunities and challenges facing genetic environmental factors in cancer epidemiology cohorts and consortia.

He reflected on why it is important to study both genetic variation and environmental variation in the same participants in observational studies. He stressed the complexity involved in the relationship between genotype and phenotype, with the factor of environmental exposures added as well. “I do want to acknowledge that you can have that complexity in mind and still fruitfully analyze factors marginally. Genome-wide association studies are a great example,” he said. He cited the reasons to study genes and environment:

- Leverage assumed effect modifiers to increase power
- Provide insights into biological mechanism
- Improve risk prediction and prognostic models

Dr. Kraft discussed what has been learned from genome-wide GxE studies over the last 15-20 years in large collaborative studies in cancer and other fields: on some levels, a lot, but on others, not as much as had been hoped originally. The examples he showed modeled environmental effect modification in some way, to try to identify loci that might have been missed in GWAS studies if environmental exposures were ignored. The number of loci identified was typically small, and gains were small by adding the potential effect modification of measured environmental exposures. The few loci identified could be attributed to limited sample sizes, measurement error, and limited diversity. Dr. Kraft provided examples of each issue.

He went into considerable detail about the Connect for cancer prevention study, which will study 200,000 U.S. adults aged 30-70 with no history of cancer, who are patients or members of partner health care systems.

Looking at the paths forward for GxE cancer studies, he cited the needs to:

- Increase sample sizes, facilitate cross-study collaborations
- Collect more and more detailed exposure measurements
- Increase participant diversity

Dr. McAllister asked Dr. Kraft about the timeline for the Connect study. He replied that it is currently enrolling, with 50,000 enrollees thus far. Full enrollment should be achieved within 3 years. Data will be made available to the research community as soon as possible. He added that there will be plenty of time for ancillary studies.

Dr. David Conti asked Dr. Kraft to elaborate on the prediction versus characterization ideas of GxE and the balance between the goals. Dr. Kraft replied that understanding the mechanism is difficult, and for prediction, the key will be transportability. He emphasized the importance of validation.

Dr. Balshaw asked, as we are building out an exposome framework, will that make exposure easier or harder to understand the very complex data? Dr. Kraft said it will be both easier and harder. The data is necessary, and there are logistical challenges to acquiring the data. The issue of sample size will remain, and the temporal pattern related to disease risk needs to be better understood.

Dr. Savasta-Kennedy commented about the balance discussed in the legal realm working with communities, which is on the one hand information is always useful and important, but on the other hand, information about exposures without some sort of recommendation or fix can be very difficult.

VIII. Environmental and Social Risk Factors in Sickle Cell Disease and NASEM Report on Use of Population Descriptors in Genomics Research

Dr. Charmaine Royal from Duke University briefed the Council on sickle cell disease (SCD) research, her work in the field, and the 2023 NASEM report on population descriptors. Dr. Royal co-chaired the committee that compiled the report.

She provided background information about the global impact and distribution of SCD. about 20 million people are affected with SCD globally, with at least 75% in Africa. In the U.S., approximately 1 in 365 live births for black Americans are impacted by SCD. She discussed the molecular basis of the disease, with its characteristic sickled red blood cells. The common clinical complications of SCD are anemia, vaso-occlusion, and chronic organ damage.

SCD patients are often subject to inequities and disparities:

- SCD disparities and inequities mirror existing “racial”, ethnic, and economic inequities and disparities in the U.S. and globally.
- Median life expectancy is reduced by at least 30 years in all countries; the rate is greater in low-income countries.
- Africa has the highest SCD birth prevalence and mortality rate—increased mortality (50-90%) in children under age 5.
- SCD has received relatively little attention and few resources from the scientific, clinical, and public health communities compared to other genetic disorders such as cystic fibrosis.
- Funding for SCD has been historically low and has decreased over the years.
- The burden of SCD on individual patients exceeds that of numerous other severe diseases.

Dr. Royal provided more details about SCD health disparities, comprised of health outcome disparities and health resource disparities. She described SCD phenotypes, ranging from less severe to more severe phenotypes, with genetic and nongenetic modifiers.

She focused on the SCD theoretical framework. “Colleagues and I have been trying to think about sickle cell disease in a much more holistic way, thinking about the complexity of disease … All of these factors [structural, environmental, sociocultural, psychological, clinical, behavioral, and biological] are operating all at the same time … Our work has been focused on the complexity of the disease,” she said.

She noted the ongoing importance of continuing to study Mendelian disorders such as SCD.

She turned to the 2023 NASEM report, *Using Population Descriptors in Genetics and Genomics Research.* Dr. Royal co-chaired the 17-member committee that authored the report.

The task before the committee involved:

- Assessing use of race, ethnicity, and other populations descriptors in the basic science of genetics and genomics, health risk as a function of our genomes, and health disparities.
- Developing “best practice” approaches for the appropriate use of population descriptors.
- Discussing obstacles to adoption and implementation of best practices.
- Proposing potential implementation strategies.

- Out of scope: use of race and ethnicity in clinical care and biomedical research generally; racism in science and genomics; providing policy recommendations to NIH and government agencies.

The population descriptors considered in the report were ancestry, genetic ancestry, geography, ethnicity, indigeneity, and race. Dr. Royal described the report's overarching framework, with five guiding principles influencing the 13 recommendations, which covered requisites, guidance for researchers, and implementation & accountability. She went over the recommendations in each area in more detail, with examples. The report's key points were:

1. The committee did not provide a menu of options, but rather a process to help researchers think through decisions about the use of population descriptors.
2. Guiding principles address ethical responsibilities and scientific standards for fostering sound best practices and trustworthy research.
3. Avoiding typological thinking, measuring environmental factors, and engaging communities are critical to achieving systemic and sustained change.
4. Genetic ancestry is inferred from various measures of genetic similarity. For many research applications, consideration of genetic similarity is sufficient without invoking the idea of genetic ancestry.
5. Use of population descriptors should depend on the nature of the study and the specific questions that the study is trying to answer. Researchers should explain how and why they decided to use the descriptors they selected.

In October 2023, an ELSI R01 research project grant funding opportunity was announced by 11 institutes/centers and 2 offices with guidance on the use of population descriptors citing the NASEM report. In May 2024, NIH hosted a meeting to discuss the NASEM report recommendations and how they relate to legacy datasets.

With the floor open to questions from Council members, Dr. Woychik asked Dr. Royal whether it is possible to reverse the genotype of a sickle cell to a non-sickle cell. She explained that the gene therapy currently in use is clearing and replacing the sickle cells. Dr. Woychik asked if anything is known about potential environmental epigenetic changes in the genome that could influence gene expression in a way that either enhances or suppresses the sickle cell phenotype. Dr. Royal said that DNA methylation has been shown to do so. The work is still in process, she added.

Dr. Hood offered a potential collaboration involving cohorts he has available, with possible microbiome work. He said there are a number of studies involving the gut microbiome and SCD.

Dr. Miller said he was involved in a project led by a researcher at Morehouse looking at the African diaspora and genetic variability, also including social determinants of health,

exposomics (the biology and the genetics), but the challenge is that it takes a very big grant to be able to do such work.

IX. Statistical Approaches to Integrate "E" with Genetics, Functional. and Multi-omic Data

Dr. David Conti from the University of Southern California described statistical approaches to integrate environment with genetics, functional, and multi-omic data, which he explained is not quite the same thing as interaction.

He first looked at genomewide association studies (GWAS), where many SNPs are tested for variability and association with traits. He referred to a data graphic illustrating the contrast between an unexposed group with no genetic effect and an exposed group with a genetic effect. What is missing is SNPs with modest marginal effect that might be important in one or more subgroups. He added data to the graph showing that the size of the marginal G effect depends on prevalence of exposure. Being able to detect that effect is the idea behind genomewide interaction studies (GWIS).

He provided details about various statistical methods of adding information to construct more efficient GWIS scans.

First, Dr. Conti showed a 2-step approach: DGIGXE. He then illustrated a 2-step approach called EDGE, which has an improved genomewide power to detect. Another way to combine information is called the 2-df joint test. There is also a 3-df joint test, which may be powerful for discovery.

He shared information on the past use of the methods based on the exposures in the studies.

He discussed single-marker analysis versus joint analysis. Single-marker analysis is one SNP at a time, whereas joint analysis is all p SNPs together. It considers the impact of other markers on the analysis.

Dr. Conti described the Polygenic Risk Score (PRS). It is the weighted sum of the number of risk alleles carried by each participant.

He noted that lack of diversity could impact health disparities, and discussed the impact of PRS and E interactions, using a large prostate cancer study as an example. PRS x social determinants of health (SDoH) has also been studied. The study he illustrated looked at the combined effect of genetic and socioeconomic risk on the prevalence of Type 2 diabetes. PRS and environment interactions can yield important information. For example, incorporating functional annotations can be used for pathway analysis.

In terms of omic data, can it clarify the impact of each SNP within a PRS with measured omic data that captures the underling biology? There is a multi-omic mediation framework for precision environmental health, with high dimensional mediation, latent mediation, and integrated, quasi-mediation. These methods can contribute to precision environmental health.

Dr. Conti discussed some of the ongoing initiatives related to the analyses he had mentioned, such as Multi-omics for Health and Disease (MHD), the PRIMED-Cancer Consortium, and USCIMAGE.

Dr. Walker asked Dr. Conti if he is finding that some of the studies he is conducting are redundant with each other, or if they are all distinct in terms of the amount of information used when integrating across multiple levels. Dr. Conti said it was actually both. Dr. Walker asked if he is seeing a hierarchy, with some datasets contributing more than others. Dr. Conti said that there are statistical and data issues involved in integration, and inevitably there will be bias toward the larger datasets. So it is important to think about what to include and why. A focus on pathways can help the situation, he noted. However, from a methods perspective, “I’d like to throw it all in and have it work itself out,” he said.

X. How do we learn what disease biology is driven by environment and GxE?

Dr. Nancy Cox from the Vanderbilt Genetics Institute at the Vanderbilt University Medical Center addressed the Council on the relationship between disease biology, environment, and GxE.

She said she wished to engage in a more philosophical discussion about why we want to get to the biology of the E and the GxE. She noted there is a much improved ability to collect data that yields intermediate phenotypes, and laid out a broad overview of her presentation:

- We have a host of ways to measure how non-genetic factors can influence the biology of disease through effects on genomes.
    - Cheaper interrogation of methylation
    - Multiplexing different kinds of studies on chromatin marks
- But how do we get from those measurements to biology?
    - We need to distinguish long-term effects of exposures being somehow encoded in the genome from direct effects of pervasive exposures.

She mentioned that there is currently “a huge missing data problem.” There are still not great ways of measuring translational efficiency. She discussed the role of RNA, with the emergence of proteomics.

She profiled the BioVU biobank, which includes approximately 330,000 samples being whole genome sequenced. It incorporates 10-15 years of electronic health records (EHRs) and much omics information on genome variation, transcriptomes, and metabolomes. The EHRs reflect substantive new investments in social determinants of health (SDoH). The records also include 2.8 million people with just EHR data. All of this information allows the opportunity to make discoveries in the phenome space. Dr. Cox called the chance to work with that vast wealth of data is "wildly satisfying."

She pointed out that genetics has been used in isolation up to this point, but different things will emerge when environmental exposures and social determinants of health are considered as well. "We now have got at least a good handle on a lot of genetic measurements in really big sample sizes, and there is no way that we shouldn't be using that to better see consequences of environmental exposures and social determinants of health," she observed. "We have this dynamic system that starts with genetics at the base, but where the environment always has the opportunity to change underlying biology," she added. Exposures can damage DNA and RNA, and RNA is the much more vulnerable molecule that can alter methylation of DNA and chromatin marks, and can also directly damage tissues. Exposures may be very short-acting or long-lived.

Some SDoH may be so pervasive that they do not need to affect biology at all but still have profound and direct effects on health and outcomes. Dr. Cox cited examples of SDoH affecting health outcomes without necessarily altering underlying biology, such as lack of access to health care.

Dr. Cox moved on to the question of what should be being done to learn how E and GxE drive disease biology. She went through some examples, with a graphic illustrating her points. The part of genetics that directly regulates expression can drive disease risk, along with other non-genetic factors. It is a huge part of why gene expression varies. Environmental exposures such as what we eat and drink have measurable effects on measured gene expression. They are important sources of variation that vary according to how we choose to measure gene expression. Caffeine is a good example. Measured gene expression as causal inference for what genes drive disease is challenging, because there is no way to know what is cause and effect just from gene expression measurements. Being able to pull out the genetically regulated part can be a useful way of moving closer to causal inference models.

The ways that having disease may feed back on methylation and chromatin marks is largely unexplored at this point, and the time courses are needed to be able to fully understand them. It can be cancer and long-term chronic diseases like diabetes. It is one of the ways that biological systems get broken.

Dr. Cox acknowledged that the situation is complicated, but sought to offer suggestions on what to do. She presented some aspects of what "inquiring minds want to know":

- What proportion of SDoH do not drive biology, but could be directly solved with money for access, better diets, etc.?
- Using the biology we can learn with the tools we have now, does biology driven by E and GxE completely layer onto what biology we know from G? Is it largely orthogonal to G?
    - Biology is measurable and modifiable even when we can't fully identify all exposures. Developing the tools to measure exposure biology at scale will also allow us to better calibrate interindividual variability in exposures and more rationally choose appropriate therapies.
- Most obvious deep drive traits…
    - Obesity
    - Inflammatory biology

"There is nothing more important than learning the biology of the genetics that have been discovered. We've invested a huge amount in genetics, there are very clearly genetic drivers of most common human diseases. We need to learn the biology of that," Dr. Cox concluded.

Dr. Balshaw asked Dr. Cox to comment on how to take the information on individual susceptibility and move forward to the next step on precision environmental health—how to guide behavior or intervention to understand risk at the individual level as well as at the population level. She emphasized that the value of the measurements, with only a partial understanding of what exposures are important, is limited. There are known exposures that are difficult to measure, and often cannot be captured because they were early exposures. However, the more data collected through multi-omics, the more kinds of patterning will be seen that will eventually be able to be linked to exposures. There is much opportunity, but there is "a huge missing data problem here," she said. But understanding the biology, there are still things to be learned, despite the missing data problem.

Dr. Woychik asked Dr. Cox whether the types of exposures that will have an effect are those that have biological consequences. She replied that there are definitely social determinants of health that may not have any direct biological consequences except for the ability to access health care. She cited income inequality and geography as examples. It will be important to solve the health consequences of income inequality, as it is the fastest and easiest way to improve health. Dr. Woychik noted that she was referring to direct and indirect effects. She said that early childhood trauma is a good example of long-term determinative health.

Dr. Miller commented that almost all SDoHs will alter biology, because if a health outcome is altered, there must be a biological signature. It may be more a manifestation of the disease progression being worse, or being farther away from homeostasis. He said there may be a lot more there that is detectable. Dr. Cox said she was trying to get at causality and consequence. Failure to get adequate health care will lead to adverse outcomes, such as when the price of insulin was so high. So the lack of access to health care and drugs creates the biology. Those factors need to be changed, because the biology cannot be.

Dr. Royal said there are a lot of things that influence health outcomes that need no further studies, but need to be fixed. Fixing them will address many health disparities. Dr. Cox agreed, but noted that some of the disparities, such as age, are not addressable. However, inequities can and should be addressed.

XI. Council Discussion

Dr. Balshaw invited Council members to comment on the issues raised in the mini-symposium, with a focus on what NIEHS should be doing as it moves forward as an institute. He asked, “Where can biology serve as an integrator of different environmental exposures, so that it can be a long-lasting record of some previous insult?”

Dr. Cox said we should be looking at exposures that we know, looking for downstream biology of exposures that we know affect the same diseases, for example, cigarette smoking and radon and lung cancer. Trying to understand whether there is any sharing of the signatures that might provide some insights into what pieces of the biology are shared. Dr. Conti said that is where the potential for the large biobanks such as the one Dr. Cox had described is. Dr. Cox said that one of the challenges is distinguishing the transcriptomic biology changes that are strictly due to the methylation signature as distinct from the transcriptomic signatures that are only there in the presence of active smoking. Part of what long-term smoking does is increase risk for addiction to tobacco and turning up the reward system biology that makes the individual more vulnerable to all addiction, changing reward system biology in the brain. That is part of what the methylation signature does long-term.

Dr. Archer commented on the issue of the missing data. He said it is very challenging mechanistically to understand how methylation influences transcription directly, because methylation changes are occurring in the context of other epigenetic changes, which have varied lifespans. Consequently, transcriptomic data are really snapshots, influenced by the existing signals they undergo. Trying to figure out how to integrate these different molecular mechanisms will be an important aspect of understanding the consequences. This will impact how to think about interventions. Dr. Conti said that is

where experimental studies can be leveraged, because they can get at the causal mechanisms.

Dr. Cox added that there is value in thinking through and trying some experiments in comparing global signatures. Analyzing multi-omics data can be integrated to find patterns that may be a good way to compare different exposures that lead to the same things. She said that there may be things to be learned through analyzing multi-omics data in each of the ways Dr. Conti had described.

Dr. McAllister briefly summarized the mini-symposium, which she said had been very helpful. She thanked the speakers from the session. Dr. Balshaw adjourned the day's open session at 5:00 pm.

XI. Report of the DERT Director

Dr. Woychik convened the September 12 open session at 10:00 am.

Dr. Balshaw began his presentation to Council about DERT developments since the June 2024 Council meeting with a staffing update. He welcomed new DERT employees Sadichha Sitaula, Ph.D., and Tracie McGraw.

He summarized DERT meetings since the last Council meeting, and looked ahead to upcoming DERT meetings.

He went over DERT accomplishments related to the NIEHS 2018-2023 Strategic Plan (SP), based on the five aspects covered by the plan: collaborations, funding, meetings, publications, and resources. He recalled that the plan includes three major themes, with 19 specific goals. In describing the one-time NOFOs that had been issued during the five years of the plan, he focused on the RESTORE program. It fit into the Biological Research element of the SP, as the goals of Generating Knowledge from Data and Emerging Issues. He pointed out that most of the RFAs cover more than one goal. He also showed the list of recurring RFAs, such as the Core Centers RFA, which covers every aspect of NIEHS activities.

Dr. Balshaw recounted several select accomplishments by SP theme, in order to highlight some of the DERT work during the SP period. Theme 1 is Advancing EHS, and he described accomplishments related to Biological Research, Individual Susceptibility, The Exposome, and Data Science. Theme 2 is Promoting Translation: Data to Knowledge to Action, and the examples were related to Evidence-Based Prevention & Intervention, EHD and EJ, and Emerging EH Issues. Theme 3 is Enhancing EHS Through Stewardship and Supports, with examples depicting Greater Workforce Diversity and Impact Evaluation.

He said that the many examples of DERT accomplishments through the SP period he had detailed were stepping stones towards the future of environmental health sciences, and the impact of the work implementing the SP sets the stage for the new priorities established in the new SP.

XII. Report of the NIEHS Director

Dr. Woychik briefed Council on Institute developments since the June 2024 Council meeting.

He noted that much of his presentation would focus on the new NIEHS Strategic Plan. His motivation for the new SP is to help bring environmental health sciences to the broader biomedical enterprise. “We’ve got to figure out ways to integrate the work that we do in environmental health into the fabric of the way we study the etiology of human disease,” he said. So many of the elements of the new SP involve collaborative efforts to help operationalize many of the NIEHS activities so that they can be used broadly across the NIH.

Before presenting the SP, Dr. Woychik turned to budgetary matters. The information coming in from the House related to the NIEHS Superfund program is not good, with the FY2025 mark in the House bill $4.7 million below FY24. He said that he found this development “perplexing,” as there seemed to be considerable support for the science; apparently it simply reflects budgetary realities. He also described the House FY25 Labor-HHS bill, which includes a portion of the NIH reform proposed by the House Energy and Commerce chair, which would consolidate NIH to 15 Institutes and Centers, with NIEHS becoming part of the National Institute on Health Science Research with NIMHD, NCCIH, NINR, and FIC. Under the proposal, the overall budget for the new organization would be $1.9 billion, which is a total increase of $20 million from the FY24 allocation for all of the combined ICs. He said it is unclear whether the proposed merger would actually take place, and that it will likely be a function of what happens with the November election. FY25 Senate Interior and Environment Bill appropriations have the NIEHS Superfund programs at a mark of $81.6 million, an increase of $1.9 million from FY24 levels. The Senate FY25 Labor-HHS bill has NIEHS flat at $913.9 million, which is $2.8 million less than the President’s FY25 budget request.

Dr. Woychik turned to the NIEHS FY2025-29 Strategic Plan: Health at the Intersection of People and Their Environments.

The new mission and vision statements of NIEHS are:

- The mission of the National Institute of Environmental Health Sciences is to research ho the environment affects biological systems across the lifespan and to translate this knowledge to reduce disease and promote human health.

- The vision of the National Institute of Environmental Health Sciences is to provide global leadership for innovative research that improves the health of people and communities.

Dr. Woychik presented a graphical diagram illustrating an overview of the SP, showing the interconnected themes of research Areas of Emphasis, Capacity and Infrastructure, and Scientific Management and Stewardship, all of them interacting with the overarching, cross-cutting themes of diversity, equity, inclusion, accessibility, and civility, as well as solutions-focused research and translation.

He described the six elements within the Research Areas of Emphasis, including the Translational Goals for each:

- Exposomics
- Precision Environmental Health
- Mechanistic Biology and Toxicology
- Data Science and Computational Biology
- Environmental Health Disparities, Environmental Justice, and Health Equity
- Climate Change Impacts on Human Health

Under Capacity and Infrastructure, the elements include:

- Scientific Workforce Development and Training
- Data Infrastructure and Management
- Human Studies and Community-engaged Research
- Exposure Measurement
- Communication and Dissemination

Under Scientific Management and Stewardship, the elements are:

- Public Trust in Science
- Sustainability
- Review, Evaluation, and Assessment Capabilities
- Leadership Core Values
    - Workforce
    - Innovation
    - Collaboration
    - Communication
    - Distributive Leadership

Dr. Woychik emphasized the NIEHS commitment to open communication and collaboration. He has and will continue to share the new SP with his fellow IC Directors. He described meeting with two U.S. Congresswomen, Valerie Foushee and Deborah

Ross, when they visited NIEHS in June, 2024. He noted that also in June, NIEHS had hosted the biannual meeting of the NIH Tribal Advisory Council. In August, the White House Climate and Health Forum was held, at which NIH Principal Deputy Director Dr. Larry Tabak spoke about the NIH Climate Change and Health Initiative, which is led by NIEHS.

He updated several recent developments at NIEHS:

- On September 4, funding for the NIH Center for Exposome Research Coordination was awarded, funding the NEXUS network, the Network for Exposomics in the U.S.
- the NIH Common Fund Complement Animal Research in Experimentation (Complement-ARIE) Program released a Notice of Intent to Publish a Funding Opportunity (NOFO), with an estimated release date of October 18, 2024.
- The Climate Change and Health Initiative has launched a new website.
- The CHORDS (Climate and Health Outcomes Research Data Systems) project has been funded by HHS, and will run from March, 2023 to March, 2026). CHORDS has launched a website housing a wealth of environmental and health data, a resource to advance research.

He mentioned that Dr. Michael Fessler has been named NIEHS Acting Clinical Director.

In light of the “bold predictions” described by Dr. Green in his NHGRI presentation, Dr. Woychik asked for Council members and meeting attendees to make bold predictions for NIEHS, answering the question:

- How will implementing the new NIEHS strategic plan change global human health in the next 5-10 years?

He asked audience member to encourage their scientific networks to read the NIEHS SP, and then make bold predictions to be emailed to NIEHSDirector@nih.gov. The results of the solicitation will be discussed at the next Council meeting in February, 2025.

Dr. Hood asked Dr. Woychik if he had spoken to the directors of the other ICs who would be affected by the proposed NIH merger. Dr. Woychik said he talked to them all the time. He described some of his recent interactions with his IC Director colleagues. Dr. Hood asked Dr. Woychik to elaborate on the plan for expansion of the P50 Environmental Justice Center program, specifically, how many more grants are planned. Dr. Woychik said that Dr. Archer has been working on that plan. Dr. Archer said that with the commitments that have been made, the number of centers will be doubled.

Dr. Nez Henderson said she was glad to hear about the NIEHS meeting with the Tribal Advisory Board (TAB), and wondered what the priorities are with relation to the Institute. Her second question focused on vaping and e-cigarette use among youth; although national data showed that rates were dropping nationally, they were rising among American Indian/Alaska Native young people. Dr. Balshaw commented that the TAB members were impressed by the activities at NIEHS related to tribal communities and environmental exposures. Liam O'Fallon said that during the TAB meeting, vaping was not addressed, but there are opportunities for scientific engagement on that topic. Dr. Woychik elaborated on the success of the TAB meeting. Dr. Fred Tyson described some of the current research at NIEHS regarding vaping-related lung injury, including flavorings and impact of vaping on pregnant women and fetuses.

Dr. Miller asked Dr. Woychik to elaborate on the possible NIH reorganization. Dr. Woychik replied that the idea is coming from the House. It is unclear what role NIH will play, as it is unprecedented to couple a reorganization with budgetary allocations. "This is new territory," he said, with a lot that would have to happen over the course of the next several months. All that can be done is to monitor the situation. It is unclear how it would change the research strategy. There is already much collaborative work with Fogarty, NCCIH, NIMHD, and NINR, for example. Dr. Bertagnolli is currently on Capitol Hill explaining to Congress that it is not necessary to reorganize NIH to get the ICs to work together.

Dr. Savasta-Kennedy commented that she could not understand why it is not a separation of powers problem, with the legislative branch potentially directing the executive branch, NIH, to reorganize. It does not seem to be their role, and it would not appear to be legally acceptable. She speculated that legal counsel is looking at the issue, which Dr. Woychik confirmed.

Dr. Holian noted that there is still much to do in the field, but with the flat budget, it may be challenging to accomplish the things that need to be done. He asked Dr. Woychik for his thoughts on that issue. Dr. Woychik replied that the flat budget necessitates reprioritizing. All organizations will always be doing new things, and it that stops, then the organization stagnates, and that is not a good position to be in. The challenge is how to continue to incentivize those in the EHS community to be doing bold new things. Also, NIEHS has traditionally been the institute that funds environmental health research, so part of the motivation in getting environmental health out more broadly across NIH is to spread out the funding base. "When I look across the entire NIH, there are things that we can be doing, and my colleagues in the other ICs can be doing, that really have an environmental health element to them," he said. He cited climate change and health as an example. He felt that the framework of the SP would provide everyone with a sense of the directions moving forward.

Dr. Cormier observed that although collaborative efforts are being encouraged, often the huge collaborative programs like the Superfund Research Program continually are cut. Collaborative team programs need more money and effort, and cutting those budgets just water them down, so less is getting done. Dr. Woychik told her to rest assured that when he meets with members of Congress, that is part of his message. They respond, however, that it is a very complicated working environment on Capitol Hill right now. Dr. Cormier asked, “Are there things that we can do?” Dr. Woychik responded that there are things that can be done. He asked Dr. Balshaw to weigh in on specific actions that members of Council, who are not Federal employees, can take. Dr. Balshaw confirmed that as private citizens, they can take advantage of their citizenship, and they can work together to advocate and ensure that their representatives are aware of the impact of their work. Dr. Janet Hall encouraged working with professional societies to spread the word. Dr. Woychik observed that as private citizens, Council members can communicate with their Congressional representatives. He suggested providing Congress members with the new SP, as it is a public document.

Dr. Engelward said that it would be great to have stories provided, with facts and figures about the benefits of NIEHS work, to help convince politicians to support the work. Dr. Gwen Collman noted that NIEHS employees are always able to educate stakeholders, who are always anxious to learn, although as Federal employees, they cannot ask others to advocate.

Liam O’Fallon provided more information about the TAB meeting. He said the committee members hoped to contribute to the conversation moving forward.

Dr. Miller contributed a bold prediction that he had entered into the chat portion of the Zoom platform. “Exposome medicine will become actionable. It will go way past measuring blood levels and start incorporating exposure profiles into clinical care,” he had predicted.

Dr. Walker asked how NIEHS has been able to come up with estimates of savings in health care related to actions regarding the environment, estimates that can be leverages as a return on investment (ROI). Dr. Woychik noted that when talking to politicians, those are the types of things that resonate with them. Dr. Balshaw provided the example of the tremendous ROI that has been documented from the Worker Training Program. Dr. Eric Persaud described the process he used, working with an economist, to quantify that ROI. Dr. Walker cited the example in Texas of the Cancer Prevention and Research Institute of Texas, a state agency that funds cancer research, which makes compelling economic arguments to support its funding. Dr. Woychik noted that the ROI from the WTP is remarkable, and observed that it is important to cite that type of information when talking to policymakers and politicians. “We have to pay more attention to not just the fabulous science returns that we have, but monetizing that [as

well],” he said. Dr. Collman said she had put several links to useful stories into the chat, and would put them all into a single email for everyone’s convenience.

Dr. Engelward suggested adding information about benefits to health span, addressing morbidity as well as mortality, to emphasize the importance of keeping people healthy.

NIEHS Congressional liaison April Bennett explained that when an individual receives Federal funding, certain rules apply. Educating is acceptable, but advocating is not. Council members or grantees should work with their university’s government relations personnel if they want to meet with policymakers or members of Congress. She also referred to two different proposals in Congress regarding NIH reorganization, which are described in the Director’s Report. She encouraged Council members to contact her with any questions at april.bennett@nih.gov .

XIII. Complement-ARIE: Complement Animal Research in Experimentation

Co-program Coordinator Dr. Dan Shaughnessy briefed Council on the Complement-ARIE program.

The program’s purpose is to catalyze the development, standardization, validation, and use of human-based new approach methodologies (NAMs) that will transform the way basic, translational, and clinical sciences are done.

The program’s goals are:

1. Better model and understand human health and disease outcomes across diverse populations.
2. Develop NAMs that provide insight into specific biological processes or disease states.
3. Validate mature NAMs to support regulatory use and standardization.
4. Complement traditional models and make biomedical research more efficient and effective.

Dr. Shaughnessy listed the members of the Complement-ARIE Working Group, comprised of personnel from several ICs and co-chaired by Dr. Woychik and Dr. Joni Rutter from NCATS. He went over the program’s development timeline.

Major work products from the program will include NAMs that incorporate:

- Complex *in vitro* models emulating population diversity
- *In silico* multi-scale systems simulating healthy/diseased individuals
- *In chemico* cell-free systems capturing dynamic changes
- Combinatorial NAMs and integrated FAIR datasets and AI-engines for all NAMs

The program builds on previous and current activities across all NIH centers related to NAMs, with support for digital twin models, *in silico* models, complex *in vitro* systems, and a variety of *in silico* and machine learning/AI models, as well as *in chemico* screening models.

Dr. Shaughnessy listed several strategic planning activities involving stakeholder outreach. The program released a comprehensive landscape analysis on the NAMs field, which was another Common Fund strategic planning activity.

The program sponsored a Complement-ARIE Challenge Prize Competition to solicit entries for new methods and approaches in NAMs. Twenty prize winners shared the total prize purse of $1 million, with each winning team receiving $50,000. Dr. Shaughnessy provided examples of the winning entries.

The program includes several components, each of which Dr. Shaughnessy described in more detail:

- Technology Development Centers
- NAMs Data Hub and Coordinating Center (NDHCC)
- Validation and Qualification Network (VQN)
- Community Engagement and Training

He discussed a potential NIH-FNIH public-private partnership, which would serve as a validation network for regulatory implementation.

He went over the NIH Common Fund Complement-ARIE Notice of Intent to Publish a Funding Opportunity (NOFO) related to support the Complement-ARIE NAMs Technology Development Centers. The estimated release date of the NOFO October 18, 2024, and detailed the program flow diagram illustrating its key components.

Dr. Woychik noted that the Common Fund proposal was unanimously supported by all of the NIH ICs, so it is clearly an area of great interest and focus.

Dr. Engelward asked Dr. Shaughnessy what the plan is for advertising the program. He said there is information on the Common Fund webpage, as well as the NOFOs that will be published, pending final approval. There will be a series of webinars as well.

XIV. Concept: Continuation of the NIEHS Environmental Health Sciences Core Centers Program

Dr. Claudia Thompson briefed Council on the concept proposing continuation of the NIEHS EHS Core Centers (EHSCC) Program. She informed Council members that the Centers are incubators for science, translational research, careers, and community

engagement/partnerships. She provided details on the Centers Program background and structure. The goals of the EHSCC program are to:

- Provide intellectual leadership and foster innovation
- Translate research into public health outcomes
- Support new ideas and collaborations
- Provide career development for future leaders
- Engage communities in multi-directional communication

There are currently 26 Centers, with 1,946 members. They were responsible for 1,682 publications in 2023, with 4,411 citations in FY2023. They have generated 338 written and educational materials.

In the period from 2017-2024, there were approximately 223 career development recipients, with approximately 135 pilot awards. Over 228 NIH grants were awarded, and there were over 2600 publications.

Pilot Projects are another hallmark of the Centers Program. Since 2007, the Core Centers have funded 595 pilot projects, with an investment of over $13 million and an estimated return on investment of nearly $159 million. Dr. Thompson provided details on the pilot project approach and methods topics, and an example of a successful pilot project.

The Core Centers have proven to be nimble, translational, and collaborative. They have explored emerging EHS topics such as nanoplastics and microplastics. They have promoted translational research, including the value of bi-directional community engagement. Dr. Thompson described several Center collaborative projects, including disaster response projects.

She went over previous Core Center Program evaluations, including identified opportunities and implemented solutions.

The proposed concept:

- Mechanism: P30
- NOFO: RFA with annual receipt dates for next 3 years
- Minimum requirement: funded research base of 3.0M in DC of supported EHS projects that can be a mix of NIH, Federal, and private grant support; at least 50% of the research base must be from NIH
- Structure: Required
    - Admin Core
    - Facility Core
    - Career Development

    - Community Engagement Core
    - Pilot Project Program
    - Translational Vision
    - Plan for Enhancing Diverse Perspectives
- Total cost for program:
    - $6.0-$7.5M/year based on availability of funds
    - New: $850K/year for 4 years; Competing renewals $1.0M/year for 5 years

The Council discussants for the proposed concept were Dr. Miller and Dr. Hood. The questions they were asked to address were:

- What input or recommendations does Council have for advancing efforts to address the gap areas?
- A new evaluation of the Core Centers Program seems appropriate. What topics or focus areas would interest Council?

Dr. Miller noted the evolution of the P30 program. He said it has developed in a very strong way. He felt that it is one of the best places for the values of NIEHS to go to the research community. As a research administrator, he observed that not all institutes have a P30 program. He said that the P30s from NIEHS have allowed environmental health sciences to thrive at many universities, at a time when occupational health residencies were closing down. When there is a P30, university administrators listen to that, they see it and build programs around it. The P30s have been "one of the marquee programs of NIEHS, because of how much it has helped build the programs at universities." He supports the concept, and felt that a structure has been arrived at that works well, with fewer complaints. Opening the eligibility is a good thing, he noted. He speculated that the coverage of the program is better than thought, when the partnerships of the P30s are considered. That information must be captured appropriately. The program is really important, and the current structure seems to be working very well, he concluded.

Dr. Hood related his experience with P30s. He said he has been a huge fan of the P30s over the years. Although he approved the concept, he noted that it is time to have a serious conversation about "leveling the playing field a little bit more." He said he was not aware of any minority-serving institutes that could meet the $3 million threshold. He felt that it was another example of "the rich keep getting richer, the poor keep getting poorer." He suggested that instead of conglomerate numbers of P30s, why not have five P20s? He felt there might be room for that in the future. He did support the concept, however, "because I am a P30 seedling myself."

Dr. Hoyo wondered whether the definition of the $3M requirement could be expanded so that it encompasses all environmental science. Dr. Thompson clarified that the $3M

base is not NIH exclusively, but could include other funding sources, as long as $1.5M is NIH. However, it does not have to be at NIEHS exclusively, as long as it is environmentally related research.

Dr. Ingram agreed with Dr. Miller's comment about encouraging institutions to partner, but called for NIH to make that less cumbersome, because for example some of the tribal colleges have less infrastructure to handle grants and invoicing.

Dr. Walker said that she was a huge fan of the program, but that there is a dichotomy emerging. She said the P30s were originally envisioned as infrastructure grants, but they are much more now. She agreed that there may be a role for a smaller type of grant. A grant with a smaller threshold should be considered, she said.

Dr. Hornbuckle said it is exciting that changes are being considered to recognize the breadth of environmental research that pertains to environmental health and not just funded by NIH. She noted that the program is already pretty competitive, and she asked Dr. Thompson if she is concerned that opening it up to many more organizations could dilute the impact of the centers or create a large challenge of how to decide which criteria to use in assessing whether it is environmental health research. Dr. Thompson said it was an excellent point. She agreed that the program is extremely competitive, and the budgets for the centers have been flat for a long time. So it is incumbent upon applicants to ensure that the grants that they are including in their base are truly conducting environmental health research. It is important to be flexible, and allow for more investigators to participate.

Dr. Engelward said that she was a Center seedling, and echoed Dr. Thompson's observation that these proposals are enormously time-consuming to compile. She suggested a pre-preproposal phase, a five-page document that could be sorted through that could help potential applicants determine whether they are competitive, perhaps saving them a great deal of time if they are not. Dr. Thompson said that was an interesting concept that would be considered.

Dr. Balshaw called for a motion to approve the concept. Dr. Miller so moved, and Dr. Hood seconded the motion. The Council voted to approve the motion.

XV. Concept: East Palestine Train Derailment

Toccara Chamberlain presented the concept related to the February 3, 2023 train derailment in East Palestine, Ohio.

She went over the event itself and the resulting exposures and health outcomes. She provided a timeline of subsequent events, focusing on NIEHS involvement in response to the disaster. Events included a special NASEM workshop in November, 2023, to

discuss research priorities and community concerns. In January, 2024, six NIEHS time-sensitive projects were awarded. They were announced by President Biden during his February 16 visit to East Palestine.

Ms. Chamberlain discussed the NASEM workshop in more detail, including takeaways, and potential short-term and longer-term strategies. She described the six NIEHS funded grant projects, along with ensuing coordination efforts, as well as Federal coordination efforts such as the Village of East Palestine Healthcare Taskforce, which includes NIEHS. Continued community concerns include:

- Children's health concerns
- Long-term follow-up
- Registries (surveillance, health effects)
- Contamination of food sources
- Impacts of relocation
- Specialized testing access
- Mental/Behavioral health

The proposed concept structure focuses on a community-academic partnership:

- Guiding Principles
    - Strong community involvement
    - Multi-directional communication strategies
    - Timely report-back of research results
- Benefits
    - Multiple projects to address community concerns
    - Minimizes burden on study participants
    - Encourages coordination and collaboration with multidisciplinary teams
    - Long-term approach to concerns
- Potential Mechanism
    - Cooperative Agreement (U mechanism)

Ms. Chamberlain concluded her presentation by listing NIEHS Program Contacts and additional resources available.

Council discussants were Dr. Cormier and Dr. Ingram.

Dr. Cormier applauded NIEHS for its rapid response and proactive stance on the disaster, which have benefited the affected communities tremendously. She felt that the concept mechanism is timely and critical. She noted that the soil samples taken in East Palestine near the derailment site, even after cleanup, still contain furans and dioxins, which are persistent compounds with long lifetimes, presenting a significant potential for long-term health risks in the community. She said that the U19 cooperative agreement

would be an appropriate mechanism. That type of coordinated effort would help the community avoid research fatigue and facilitate long-term study. The U19 would also increase data harmonization, making it an economical use of shared resources.

Dr. Ingram said that her discussion points came from her experience working on the 2015 Gold King mine spill in central Colorado. The initial response to that disaster was terrible, and the community had a very negative feel for the experience. In this instance, it looks like there is really good coordination, she observed, among both NIH-funded agencies and others as well. She said that in her experience, the communities do not care where the money is coming from. They want understandable, comprehensive information. She recommended keeping those points in mind in the East Palestine efforts. In the new funding opportunities, she hoped that the researchers would already have established connections to the area, so that trust-building has moved forward. She stressed that the mental health aspect is huge. The coordination aspect is most important.

Ms. Chamberlain noted that several of the teams have visited the area and have established relationships with the community.

Dr. Hood, as an Ohioan, noted that he had been pulled in to the disaster response. He said the experience was “one of the most fulfilling chapters in my life.” He said that a great deal has been learned that can be applied if it happens again, and it will happen again somewhere.

Dr. Walker wondered how this type of mechanism will work in the future when similar sorts of disasters happen. She asked how much credit NIEHS is getting for all of the good work that is being done in this instance. Ms. Chamberlain said that NIEHS is getting recognition, and is being pulled into many conversations across the government to provide technical assistance and to highlight the projects. Dr. Thompson added that there is a fact sheet available about the six groups being supported. She said there has also been considerable Congressional interest in the program. She said that the time-sensitive program itself is always open to any disaster that is happening, and whether that elevated into something else is on a case-by-case basis. The Deep Water Horizon Gulf oil spill was the last example of that happening.

Dr. Woychik noted that the DR2 program is led by NIEHS, but is an NIH effort, with other ICs participating. Dr. Collman said that there are close to 20 different groups involved in the interagency working group on disaster response. She said that anytime such a disaster happens, there is a government-wide response. There is both recovery and research involved. In the NIEHS effort, there is also a partnership with the National Science Foundation related to rapid response. The time-sensitive disaster response program has funded much work over the years on climate-related disasters. When a

disaster occurs, many of the Federal agencies are front and center because they are focused on recovery, but eventually fall back as the focus shifts to research assessing short-term and long-term health effects, along with community engagement and environmental justice work. NIEHS does receive appropriate credit for its involvement, both now and into the future, she observed. Dr. Woychik added that the NASEM workshop was co-funded by multiple ICs.

Dr. Savasta-Kennedy asked to what extent the work that NIEHS is doing in the context of climate and climate justice. Dr. Collman replied that the annual meeting of the Partnerships for Environmental Health program earlier in the year had focused on community engagement work, environmental justice and climate justice. She said that all NIEHS programs in the climate initiative have community engagement components. She listed several other examples.

Dr. Balshaw called for a motion to approve the concept. Dr. Cormier so moved, and Dr. Savasta-Kennedy seconded the motion. The Council voted to approve the motion.

XVI. Adjournment

Dr. Woychik thanked the Council members for their work on the meeting, and all attendees for their participation. Dr. Archer added his thanks to Council for its engagement and important advice. Dr. Woychik adjourned the open session of the meeting at 2:58 p.m., September 12, 2024.

CLOSED SESSION

This portion of the meeting was closed to the public in accordance with the determination that it concerned matters exempt from mandatory disclosures under Sections 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. The closed session adjourned at 4:30 p.m., September 12, 2024.

REVIEW OF APPLICATIONS

The session included a discussion of procedures and policies regarding voting and confidentiality of application materials, committee discussions and recommendations. Members absented themselves from the meeting during the discussion of, and voting on, applications from their own institutions or other applications in which there was a potential conflict of interest, real or apparent. Members were asked to sign a statement to this effect. A total of 583 applications (420 primary and 163 secondary), requesting support of $288,354,035 received second-level review during this Council meeting. The Council concurred with IRG for all applications reviewed.

CERTIFICATION:

Richard P. Woychik -S
Digitally signed by Richard P. Woychik -S
Date: 2024.11.20 08:47:29 -05'00'

Rick Woychik, PhD
Chairperson
National Advisory Environmental
Health Sciences Council

David M. Balshaw -S
Digitally signed by David M. Balshaw -S
Date: 2024.11.18 09:16:52 -05'00'

David Balshaw, PhD
Executive Secretary
National Advisory Environmental
Health Sciences Council

Attachment:
Council Roster