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 12-13, 2023

The 170th meeting of the National Advisory Environmental Health Sciences Council convened on September 12 and 13, 2023. Open session convened at 9:03 am and ended at 3:52 pm September 12. A closed session took place from 4:00 pm to 4:16 pm September 12. Open session began at 9:02 am and adjourned at 1:44 pm on September 13. Dr. Rick Woychik, Director, NIEHS, presided as chair.

Participating Council Members

Philip Bourne, PhD (attended via Zoom)
Yulia Iossifova Carroll, MD, PhD (*ex officio*)
Suzanne Fitzpatrick, PhD (ex officio) (attended via Zoom)
Andrew Geller, PhD (*ex officio*)
J. Timothy Greenamyre, MD, PhD
Irva Hertz-Picciotto, PhD
Andrij Holian, PhD
Darryl Hood, PhD
Keri Hornbuckle, PhD
Jani Ingram, PhD
Andrew Jorgenson, PhD (attended via Zoom)
Gary Miller, PhD
Gökhan Mutlu, MD
Patricia Nez Henderson, MD
Trevor Penning, PhD
Maria Savasta-Kennedy, JD
Karen Vasquez, PhD

NIEHS Staff

(Personnel listed in *italics* below attended in person.)

Kathy Ahlmark
Trevor Archer, PhD
David Balshaw, PhD
Jennifer Baker
Linda Bass, PhD
Sharon Beard
Abee Boyles, PhD

Danielle Carlin, PhD
Jennifer Collins
Gwen Collman, PhD
Yuxia Cui, PhD
Christie Drew, PhD
Beverly Duncan, PhD
Chris Duncan, PhD
Anika Dzierlenga, PhD
Benny Encarnacion
Kelly Ferguson, PhD
Amanda Garton
Nidhi Gera, PhD
Kimberly Gray, PhD
Jenny Greer
Arshya Gurbani
Janet Hall, MD, MS
Astrid Haugen
Michelle Heacock, PhD
Heather Henry, PhD
Jon Hollander, PhD
Mike Humble, PhD
Gary Johnson
Deborah Jones
Bonnie Joubert, PhD
Melissa Judd-Smarr, PhD
Alfonso Latoni, PhD
Cindy Lawler, PhD
Gerald Lilly, MD, MPH
Mbeja Lomotey, Dr.P.H.
Kamel Mansouri, PhD
Lindsey Martin, PhD
John Maruca
Jacqui Marzec
J'Ingrid Mathis
Kimberly McAllister, PhD
Elizabeth McNair
Carolina Medina
Latavia Miller
Parris Milly
Nathan Mitchiner
Srikanth Nadadur, PhD
Robert Neiberger
Sheila Newton, PhD
Liam O'Fallon
Suzy Osborne
Eric Persaud, DrPH

Kristi Pettibone, PhD
Nicole Popovich
Ashlinn Quinn, PhD
Lingamanaidu Ravichandran, PhD
Scott Redman
Jim Remington
Caleb Rogers
Trey Saddler
Chris Schur
Thaddeus Schug
Carol Shreffler, PhD
Varsha Shukla, PhD
Melissa Smarr, PhD
Claudia Thompson, PhD
Brittany Trottier
Steven Tuyishime, PhD
Fred Tyson, PhD
Leroy Worth, PhD
Rick Woychik, PhD
Darryl Zeldin, MD

NIH Staff
Joshua Denny, MD, *All of Us* Research Program
Jodie Fleming, CSR
Rachele Peterson, *All of Us*

Members of the Public Present

Bok Baek, PhD, George Mason University
Marzyeh Ghassemi, PhD, MIT
Thomas Hartung, MD, PhD, Johns Hopkins Bloomberg School of Public Health
Ernie Hood, Bridport Services, LLC
Elizabeth O'Nan
Chirag Patel, PhD, Harvard Medical School
Michael Snyder, PhD, Stanford Medicine

OPEN SESSION
The meeting was open to the public on September 12, 2023 from 9:03 a.m. to 3:52 p.m. and on September 13, 2023 from 9:02 a.m. to 1:44 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, 2023 from 4:00 p.m. to 4:16 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 in the room and present on the Zoom call 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.

II. Consideration of June 2023 Meeting Minutes

Approval of the June 2023 meeting minutes was moved by Dr. Penning and seconded by Dr. Holian. Council voted to approve the minutes, with all in favor.

III. The *All of Us* Research Program: Using Environmental Factors to Shape Precision Medicine

Dr. Joshua Denny, Chief Executive Officer of the *All of Us* Research Program, addressed the Council on the use of environmental factors to shape precision medicine. He provided background information about the *All of Us* program, including its mission and core values. There are currently more than 700,000 participants enrolled since the program's May 2018 launch, with nearly 400,000 having shared their electronic health records. Over 80% of participants are underrepresented in biomedical research.

Data is being collected from *All of Us* participants through electronic health records, participant surveys, physical measurements, biosamples, and wearable data. Dr. Denny described the program's strategies for return of genetics and genomic information to participants, as well as the four tiers of data access for researchers, including a public tier, with a public data browser. The researcher workbench data is diverse and longitudinal, with nearly 250,000 genome sequences as of April, 2023.

The program's link to American Community Survey data is one of its first to provide environmental data, particularly location information.

Dr. Denny discussed several of the current funding opportunities associated with the *All of Us* Research Program. The program currently has 6,789 registered researchers at more than 580 institutions, including 40 Historically Black Colleges and Universities and 54 Hispanic Serving Institutions. There are currently 6,794 active research projects, with

the top conditions being studies being cardiovascular disease, hypertension, mental health, cancer, and diabetes.

He acknowledged that to meet scientific priorities and goals for precision medicine, *All of Us* will need to integrate individual location and environmental exposure data. Thus the collaboration with NIEHS will continue and expand going forward. In 2022, All of Us and NIEHS hosted a workshop and summit series called "Accelerating Precision Environmental Health: Demonstrating the Value of the Exposome," which was designed to develop a roadmap for integrating exposomics into health and disease research. The entire *All of Us* cohort will participate in integrating locational information into the *All of Us* workbench, along with work to integrate geospatial, environmental, and social determinants of health data into the workbench. A subset of the cohort will participate in an ancillary health study to link exposomic and methylation data with various phenotypes. A new award funding the Center for Linkage and Acquisition of Data (CLAD) will build a broad dataset including behavioral, biospecimen, environmental, health, and other data over an individual's life course. Also, the first large *All of Us* ancillary health study with explore Nutrition for Precision Health.

Dr. Vasquez commented that despite the tremendous resource represented by *All of Us*, it seems that the limitation is the number of people who are participating. She asked how it will prioritize for the future, particularly regarding surveys and biospecimens. Dr. Denny replied that resources are limited, and one of the most precious is participants' time. In terms of surveys, he said that the program is roughly limited to one per year. He said the program is currently working on re-assessments, looking at the highlights of previous surveys and how to not repeat what has already been done. In terms of biospecimens, he noted that they collect much more than just DNA, and there is the funding and mandate from Congress to generate sequence data. Most of the other biospecimen information will be generated through ancillary studies. Much comes from partnerships with NIH institutes and centers, as well as public/private partnerships. There are also plans to eventually make data available to external researchers. He noted that environment is one of the program's foci right now.

Dr. Bourne said that the program represents what could be a powerful message regarding changing environments and changing health. He said that the longitudinal studies related to the environment will be important to communicating the message about the changing environment and its effects on health. Dr. Denny agreed about the importance of longitudinal data. He emphasized that "we are a platform," presenting opportunities for gene/environment studies, mental health surveys, and epigenomic changes, among many others. Dr. Bourne noted the importance of the program to helping to educate the next generation of researchers to explore those problems. He said there is an absolute explosion of young people interested in acquiring quantitative skills and addressing societal problems.

Dr. Ingram asked about the absence of a listing for American Indian/Alaska Natives in the materials Dr. Denny had presented. She asked if the program has the data, and if it is not yet approved, where the approval process might be. Dr. Denny said that with the program's consultation process with tribal communities, they had deliberatively not yet put the data in the curated data repository that is released to researchers. COVID delayed the process for a period of time, but it is again being pursued. He wondered how *All of Us* can partner more with tribal communities, and understood that it may be a tribe-by-tribe process.

Dr. Woychik observed that there are real opportunities for ancillary studies, which could be a model for other ICs and entities involved in biomedical research, working with the *All of Us* cohort to conduct the types of gene/environment studies that are needed, as well as to bring to *All of Us* the appropriate exposomic data.

Dr. Miller, who is also on the *All of Us* advisory committee, said that it would be important to look at some of the other biobanks that are farther along, such as the UK Biobank. Learning from their results and practices would be important for the environmental health field, representing endless possibilities for ancillary studies.

Dr. Penning asked whether there is a way to establish partnerships with other biobanks, avoiding duplication. He also asked about the program's relationship with EPA, particularly regarding exposure assessment. Dr. Denny said that *All of Us* is working with biobanks across the world, and is working deeply with UK Biobank. He said that in terms of exposome data, they are guided by their colleagues at NIEHS in the process, and are eager to use and re-use data generated by the EPA and others.

Dr. Savasta-Kennedy asked what *All of Us* tells potential participants who are concerned about privacy and who else may have access to their data. Dr. said that the program works to be very clear in its video and document-based consent process that the data will be broadly accessible to researchers. They promise that they will do all they can to remove any personally identifiable information, but also promise that it is not impossible that someone could re-identify them. There is a risk, but there is also a degree of trust involved, and they work to maximize transparency and communicate that they do all they can to protect privacy.

Dr. Nez Henderson asked Dr. Denny about how the program would ensure that people participating are not from the tribes that have a moratorium on genetic studies. Dr. Denny said that right now the program is not recruiting on tribal lands, and works on self-identification. He noted that although the tribal genetic results are not currently being released to researchers, they are available to tribe if they want them.

Dr. Hood asked about the use of machine learning and ChatGPT by *All of Us*. Dr. Denny explained that ChatGPT does not currently have access to the system, but

people are using artificial intelligence (AI) algorithms. He cited an example of a paper published through the system on using AI to determine who would need surgery for glaucoma. When applied to the *All of Us* system, the algorithm did not work. He noted that as a problem with AI applications, that when they are used with diverse populations, they fail. He said that UK Biobank is a tremendous resource, but is not a diverse resource, which is a limitation. Both types are needed, however.

IV. AI, NAM and Toxicology

Dr. Balshaw introduced the next series of presentations, which concentrated on AI, machine learning (ML), and what can be done with very large datasets. The segment began with Dr. Thomas Hartung from the Johns Hopkins Bloomberg School of Public Health director of the Center for Alternatives to Animal Testing, who addressed the emerging role of AI and non-animal methods or new approach methods (NAM) in toxicology.

Dr. Hartung shared data showing that AI was involved in 2.5% of all publications in 2021, with a tremendous number of journal citations and patents coming from China. He showed information from the 2023 World Economic Forum that illustrated how AI is influencing several areas of healthcare. A virtual Keystone Symposium on AI in Biomedicine in early 2023 is currently in preparation.

Dr. Hartung described what he called the “Toxicologist’s Christmas Wish List,” listing several areas in need of advances. He noted that there are currently approximately 350,000 chemicals in commercial use, but there are good assessments for only 5,000-10,000 of them. Animal testing is expensive and slow, and there is considerable room for improvement. “AI promises to be exactly this,” he said.

Big data is necessary for AI, particularly complementary pieces of information from different areas. Volume, Variety, and Velocity are all important in Big Data. AI is making Big Sense of Big Data. There has been an enormous synergy of data generation, computing power, and AI models. All three areas have grown tremendously, just in the last few years. Ultimately, the power of AI has increased more than one billion-fold over the last 60 years.

Deep learning was the turning point, and today with more data deep learning is increasing its predictive power. Dr. Hartung described the tools involved in big data and AI, including tools such as robotized testing and high content imaging. He discussed what he called “ToxAIcology,” comprised of “Big Data” and “Big Computer.”

He noted that natural language processing has been important, including data extraction from literature, reports, and databases. Last March, GPT-4 was launched after GPT-3.5 in November 2022, with 400 million people signing up for it. GPT-4 was

the fastest roll-out of any technology ever seen. Science and health was determined to be 9% of the information being accessed, particularly information coming from open access publishers. Dr. Hartung showed data stating that AI has now surpassed humans at a number of tasks. There are now 8.8 million AI researchers world-wide, with steep increases in the number of scientific articles over time. BioGPT has out-performed humans in annotating scientific papers. It is predicted that by 2030, AI models will out-perform humans in drafting scientific papers. Going forward, humans will need to focus in their writing on things that are not easily accessible, such as ideas, inspiration, experience, and opinions.

Dr. Hartung provided several examples of AI surpassing humans in capability, such as chess and drug design. In “ToxAIcology,” the big data and big computer power are combining to yield big sense, in the forms of data retrieval, evidence integration, predictive toxicology, digital pathology, and reporting.

He listed several AI use cases, including speech, vision, language processing, expert systems, planning & optimizations, robotics, and machine learning. He described instances of transfer learning, combining read-across with machine learning. The trend is toward AI outperforming animal test reproducibility. This is providing enormous and growing potential for replacement of animal use.

Dr. Hartung acknowledged that there is a dark side to AI. Humans need to be in the loop, and the challenges include causality, validation, and bias in data leading to bias in results. Data integration technology can be used to identify adverse effects, off-target effects, biomarkers, interspecies differences, and adverse pathways. “This is part of the next wave of revolutionary changes which are possible in toxicology,” he said. He mentioned that knowledge in the field is doubling every seven (or less) years, and it might be time to consider “Toxicity Testing in the 21st Century 2.0.” There has been a call for a DoD workshop on the Future of Toxicology and Human Exposome Project that will be exposure-driven, technology-enabled, and evidence-integrated.

He described a European Union ONTOX project to address liver, kidney, and the developing brain, which is developing AI toxicology software in a five-year project. One starting point is the sysrev.com platform, which integrates data from literature, and is complemented with public databases, and the internet. Dr. Hartung provided details about the approaches to determine probability of hazard, as the field moves toward probabilistic risk assessment. He then showed how combining brain microphysiological systems (MPS), sensors, and AI to produce organoid intelligence (OI) which suggests that these models can learn. OI will be the new frontier in biocomputing and intelligence-in-a-dish.

Dr. Hartung said that AI will be useful in integrating scientific knowledge, accelerating drug development, optimizing public health and prevention, and democratizing healthcare access. The smart path forward will utilize open access, machine-readable literature, identification of bias in data, and explainable AI.

Dr. Penning asked Dr. Hartung about his algorithm for read-across analysis, and whether it is taking repeat dose and metabolism into account. Dr. Hartung said that repeat-dose aquatic toxicity was part of the original work but for human toxicity is only now part of the ONTOX work program. Metabolism was included in work to predict human skin sensitization, but with overall somewhat disappointing impact. Dr. Penning asked whether the algorithms are using metabolic simulators. Dr. Hartung said that his group was not impressed with metabolic simulators. Dr. Penning asked whether the algorithms take into account exposure assessment of toxic threshold of concern (TTC). Dr. Hartung said that the ONTOX project does have an exposure arm, which includes TTC. Dr. Penning asked Dr. Hartung how easy it would be for research scientists in academia to access some of the tools that have been developed. Dr. Hartung said that the model is to develop full access within ONTOX.

Dr. Bourne asked what Dr. Hartung thought funding agencies should be doing with respect to AI development, with the field moving so incredibly fast. He also asked about training the next generation in the field, and whether he thoughts students were being adequately prepared to take the field to the next level. Dr. Hartung said there has been a wave of pre-trained and highly motivated students who want to apply AI in all parts of life. He felt that AI is the answer to “information flooding.” He noted that there are 20,000 articles in PubMed per year on toxicology alone. AI helps to condense and extract the information. However, there must not be autonomous AI; the responsibility must remain with humans. AI can also increase productivity by reducing duplication. In terms of funding, the agencies can enforce open access publishing, machine-readable publishing, and FAIR data accessibility.

Dr. Woychik asked Dr. Hartung how he envisions the powerful tools he has described being used to better understand how individuals respond differently to different environmental exposures; the gene-by-environment effect, integrating complex genetics and genomics, including epigenetics. Dr. Hartung replied that to understand individual differences is the holy grail of toxicology. He noted that the first requirement is data, and that AI is no solution if there is no data. He said the MPS and stem cell systems are ideal to synergize the information, such as his group’s work in autism. Dr. Woychik said that all can appreciate the value of the NAMs approaches, but many of the biological impacts on individuals are going to be epigenetically driven as a consequence of environmental exposures. He asked how well the *in vitro*, 3D, MPSs recapitulate some of the epigenetic modifications that may be occurring withing the individual. Dr. Hartung said that unfortunately most of the epigenetics are wiped out. However, in some

diseases such as Alzheimer's, the histopathology of stem cell-derived neurons shows the effects of the disease. It will be necessary to apply epigenetic pre-treatment of the systems to create the memory that can be detected subsequently.

V. Democratizing Chemoinformatics: MOVIZ Pipeline for Intuitive Modeling and Visualization Using Low-Code Machine Learning

Dr. Mary Wolfe from the Division of Translational Toxicology (DTT) introduced Dr. Kameal Mansouri, a DTT computational chemist in the Predictive Toxicology Branch, with the NTP Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM).

Dr. Mansouri spoke about a particular application of AI, which will contribute to democratizing chemoinformatics.

In the early days of computers, their use required expertise in coding and programming. Today, with graphical user interface, computers are available to everyone. This is the democratization of computers. Dr. Mansouri said that in the next few years, the same process will extend to complicated machine learning applications.

Chemoinformatics needs modeling and prediction, data storage and access, data analysis and visualization, and data mining and curation. Currently, most of the processes are mainly available to experts because programming is time consuming and challenging. Such processes will soon give way to no-code and low-code development, with software creation through graphical user interfaces and configuration, brining benefits of access, cost-efficiency, automation, agility, integration, flexibility, and easy deployment.

Dr. Mansouri described the KNIME Analytics Platform, which is an open-source, no-code/low-code software platform based on the visual programming paradigm. It covers diverse data science needs, and allows use of commercial or proprietary tools. He showed the workflow associated with the KNIME Server WebPortal. He discussed the Modeling and Visualization or MOVIZ Pipeline, which involves modeling and prediction, data storage and access, data mining and curation, and data analysis and visualization. The NIEHS KNIME WebPortal is characterized by flexible input/output formats, easy to add or remove workflows, different developers or groups, multiple purposes or fields, and workflows controlled by owners. It is currently behind the NIEHS firewall, but eventually it will be made available to the public.

One of the applications of the workflows is chemical grouping. Dr. Mansouri illustrated how the KNIME workflow process can be used for that purpose, in a very flexible way using various characteristics, depending on the goal of the study. He provided details about how the workflow process works, including results and interpretation using AI and

machine learning, such as GPT interpretation. He demonstrated how to use the process.

He said that the workflow is already being applied to solve specific problems within DTT and in collaboration with other teams. It is being used for clustering and prioritizing for testing of chemicals.

Dr. Hood asked Dr. Mansouri how the system works with respect to dimension reduction. Dr. Mansouri explained that it does incorporate dimension reduction, which is a very important step in the process.

Dr. Penning asked Dr. Mansouri to comment on how the cluster analysis differs from more traditional decision trees based on chemical structure. He also mentioned a recent paper that identified 14,300 different PFAS chemicals, arranged into 140 chemotypes, based on a more traditional decision tree approach. Dr. Mansouri said that decision tree is actually one of the algorithms provided in the workflow application, among several. He said there is an advantage because it guides the user through all of the different steps, without skipping any important step. Regarding PFAS, he agreed that there are many PFAS chemicals, and said that the important question is what specific property is being studied.

VI. Multi-modal AI to Interrogate the Complex Exposome in Complex Traits

Dr. Chirag Patel from Harvard Medical School briefed Council on a multi-modal future for exposomic research—data, use cases, benchmarks, and models.

He listed the key questions for multi-modal approaches in exposome research:

- Is it possible to unlock causes or refine existing models of disease via integration of multiple modes of the exposome?
- What is the relationship between multiple domains of the exposome with disease?
- How does the exposome exert biological change, and how do these changes relate to health?
- Does the exposome explain disparities in health outcomes?

Dr. Patel provided several examples of biobanks, which allow an opportunity to combine phenotype, genotype, and exposome in large scale. He said there are many multi-modal approaches geared toward integrating across diverse data inputs. Current use cases feature maximization of predictability of health outcomes across domains, raising the question, what are the use cases for the exposome?

He discussed the fundamental model of phenotype/disease prediction and variation: P=G+E (phenome=genome+exposome). Combining with biobank-scale data, larger and larger sample size has allowed a large increase in the number of genotype-phenotype associations.

The genome-wide association study has helped refine genetic models of phenotypic variation, shedding light on how many variants and what genes are associated with a particular phenotype, how to replicate to assess reproducibility, the confounders involved, and what experiments need to be conducted to understand causality. Whether the GWAS studies are predictive of phenotype and disease is where the field may fall short. A progress report in 2009 evaluated explanations for missing heritability, and there is now an architecture of genetic variants associated with phenotypes, such as human height. Now, thanks to new ways of measuring, the field is moving toward omnigenic models to describe GWAS findings. Dr. Patel described recent publications on the external exposome—systematic exposures across domains and modalities. He noted that modalities of the exposome in the biobanks are time-dependent, correlated, and interactive.

Dr. Patel related that multi-modal approaches must optimize: (1) how much variation attributable to environment there is in disease, and (2) how and what factors of the exposome are associated with disease. The total aggregate exposome, or the total architecture of phenotypes, is a combination of shared and non-shared exposome. It includes such factors as weather, air pollution, and census socioeconomic status, along with clinical data warehouse information. Dr. Patel provided several examples of such a multi-modal approach, including the creation of an exposome-phenome atlas. In one example, he noted that with a dense correlation between age, ethnicity, income, and the exposome, most associations are concordant, but decrease in size when correcting for demographics.

He said it is believed that the exposome exerts biological change. He cited an example of a study that showed that dietary metabolic signatures are strongly associated to risk. The study showed that the metabolome predicts food group better than total caloric intake alone, and is more precise in predicting risk. Diet-metabolome patterns were predictive of diabetes and cardiovascular disease. Dr. Patel discussed a UK Biobank study that looked at 111 modifiable and non-modifiable exposures to build a poly-exposure risk score (PXS), as opposed to a polygenic risk score (PRS). He also described a study of the COPD exposome building a socioeconomic plus exposome risk score (SERS) across smoking status. Smoking was seen to be a key determinant of COPD, but adding exposome and genome data added predictive power for current smokers.

Dr. Patel concluded his presentation by mentioning opportunities and challenges for new multi-modal strategies and exposome research:

- How the exposome interacts and co-occurs within and across domains and modalities
- Modality measure across different scales, from the molecular to the geospatial (and even genetic!)
- Multi-modal exposome models may enhance (or displace) candidate models
- A major threat includes bias: need benchmarks like the exposome-phenome atlas to gauge and validate predictions, especially in observational settings

Dr. Vasquez commented that the more is heard about AI, omics, and large datasets, it becomes more clear that mechanistic studies are needed to understand the information. She asked how taking large numbers of averages, looking for correlation, helps individualized medicine. Dr. Patel agreed that mechanistic studies are needed to get to mechanism and causation. The exposome data structure could enable those communities to talk to each other, and the multi-modal strategies may be helpful in stitching the data together. He said that the poly-exposure score can be used at the bedside, even though it is not predictive. Advocates would say that it is helping patients. He said that we can do so much better with environmental risk, through tools like the poly-exposure score. Testing whether it is effective for screening disease or as a diagnostic would be one way of getting to the bedside.

Dr. Hood asked Dr. Patel to elaborate on the Charlotte study he had alluded to. Dr. Patel mentioned that this graphic was an example of how to match the residential location of twins to estimate the shared environment. The twin study incorporate Charlotte, but zip codes also around the entire US. Dr. Patel said it was an example where biobanks will be helpful. Dr. Hood asked Dr. Patel where we should be looking in terms of the exposome. Dr. Patel replied that the tools that have been developed could tell where we shouldn't look, as a start. Dr Patel also mentioned that the point of the exposome is not to be asking "what to look for", but to measure as most as one can comprehensively.

Dr. Mutlu asked about the impact of the exposome on chronic diseases like COPD or diabetes, which develop over years. Dr. Patel said it will take integrating across the life course. It may not be able to be done at the individual level. However, the exposome may be useful to model attributes that are stable over time, or change over time, as well as elements like diet or genetic variations.

Dr. Hertz-Picciotto asked Dr. Patel about the study of height he had described. He said that when studies like that are done, they are asking where the heritability is, i.e. the genetic component of the phenotypic variation.

Dr. Woychik asked Dr. Patel for his thoughts on how to characterize the exposures that happen before birth. Dr. Patel replied that parents certainly have an effect on variation seen in subsequent generations. He said he did not know the answer, but the easy answer would be to measure the exposome in parents and determine the correlation in children, but it would be a challenge to operationalize that.

VII. The Pulse of Ethical Machine Learning in Health

Dr. Marzyeh Ghassemi from MIT briefed Council on the pulse of ethical machine learning in health. Her group at MIT is the Healthy Machine Learning Lab, which emphasizes creating actionable insights in human health.

She presented a case study on building an X-ray triage model. The model development pipeline process in machine learning involves problem selection, model collection, outcome definition, algorithm development, and ultimately, postdeployment considerations. Models obtain state-of-the-art (SOTA) performance on a given task. She shared several examples of models where SOTA clinical AI performs at or above humans. She noted that models are regulated advice givers.

Describing her triage model, she said that AI is trained by the data it is fed from human practice. Learning from human knowledge has inherent limitations, such as the rarity, biased nature, and sometimes wrongness of randomized controlled trials. This can result in machine learning that is wrong. So moving forward with ethical AI in health requires considering the entire pipeline. Dr. Ghassemi showed the result of such inherent biases in the chest X-ray triage model, which underdiagnosed several groups. She illustrated how racial/ethnic biases occur in clinical word embeddings, which come about because of human biases. She elaborated on the root causes of the biases occurring during the machine learning model development pipeline. She noted that with intelligent and intentional targeting, models can move beyond reproducing existing biases in healthcare systems.

Better open data with diverse datasets is needed to improve health AI. Health currently lags behind other machine learning subfields in reproducibility, due to so few people releasing their data. Improving descriptive labels would help improve the models. Models using descriptive labels are harsher, with higher false positive rates. Having the right data can improve the outcomes. Dr. Ghassemi also found that using group attributes can result in worse subgroup performance while improving overall model performance.

She discussed how to get to a safer integration of technology, through regulation, a culture of safety, and training, citing aviation as a good example. She noted that there are many agencies such as the FDA, AHRQ, and others, who could have roles in regulation of the field. She said it will be important to remember that there are problems

unique to health, such as inequity in underlying data/processes that will be learned and automated.

Moving forward with ethical AI in health will be an ongoing process that requires diverse data and diverse teams. It will be important to consider sources of bias in the data, evaluate data comprehensively, and understand that not all gaps can be corrected.

Dr. Vasquez asked Dr. Ghassemi if "we are ahead of ourselves in implementing AI." Dr. Ghassemi agreed, and noted that it is the specific goal of many in the AI community to deploy ahead of regulation. Dr. Vasquez asked who is in charge of regulation. Dr. Ghassemi said there are many entities involved, as is the case with aviation. It is a process that develops over time, often many years, as a field develops and matures.

Dr. Archer asked how to find out if these types of systems are being applied or utilized in one's healthcare. Dr. Ghassemi replied that covered entities are not currently required to disclose to individuals whether any algorithms were used in the delivery of healthcare. She said it is very difficult to know as a healthcare consumer whether your care has been delivered with the use of an algorithm, although now it is easier because you can requisition your clinical records. There is need for regulatory systems that can enforce standards for AI.

Dr. Bourne asked Dr. Ghassemi if she thought there were other analogies to ethical machine learning in other fields beyond health care. She described a field in machine learning more broadly called "algorithmic fairness," resulting in some give and take in performance, as adjusting a model to be more fair to specific subgroups may compromise the overall performance of the model. As a result, accuracy is not a good metric. She mentioned that in AI, conferences are the major communication mode, since they move faster than journals. She described the two major fairness conferences. Dr. Bourne noted that the issues apply beyond academia, particularly in the private sector. Dr. Ghassemi agreed, and pointed out that sectors such as finance are regulated, whereas in healthcare, some areas are not regulated at all.

Dr. Hood asked about how to balance the input in machine learning towards equity, particularly as it relates to electronic health records. Dr. Ghassemi said that all of the studies she had cited used open datasets. She felt that the goal should be for data to be diverse and representative. She discussed how difficult it is currently to access data, particularly since there is no requirement for sharing data.

Regarding the chest X-ray use case Dr. Ghassemi had described, Dr. Mutlu asked who would be responsible if an X-ray was used to decide to send a patient home who then died from an adverse event—the AI or the hospital? Dr. Ghassemi said there had recently been legislation proposed in this area, which suggested that it would be the doctor and covered entity held liable. Despite bad advice, the provider is still liable for

the end result. However, she felt that there should be some shared liability under the regulations.

VIII. Probing Health and Exposures Using Deep Data

Dr. Michael Snyder from Stanford Medicine described his group's efforts related to big data and exposures, working to integrate the information.

He noted that health is a product of the genome and the exposome. This can be documented through the use of longitudinal personal omics profiling. He cited an example from his group, a study that involved billions of measurements of 109 individuals over ten years. It is designed to help determine what a healthy profile looks like. "We're all very different, and so building these personal profiles is absolutely critical for monitoring your health," he said. The study has yielded 49 major health discoveries, spanning cardiovascular, heme/oncology, infectious disease, metabolic, and other areas, all pre-symptomatic. He likened the process to a jigsaw puzzle, building a more complete picture of the individual's health by collecting many more pieces. The first 70 people's genomes have been sequenced, and 12 were discovered to have important pathogenic mutations.

Dr. Snyder and his group have come up with new AI methods for making predictions about people's complex disease patterns, characterizing much of the heritability. Genome sequence combined with key electronic health record information can improve predictability, with clinical utility. Dr. Snyder observed that adding environmental exposure information should drive the predictive power even higher.

He added that by doing the deep profiles, it can actually be seen how people are aging. Everyone ages differently, based on "ageotypes."

These technologies, such as wearables and microsampling, should lead to an explosion of data collection and information, by allowing many measurements and sample collection to be made at home. He provided several examples, including use of wearables such as smartwatches and FitBits to detect and measure conditions like Lyme disease and COVID-19, often at or before symptom onset. Continuous glucose monitoring has shown that different people spike to different foods, including non-diabetics. Microsampling can be used for remote monitoring. Ultimately, these methods will be used to correlate physiology and biochemistry on a personal, individual level.

Part of these developments will be the ability to identify personal exposomes. Dr. Snyder provided examples of individuals (including himself) who had worn the monitoring device over various periods of time and in various locations. The study showed that people's exposures were very personal and dynamic, and that season and location matter. More than 2000 chemicals were found in the samples. Chemicals were

correlated with biologicals. The goal is to correlate exposures with the microbiome and other internal measurements. In the study Dr. Snyder described, the gut microbiome was associated with the external exposome, with high correlations, many strongly associated with inflammation.

In summary, Dr. Snyder noted:

- Wearables are powerful devices for tracking infectious disease and glucose dysregulation, prior to symptom onset.
- We have developed a method to track personal exposome spatial-temporally.
- The human exposome is vast and highly dynamic and driven mainly by locations/lifestyles and season.
- Our chemical and biological exposomes are correlated, mostly in a location-based pattern.
- Strong correlations between external and internal factors.

Dr. Woychik asked Dr. Snyder where epigenetics factor into the discussion. Dr. Snyder said that his group had held off on considering epigenetics, because the impact is mostly unknown at this time. With the drop in sequencing costs, there is desire to explore the question. He related some of his own experience with developing Type II diabetes following viral exposures and the associated effect on his methylome. He added that an important, unexplored area is the association of mitochondria and aging.

Dr. Balshaw asked how much of the correlation between the microbiome and chemical exposures might be due to metabolic transformation by microbes of the environmental factor. Dr. Snyder said the answer is unknown, but it seems likely that is what is occurring in many cases.

Dr. Penning said that the technologies described by Dr. Snyder are sophisticated, in a nation with a large number of people who are uninsured. The question is how to use the technology to improve everyone's health, not just the wealthy, insured people. Dr. Snyder said that technologies always roll out inequitably. He cited the example of genomic sequencing. He said that technologies such as wearables and smartphones are more accessible because they are cheaper and widespread. He said that some of the technologies can be democratized. Microsampling will be inexpensive as well. Even mass spectrometry is becoming cheaper, particularly the assays themselves. So, personal exposures can be measured at a scale that was not possible ten years ago. People could also be given discounts or free access to the technologies when they sign up for a health plan. Dr. Penning pointed out that even $50 for a smartphone is still not feasible for people in many parts of the world. He asked Dr. Snyder about interpretation of the data. He asked if the massive amounts of data could be brought together via AI and machine learning. Dr. Synder said he felt that would take place, likening the

situation to one's car. He envisioned a "personal dashboard" where all of the information is consolidated, with AI-driven programs making knowledge from the data.

Dr. Bourne asked about other technologies related to sensor technology or quantum computing on the horizon. Dr. Snyder said the rate-limiting factor at present is scaling. He said it is computationally intensive to do so, and that his group is computationally agnostic. He said it will be important to get more studies funded. "There is no reason not to collect exposome information," he observed. He felt that more NIH agencies need to be talking to each other, reducing siloing.

Dr. Woychik mentioned that it will be up to the IC directors to declare that they want to use the *All of Us* cohort to develop the types of exposomic tools that can be used to collect the exposure data in a way that it can be seamless integrated into the overall program. He said he has been working with other IC directors on how to collect environmental data to better understand the role of environmental exposures in a variety of disease processes. He noted that it is not all genes, it is not all environment; there are some very important contributions of complicated gene-environment effects, along with epigenetic processes. He said it is "up to us" to develop the vision and the implementation strategies to bring these elements together. Dr. Snyder agreed, and said that exposure studies should be started very early.

Dr. Vasquez noted that many factors complicate gene expression and regulation. Dr. Snyder said that many of the elements Dr. Snyder had mentioned are molecular features being used as phenotypic readouts. "We don't always know how to interpret them in health effects, but we will," he said.

Dr. Holian asked how to separate out the microbiome, which depends on environmental exposures and diet, which will in turn change the epigenetic outcomes. He called it a wheel of interactions. Dr. Snyder replied that mediation analysis can help.

Dr. Archer asked Dr. Snyder about the microbiome measurements he had shown, and whether they took into account changes over time. Dr. Snyder replied that they did not, and that they were only capturing a snapshot.

IX. Council Discussion

Dr. Balshaw opened a discussion session centering on AI, a technology that is moving extraordinarily quickly, with NIEHS time scales that do not necessarily match. He asked Council to discuss how to approach the field in terms of programmatic development.

Dr. Miller said that content will always be a problem, but training the next generation should be a priority, because "we have to learn how to learn faster and keep up with those technologies." Dr. Woychik asked who we are teaching—the older people to catch

up, or the younger folks? Dr. Miller felt that the younger generation that is more adept can help the older people. Dr. Vasquez said both would be important, in that the younger people can help with the computational aspects and how to use AI, whereas the older people can help as mentors in how to apply good science. Dr. Woychik agreed that it would be a combination of both things. He said it would be important to design the types of experiments that would utilize data-intensive protocols effectively. It may not be important to know how to program a computer, but it would be important to understand the emerging tools. Dr. Miller said that the idea that data is machine-readable and open science initiatives will be a critical part of making sure the right information can be harvested.

Dr. Penning questioned whether training in AI would even be necessary, because the tools should be "shovel-ready and idiot-proof," not requiring programming knowledge. He said that may be where support could be found.

Dr. Bourne said his group is working to be actionary versus reactionary. He noted that many in the field were taken by surprise at the sudden emergence of large language models, even though they had been around for a long time. Suddenly became mainstream, user-friendly, and human-like. Now everyone is trying to play catch-up, he said. His group is making an effort to be more futuristic, working backwards. He said that approach could apply to the scientific process as well, working backwards to think about funding and training.

Dr. Balshaw asked the Council how NIEHS/NIH might think about guardrails on the tools and technologies so that they are developed in ways that are fair and equitable, and can be applied in some of the other focus areas such as environmental justice communities. Dr. Ghassemi said that is a very hard question, because even many of today's technologies are not fair. She felt that technology is being shaped now, and society will be shaped by it moving forward. She added that it will be useful for many of the agencies looking at research questions to understand the potential normative tasks to which methods could be applied, making sure that any data collected or research funded has considered the issues.

Dr. Hertz-Picciotto said that how the questions are navigated is not obvious. She recommended incorporating linkage of the technologies to guardrail issues within RFAs.

Dr. Woychik said there should be a better job rewarding people for working collaboratively together. He cited the example of the climate change and health program as requiring a collaborative framework. He noted that he is interested in exposomics being integrated into the study of human disease and health across the entire biomedical enterprise.

Regarding environmental justice communities, Dr. Hood said he had seen EPA has taken on a public stance with respect to implementation of Justice40 in its RFAs. He noted that EJ requirements are spurring innovations and collaboration. Dr. Woychik said that Dr. Archer has led an NIH-wide initiative to come up with actions to be completed in the next 18 months.

Dr. Geller discussed EPA's ability or inability to get risk assessments out under TSCA. He mentioned Dr. Hartung's "Toxicologist's Christmas Wish List" and said that it would be wonderful if it represented AI tools that can actually be used to create regulations. On the equity side, he said there is a huge challenge doing TSCA assessments as they are today. The law may allow for the inclusion of more vulnerability and equity factors, but the risk assessors are asking how that could be done. Perhaps AI approaches are the way to ask such questions and add those factors. The platforms could be used to run scenarios that are desperately needed to be able to start incorporating equity. He noted that the field is still dependent on animal testing, but AI may offer a way to make those changes. "If you can fund some of that, we can fund some of that," he said, referring to NIEHS and EPA. Dr. Woychik said that is exactly the model needed going forward, working cooperatively, doing things that are synergistic while avoiding duplication of efforts. Dr. Geller noted that the tools have started making inroads into the Superfund Research Program.

Regarding TSCA and safety assessments, Dr. Penning recollected that under the European REACH guidelines, many chemicals used in cosmetics and fragrances cannot be used in animal testing. He said that perhaps there is a volume of useful information there. He discussed issues with the REACH guidelines. Dr. Geller noted that EPA had been asked long ago to stop doing just hazard identification, adding understanding of dose response.

Dr. Vasquez asked if NIEHS has something about AI in its mission statement, or if it should. Dr. Balshaw responded that there is an element on data science and analytics, but not specifically AI. Dr. Woychik said it is not in the mission statement, but AI is more an integral part of how the mission is performed, and is not appropriately put into a mission statement as an overarching umbrella. It will be incorporated into the new strategic plan as an emerging theme.

Dr. Ingram mentioned a project she had been working on for Native American students and the barriers to them going into STEM fields. Many concerns were expressed about having to use animals or people in training. AI holds potential to bypass some of those concerns among students and add to diversity in who pursues different scientific areas.

Dr. Woychik said he was concerned whether enough attention is being paid to teaching people how to structure their data and develop the types of data repositories that will be

needed going forward to conduct AI/ML work. He felt that currently, that situation is “a mess,” with heterogeneous data being collected, making it difficult to integrate the data sets.

Dr. Hood asked Dr. Woychik to comment on the retirement of Dr. Brennan as director of the National Library of Medicine. Dr. Woychik said he had been involved in working on the databases moving forward, as they are increasing exponentially. A framework for sustainability is needed, he said, for example establishing one place for all of the genome sequences or environmental exposure data.

Dr. Penning observed that no one is providing a vibrant commentary on what is being captured in electronic medical records in terms of exposure data, and that is something the EHS field could facilitate. Dr. Woychik agreed, and said he would love it if physicians would ask their patients pertinent questions and enter the answers into the medical record. It should be incorporated into an overarching operationalization of exposomics, he said, with physicians thinking about exposomics in their interactions with patients.

Dr. Hertz-Picciotto mentioned that there is now such a linkage in California medical records, which could be a model for the academic hospital world. There should be developments in how physicians can take that data and understand how to use it, she suggested. Dr. Woychik said the first step is getting clinicians to realize that there are environmental exposures that may be associated with their phenotypes. Dr. Greenamyre agreed that there is much ignorance to be quelled, but that it will be a huge challenge to add extra minutes to physician-patient interactions. Dr. Balshaw said he had heard that there is a proposal to add blood PFAS into the Medicare reimbursable list, which could be a cost factored into healthcare. However, an academic hospital lab probably would not have the capability of measuring blood PFAS and state labs would also be limited, leaving it to the commercial labs to develop their capabilities. Dr. Greenamyre added that it should be added to medical school curricula, where there is almost nothing taught regarding environmental exposures.

Dr. Mutlu agreed that physicians are not given adequate time to do analysis of exposure. He said that in his field, it is well recognized that exposures cause many of the lung diseases. Dr. Archer asked when exposures might be put into electronic medical records, citing PFAS as an example, and wondered how much useful input would be gained. Dr. Mutlu talked about some of the questions for patients that incorporate potential exposure information.

Dr. Hall discussed the issue of communication from the environmental science community to medical students and physicians. The deeper and deeper levels of data

collection do not help with that, but the field should consider the packaging of the information. It should be part of the NIEHS mission.

Dr. Ingram mentioned a former student who wished to pursue an MD/PhD in environmental toxicology, but had been discouraged by others. She said that the big school need programs to encourage such students. Dr. Woychik agreed that getting the word out is part of the responsibility of environmental health sciences, including the data and associations between environmental exposures and health outcomes. The curriculum needs to be developed and added to medical school curricula.

Dr. Geller said he was surprised there has not been more interest from big providers, citing the example of lead. He added that there need to be more cost/benefit studies, for example, of chemicals associated with Parkinson's disease. Dr. Greenamyre agreed that the way forward would be to convince the payors that it is worth paying for.

Dr. Penning said that the place to start to change the medical school curriculum would be the AAMC. Also, he noted that patients filling in their own exposure history on an iPad would be a way to streamline the process and save time.

Dr. Woychik thanked everyone for their contributions during the Council meeting's first day. He adjourned the open session of the meeting at 3:52 pm, September 12, 2023.

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 4:16 pm, September 12, 2023.

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. The Council considered and recommended 517 applications requesting $271,059,315 in total costs. For the record, it is noted that secondary applications were also considered en bloc.

OPEN SESSION

The meeting was open to the public from 9:02 am – 1:44 pm September 13, 2023.

X. Report of the NIEHS Director

Dr. Woychik briefed Council on Institute developments since the June 2023 Council meeting.

He recognized retiring Council members Drs. Hertz-Picciotto, Penning, and Vasquez and presented them with certificates. He thanked them for their service.

Turning to budgetary matters, Dr. Woychik began with the FY2023 Omnibus, which had a healthy increase of approximately 3.5% this year, reflecting considerable support for the NIH. He said that FY23 is in "pretty good shape—we can continue to absorb some of the increasing costs, with some money left over to support some of the innovative new things that we want to be doing." He noted that due to the law that increased the federal debt limit, there were spending caps set that will result in the NIH appropriations being essentially flat for FY2024. The final outcome will not be known until a budget is actually passed. He went over the proposed expenditures in the President's budget and the House and Senate marks. Since inflation is not flat and the cost of doing science is not flat, there are some budgetary challenges ahead, with much uncertainty. However, he noted that a relatively flat budget still puts NIEHS in a better position compared to many other ICs and federal agencies. Also, there is a risk of a government shutdown in the near future if a budget is not passed by the end of September. It is possible that Congress may pass a Continuing Resolution, which would allow operations to continue in a limited fashion.

Dr. Woychik updated progress on development of the 2024-2028 NIEHS Strategic Plan. He summarized the different mechanisms involved in the initial input phase, which took place in spring 2023. The integration/curation phase lasted through August 2023. The analysis and draft phase will last through February 2024. In early 2024, a strategic plan draft will be circulated to Council for review and approval.

Dr. Woychik updated developments in the six NIEHS emerging scientific priority areas, beginning with Environmental Justice (EJ) and Health Disparities. He described cross-NIH environmental justice strategic actions, one of which was to identify a senior leader point of contact. NIEHS Deputy Director Dr. Trevor Archer was named to serve in that capacity, to be assisted in the effort by several other NIEHS personnel. Additionally, all operating divisions within HHS were requested to identify three strategic and transformative EJ actions, which are to be implemented within the next 18 months. Under Dr. Archer's leadership, NIH will:

- Develop and release a Centers of Excellence in Environmental Health Disparities and Environmental Justice grant program.
- Develop and implement an Environmental Justice Scholars program.

- Establish a new Environmental Justice Training Program for communities, workers, researchers, health care and public health professionals, and policy makers.

Regarding efforts associated with climate change and health, Dr. Woychik discussed the NIH-Wide Initiative on Climate Change and Health (CCHI). The program's goal is to reduce health threats across the lifespan and build health resilience. Research strategy is focused on multidisciplinary approaches. The program involves a broad assortment of supporting science. One of the major initiatives is the collaboration between the NIH and the National Science Foundation (NSF). It includes the RAPID program based at the University of Washington, which provides access to new technology and resources for research in the wake of climate disasters. CCHI has issued a call for proposals for case studies to advance research on climate change adaptation strategies. Dr. Woychik described the new competitive funding program called the Intramural Targeted Climate Change and Health (ITCCH) program, that provides seed funding to stimulate research activities from NIH intramural investigators at multiple ICs. There will also be a new intramural Laboratory/Branch/Center at NIH to focus on biological mechanisms of the health impact of climate change.

The exposome priority area has seen substantial activity recently. Dr. Woychik went over background information about efforts to define the exposome and build technological capabilities to study it. He provided details about a multi-project exposome research program, which would include comprehensive exposure assessment, understanding of bodily responses to exposures, and integration of fragmented health research silos. He described a Notice of Funding Opportunity for a Center for Exposome Research Coordination, which will involve several NIH ICs, including NIEHS.

Precision Environmental Health (PEH) is another of the NIEHS scientific priority areas, which integrates genetics, epigenetics, and omics data. Dr. Woychik described the concept of implementing PEH by addressing complex traits associated with environmental exposures. He discussed the International Common Disease Alliance (ICDA) and its Maps to Mechanisms to Medicine Challenge. He said the EHS community needs to engage with the ICDA to include exposomics and epigenetics into its efforts. He also talked about the efforts to include environmental exposure data such as geospatial environmental exposures in the *All of Us* Research Program. The proposal would be achieved in three interrelated efforts that could be developed at least partly in parallel:

- Phase 1: Location
- Phase 2: Geospatial Environment
- Phase 3: Health

PEH is also being advanced by the NIEHS Personalized Environment and Genes Study (PEGS).

Dr. Woychik stressed the importance of working collaboratively across NIH. For example, he discussed the upcoming National Academies virtual workshop on Public Health Research and Surveillance Priorities from the East Palestine, Ohio Train Derailment, which will be a cross-cutting collaboration among several NIH ICs and CDC, including NIEHS.

He updated Council on NIEHS DEIA efforts, including a Distinguished Olden Seminar on September 19 featuring Dr. Ana Diez Roux from Drexel University. He also reported that NIEHS continues to recruit for a Scientific Diversity Officer (SDO) for the new Office of Environmental Health Research Strategy. The final candidate will provide an all-hands seminar on September 15 and meet with staff and leadership. The NIEHS DEIA Council is working to bring a unified approach to current DEIA activities across NIEHS divisions and foster DEIA values within NIEHS. It will be chaired by the SDO; it is currently chaired by the Deputy Director. Coming soon will be an NIEHS Mentoring Program pilot, which has been created in response to employee input. It will be designed by a cross-organizational team with the mission of leveraging mentoring as a tool for growth and DEIAC.

Dr. Woychik recognized recent awards and recognition given to NIEHS personnel.

He concluded his presentation with an update on recruitment of a Scientific Director for the Division of Translational Toxicology (DTT), which is ongoing.

Dr. Hornbuckle asked if the Center for Exposome Research would be one award. Dr. Woychik replied that it is one award, with the purpose being for one group to take a leadership position and to coordinate among the entire community. Dr. Balshaw added that it is a coordinating center, intended to facilitate conversation among the entirety of the global community.

Dr. Geller commented on EJ and health disparities. He said he appreciated the strategic and transformative actions Dr. Woychik had described, but that he would like to see a harder push in those areas. He noted that a Centers of Excellence program is just that, not full coverage admitting EJ and equity into everything they do, which is the order from the White House. He asked how it was being embedded into NIEHS programs, and how NIEHS is contributing to the HHS Equity Action Plan. Dr. Woychik said that would be done on an NIH-wide level. Dr. Geller said that EJ is an environmental health issue, and a function of the exposome. He said that all of the exposures occur within the social exposome, as a nested construct. He asked about an IC-wide exposomic approach that recognizes the profound influence of environment on health equity as a transformative response. Dr. Woychik noted that Dr. Archer and the working group had

only had two weeks to formulate the program, and that EJ has long been part of the fabric of how NIEHS does its science, and much of the exposome overlays with EJ. Dr. Archer said it was the first draft of the program, and the cross-NIH working group will meet regularly to bring the work to all of the NIH system. Dr. Geller asked how NIEHS is represented at the new OSTPCEQNSTC (Office of Science and Technology Policy Council on Environmental Quality National Science and Technology Council) EJ Council. Sharon Beard said that HHS is working to implement the Executive Order 14096 (Revitalizing Our Nation's Commitment to Environmental Justice for All), focusing on gathering all of the information, resources, and tools available. Dr. Woychik asked Mrs. Beard to ensure that there are points of intersection on EJ with the EPA.

XI. Report of the DERT Director

DERT Director Dr. David Balshaw briefed Council on DERT activities and accomplishments since the June 2023 Council meeting.

He related DERT staff developments, including a new role for Kathy Ahlmark and new hires Murali Ganesan, PhD, Eric Persaud, DrPH, Ashlinn Quinn, PhD, Caleb Rogers, and Alicia Zorn. He summarized DERT meetings since the last Council meeting and looked ahead to upcoming DERT meetings.

Dr. Balshaw reviewed funding strategies for FY24. As Dr. Woychik had alluded to, there are uncertainties associated with the FY24 budget. He highlighted the grants budget, which is roughly half of the Institute's total budget. It is comprised of four major buckets: outyear commitments, taps and assessments, programmatic priorities, and investigator-initiated science. He recapped the FY22 budget for research project grants (RPGs), with 160 competing awards totaling $72 million and 436 non-competing awards totaling $208 million. He reviewed the definition of a "payline" and went over the current practice, which has been in force over the past decade, with a fixed 10% payline for R01, R21, and R03 grants, and no fixed payline for R15, F, K, T, SBIR, and others. This has allowed reserving of funds for "Raise to Pay" (RTP) grants. He noted that the cost and count of the 10th percentile payline is volatile but going up. The unsolicited payline uses over 50% of the RPG dollars.

He described the realities of FY24 and beyond:

- With the potential flat budget and increasing costs of maintaining a fixed 10% payline:
    - We project we will have little if any flexibility for RTP.
    - If the budget is less than flat, we will be unlikely to maintain 10%.
    - Long term, even with increased budgets, 10% payline may not be tenable.
- With a new strategic plan coming it is increasingly important to maintain flexibility to support RTP as well as highly meritorious research.

- We need to maintain ability to respond to Congressional/Executive and NIH priorities (ESI, New Investigator, At-Risk)

Dr. Balshaw presented a proposal for Council reaction:

- An alternative strategy to preserve an emphasis on both investigator initiated, highly meritorious research across the environmental health sciences, and
- Recognize the need to factor in programmatic considerations such as alignment with strategic plan, programmatic balance, and other priorities
- Rather than paying to a fixed percentile score, reserve the majority (a fixed percentage) of the funds available for competing awards to “payline” and the remainder to select pay.

This would translate to roughly 49.7% unsolicited, 21.8% unsolicited RTP, and 28.4% solicited. The advantage of the approach is that it allows the ability to accommodate both types of grants, and it scales directly with the budget. He noted that communication of the approach to the research community would be more challenging.

Dr. Balshaw invited Council to discuss the proposal based on these questions:

- Thoughts, comments, or concerns on shifting from a fixed score payline to a fixed percentage of the budget payline?
- What additional factors should be considered in RTP discussions?

Dr. Hornbuckle said she was part of the Superfund Research Program, and she described it as “rather prescriptive” about how the funds must be allocated within the proposed center. She wondered if that is also true for other funding solicitations, if there is opportunity for loosening the requirements on the applicants for spending that could also result in better opportunities for funding more centers, with more flexibility for NIEHS in deciding how to move money around. Dr. Balshaw said that when DERT is designing solicitations, one of the conversations is about how stringent they should be in terms of the parameters for funding. There is some flexibility in the program to “tweak.” Every new solicitation shifts a bit in their requirements. Dr. Hornbuckle asked him to speak more about review of proposals. He said a specific concern had arisen around applications that are reviewed by CSR, with respect to assignment to science sections.

Dr. Hertz-Picciotto felt that the approach suggested by Dr. Balshaw was a good idea. She expressed some concerns about increasing requirements for data sharing, which she found to be onerous. Dr. Balshaw suggested that grants should be designed to request a budget that will meet all of the needs of the project being proposed, including requirements for data sharing and community engagement. He noted that the new data sharing requirements do allow for additional funding provisions.

Dr. Miller said there should be some provision for a specific grant score. He suggested there should be perhaps “a hard 8.5 or 8, and then squishy after that.” Dr. Balshaw said that a lower fixed percentage was an option that had been explored. He was concerned that a low percentage might steer applicants in other directions. Dr. Miller said that perhaps it could be more of an unwritten approach. He said the anxiety from an unspecified score is not trivial.

Dr. Ingram said that understanding the system is difficult, particularly for ESIs. It could drive applicants who are not funded to other sources, such as industry. It is important for the process to be able to be clearly understood, to avoid frustration, perhaps even to drive people away from conducting research altogether.

Dr. Penning said he was worried about the stress the proposed approach would put into the system. It would increase uncertainty from year to year, creating stress for the investigators, as well as raising questions of fairness. He suggested re-introducing a cap on R01s, while making it more reasonable. That would allow retention of the current payline, with RTP. Dr. Balshaw said that modular budgets are decreasing, although there has been conversation about expanding that scope. He noted that there is insufficient staffing to allow for going through individual budgets with a fine-toothed comb. He said that instituting a budget cap has not been explored, although it may be an option. Dr. Penning suggested that perhaps NIEHS could issue its own PARs for R01s with a budget cap. Dr. Woychik said it would be important to ensure that NIEHS does not lose some of its best investigators to other ICs, which could happen if a budget cap was introduced.

Dr. Vasquez said that maybe NIH could make some changes, because the budgets are “absolutely ridiculous.” There are many people with multiple R01s, so they would not necessarily be lost. Many budgets are inflated, and NIEHS is losing people by having a low percentile, rather than a low budget. Dr. Woychik said this is a topic under intense discussion among IC directors. There is a tension between doing something NIH-wide and having flexibility among individual institutes. He said it is desirable to do things that make the most sense without putting NIEHS in a less competitive position. He noted that Dr. Tabak has emphasized that the future of the budget will be different than what has been experienced over the last several years.

Dr. Holian said he did not hear clear information about new investigators. He said that many young people he had spoken with were unenthusiastic about pursuing academic careers because of the budgetary challenges, and the situation is getting worse and worse. Dr. Balshaw said that all ESI were considered carefully, although not all were funded. First renewal of awards is also a consideration. Program staff are available to help ESIs with guidance and career counseling. Dr. Woychik said this is a topic of great

interest and concern across the NIH, as is the fact that in many instances, senior investigators with large research groups are taking up a large proportion of the budget.

Dr. Hertz-Picciotto asked about the concept of co-funding. Dr. Woychik said that it will happen increasingly in the future. He noted that partnerships with other ICs will introduce the environmental health component in studying the etiology of human disease. He cited the DR2 program as an example.

XII. Report on Multi-Omics Program with NCI

Dr. Kim McAllister provided background information and a report on a new multi-omics consortium, Multi-Omics for Health & Disease (MOHD), a collaboration with NHGRI and NCI.

The effort aligns with the NIEHS framework on precision environmental health. The idea behind precision environmental health is to identify exposure-response relationships with multi-systems approaches, including multi-omics, to predict disease risk with an overall goal focused on prevention and intervention.

Dr. McAllister discussed omics and the advances in high-throughput technologies. It is known that many environmental factors induce biological responses at many levels and drive many complex disease outcomes, she noted. Recent papers have shown that looking at a combination of multiple omics with environmental data, rather than just a single omics layer, can greatly improve risk predictions and confidence in detecting environmentally relevant pathways. However, many challenges remain to prevent routine application of multi-omics to disease studies, because the omics layers are highly interconnected and correlated, and it is complicated to truly integrate them in meaningful ways.

The challenges for integrating environmental data with other omics include:

- Heterogeneity of data
- Measurements with different instruments/surveys and at different scales
- Lack of methods to analyze high dimensional environmental data from wearable devices, electronic health records, cell phones, GIS systems, etc.
- Dose and temporality of exposures
- Lack of analytical tools/techniques to assess longitudinal environmental data and environmental mixtures

Two NIH workshops in recent years have explored the challenge of multi-omics studies in depth. The first was in 2021, sponsored by NHGRI. It issued recommendations on how to address a lack of robust and reproducible omics data. The second workshop took place at NIEHS in February, 2023, and was the first workshop to emerge from a

Cancer and Environment Working Group from NIEHS and NCI. It specifically focused on integrating environmental data with other omics for cancer epidemiology.

The new consortium will start this fall. MOHD will focus on establishing best practices and developing new methods for integration of omics with environmental exposure data, measuring multiple omics as well as social determinants of health on the same individuals and the same tissues at the same time, as a longitudinal study that will place a strong emphasis on ancestrally diverse populations. It will attempt to use multi-omics datasets to identify molecular signatures or profiles associated with various disease states. It will develop generalizable data. The dataset will be shared with the broader scientific community and will be interoperable with existing resources.

The MOHD will be composed of three components: a Data Analysis and Coordination Center (DACC), an 'Omics Production Center (OPC), and Disease Study Sites (DSS). The DSS will be the heart of the consortium in terms of the samples to be analyzed. They will study a selected clinical condition, each with 200 participants with a disease along with 100 generally health participants, with more than 75% of individuals underrepresented in genomic databases. They will collect biospecimens at a minimum of 3 timepoints. Dr. McAllister provided more details about the OPC and the DACC.

The MOHD RFAs were released in early fall, 2022. Awards are imminent. There will be a virtual kick-off meeting in late September 2023, and a first in-person meeting January 11-12, 2024. In the consortium's first year, network-wide protocols, plans, and approaches will be developed, a process to be coordinated by the DACC. Year 2 will be devoted to enrollment of participants, collection of baseline measures, and collection of samples. During years 3 and 4 the consortium will collect subsequent measures and biospecimens, will contribute intellectually to data analysis and development of generalizable methods, and work toward standardizing and harmonizing data. Year 5 will see finalized analysis followed by data release and dissemination.

Dr. McAllister described the gaps and opportunities the consortium can address:

- Production of multiple 'omics data from same sample over multiple timepoints
- Innovative computational methods to integrate, analyze, and interpret multi-omics data
- Prospective data collections to be broadly shared

She revealed the awardees for the MOHD, who had just been selected. The DSS has 6 awardees (4 of the 6 with a substantial environmental component), the OPC and DACC 1 each. NIEHS will be co-funding 3 of the DSS awards with substantial environmental risk factors.

Dr. Ingram asked Dr. McAllister about the issue of broad consent. She said it is not a plus for many communities. Dr. McAllister noted that the studies are relatively small and will be recruiting with new populations. Within the recruitment among underrepresented populations, there will be considerable education about how samples will be used and the privacy provisions.

XIII. EPitranscriptomics CrOsstalks and Toxicants (EPCOT) Concept

Dr. Fred Tyson, Program Director in the NIEHS Genes, Environment and Health Branch, briefed the Council on the EPCOT Concept.

He provided an introductory overview of epitranscriptomics, which is the study of reversible chemical modification of RNA transcripts. There are currently more than 170 known modifications, with more than 60 identified in eukaryotes. The most prevalent and best characterized is m6A, along with its complexes that read, write, and erase this chemical modification. Dr. Tyson provided details about the m6A RNA modification complex.

He discussed the importance of epitranscriptomics, which are associated with approximately 100 diseases, including cancers, metabolic disorders, and diseases of aging.

A growing portfolio of research grants are being supported by NIEHS interrogating the impact of toxicants on epitranscriptomic processes. Approximately 40 grants are currently actively supported.

Dr. Tyson described the role of crosstalks. M6A readers can be involved in a number of different processes. Readers, writers, and erasers all participate in epitranscriptomic crosstalks with epigenomes.

The goal of the EPCOT program is to support research that interrogates how environmental exposures impact this layer of cellular regulation. The scientific areas of interest for the program are to:

- Solicit applications that identify exposure-induced crosstalks
- Elucidate mechanisms
- Utilize multi-omic platforms
- Conduct integrative analyses
- Employ informatics and computational approaches

Council reviewers were Dr. Vasquez and Dr. Mutlu.

Dr. Vasquez said this is a very novel, understudied area. RNA modifications have long been known, but have not been extensively studied. They can change the structure of

RNA and DNA, and the structure leads to function. She recommended adding that layer to the program. She felt that the concept is important and timely, tying together environmental exposures, gene function, and disease etiology. She said it fits in with the multi-omics that have been discussed during the meeting. She asked when the program would start and how long it would last. Dr. Tyson said those issues were yet to be determined.

Dr. Mutlu largely agreed with Dr. Vasquez's statements. He said that understanding of epigenetics will be incomplete without the study of epitranscriptomics. He noted that environment affects our DNA and there is much emphasis on how the environment affect the epigenome, and it is also important to pay attention to RNA modifications. He said it is a new and exciting field, with an additional layer of complexity.

Dr. Miller asked if there is a sufficient applicant pool to study the mechanisms. Dr. Tyson said that there is a sufficient supply of qualified researchers in the area, and he named several potential applicants. Dr. Vasquez said that the RFA would bring in people not only from the immediate field, but also from outside, encouraging collaborations.

Dr. Hood noted the disease states shown by Dr. Tyson, and said several would be exciting in terms of cross-IC collaborations. Dr. Tyson said that several other ICs have been in touch expressing interest in potential partnerships.

Dr. Penning asked if there had been any consideration of carbon-one metabolism, in that there may be a dietary component to the mechanism. He asked Dr. Tyson if diet was included in the RFA. Dr. Tyson replied that diet is typically not considered, but it could be part of proposed studies.

Dr. Balshaw asked for a motion and second to approve the concept. Dr. Greenamyre moved to approve, Dr. Hertz-Picciotto seconded. Council voted to approve the concept.

XIV. Worker Training Program Concepts

Worker Training Program (WTP) Director Sharon Beard and her program colleagues presented the WTP concepts for Council approval. The concepts were:

- Hazardous Materials Worker Health and Safety Training – U45
- HAZMAT Training at DOE Nuclear Weapons Complex – UH4
- NIEHS WTP SBIR E-Learning for Hazmat – R43/R44

She provided an overview of the history, funding mechanisms, and program areas of the WTP, along with FY23 funding for each, including special appropriations for disasters and emergencies. She detailed the numbers of workers trained in several of

the programs, as well as WTP engagement with other federal agencies and working groups.

Jim Remington presented the list of recent workshops and webinars conducted under the program. He described the Hazardous Waste Worker Training Program (HWWTP), which provides occupational safety and health training for workers engaged in activities related to hazardous waste removal, containment, or chemical emergency response. HWWTP received $18.9 million in FY23 funding.

He provided examples of successful health and safety partnerships, including a program addressing PFAS concerns among workers.

The HAZMAT Disaster Preparedness Training Program has received $3.4 million funding dollars in FY23, with 14 current grantees. It supports the development and delivery of training for hazardous material and debris cleanup commonly needed after natural and man-made disasters.

Dr. Eric Persaud discussed the Environmental Career Worker Training Program (ECWTP), which delivers pre-employment and life skills training for un/underemployed individuals in disadvantaged populations and helps individuals obtain sustainable careers in environmental cleanup and emergency response.

The long-standing program received $4.2 million in funding dollars in FY22, with 6 current grantees. The ECWTP has more than 28 years of success in training and empowering un/underemployed individuals, having trained more than 14,000 people, with a rate of 70% employment each year since 1995. It was selected by HHS as a pilot for the Justice40 Initiative.

Dr. Persaud mentioned several success stories from the program.

Mrs. Beard detailed the next steps to expand priorities for the WTP:

- Push an all-hazards approach to training to cover existing and emerging threats
- Continue focus on infectious disease, opioids, climate change, equity, and justice
- Promote Justice40 Initiative and ECWTP
- Encourage grantees to use adaptable and innovative methods to respond to future training needs
- Continue focus on evaluation across all programs
- Expand partnerships at the federal, tribal, state, and local levels

She turned to a discussion of the NIEHS/DOE Nuclear Worker Training Program. The concept involves the continuation of successful collaborations to support training at the Department of Energy for training workers engaged in nuclear waste cleanup and

construction at DOE sites. She provided background and historical information about the program, which is celebrating its 30th anniversary. It received $9.3 million funding dollars in FY23, with 7 current grantees.

Kathy Ahlmark took the podium to outline the NIEHS WTP SBIR E-Learning for HAZMAT and Emergency Response. Under the program, training is provided to workers across many occupational sectors, such as:

- Environmental cleanup workers
- First responders
- Health care employees
- Industrial or construction workers
- Law enforcement officers
- Transportation or rail workers

The goal of the E-learning SBIR is to further the development of technology-enhanced training products for the health and safety of:

- HAZMAT workers
- Waste treatment personnel
- Skilled support personnel associated with an emergency/disaster
- Emergency responders in biological hazard response, infectious disease response, and medical waste cleanup
- Emergency responders in disasters
- Worker resilience training

The program received $699,212 funding dollars in FY23, with 6 current grantees. Ms. Ahlmark described several successes in the WTP SBIR program.

Dr. Persaud discussed a new fact sheet from the NIEHS WTP SBIR E-Learning for HAZMAT Program, which includes how the program has:

- Impacted worker training in various occupational sectors.
- Provided opportunities for commercialization and patents.
- Facilitated partnerships among small businesses that develop technologies and WTP consortiums that deliver training.

He noted that the SBIR evaluation findings support that the program has contributed to improved use of technology in training for workers performing duties in hazardous environments and to learn and experience hazardous situations and content safely. A report on the evaluation is being finalized and will be shared at the American Public Health Association’s 2023 Annual Meeting.

Drs. Hood, Hornbuckle, and Penning were the Council reviewers for the WTP concepts.

Dr. Hood said that the presentations had grounded him and given him some principles about the program. With the re-emergence of infectious disease and the health effects of climate change, it will be very important. While there is much discussion of AI and ML and how they are going to replace jobs, “not so fast.” While that may happen, for the next decade, there needs to be a focus on the ability of NIEHS to continue to contribute to helping the WTP programs exist. He said he would like to see more about Justice40. Mrs. Beard said that the program will continue to do much work related to environmental justice.

Dr. Savasta-Kennedy applauded the work of WTP, particularly its work with day laborers. She asked if the grants also cover equipment. Mrs. Beard said that a lot of the materials being developed include providing appropriate personal protective equipment, including to day laborers, as Dr. Savasta-Kennedy had inquired.

Dr. Penning reminded the Council that the funding for the WTP is not just from NIEHS. He noted that the Superfund Research Program funding is flat. He said that the issue needs to be put in front of Congress, because the need for the WTP will increase. He said the supplements provided previously have been given in a reactive way, and they should be considered proactively, because disasters are increasing. Dr. Woychik said he remains astonished that Congress is not more supportive of the program. He noted that funding increases have not kept up with Labor/HHS increases, despite efforts with Congress, where the feedback has been consistently positive. He asked Mrs. Beard what she thought might be done. She replied that there have been discussions about the issue of transfer authority for funding from other federal agencies who wish to partner with WTP. There is currently no such transfer authority anymore. Dr. Woychik said the barrier to transfer authority is incomprehensible, and that although everyone wants the situation to be fixed, it somehow never is.

Dr. Penning suggested taking representatives of the ECWTP to Congress. Mrs. Beard noted that there are grantees with entry into apprenticeship programs, some of whom have met with senators in the past.

Dr. Hornbuckle praised Mrs. Beard for her leadership of the program, which is clearly successful. She suggested adding more information to her summary on the program’s emphasis on directly serving disadvantaged communities, and its impact. Mrs. Beard said the program’s grantees have been doing so for years, and the supplemental funding has helped expand that type of work. The hope is to move that type of funding into regular funding, and beyond the supplementals.

Dr. Geller asked about latitude in funding within the SRP. Dr. Balshaw said it is zero sum between the SRP and the WTP. Dr. Geller wondered if there may be a restoration of the Superfund tax. Dr. Balshaw said that is not anticipated.

Dr. Ingram asked about the various locations illustrated in some of the training programs. Mrs. Beard said that much of the training that takes place is regionally focused, and thus it may appear that there is an imbalance.

Dr. Hertz-Picciotto said the program's progress has been "astounding," and that it has mushroomed in its impact and the number of people affected.

Dr. Balshaw asked for a motion and second to approve the concepts. Dr. Hertz-Picciotto moved to approve; Dr. Vasquez seconded. Council voted to approve the concepts.

XV. Adjournment

Dr. Woychik thanked everyone who had been involved in the meeting for a very engaging Council, "the best yet." Dr. Balshaw reminded Council members that the next meeting will be virtual, on February 12-13, 2024.

Dr. Woychik adjourned the meeting at 1:44 pm, September 13, 2023.

CERTIFICATION:

/s/

Rick Woychik, PhD
Chairperson
National Advisory Environmental
Health Sciences Council

/s/

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

Attachment:
Council Roster