U.S. Department of Health and Human Services
National Institutes of Health

Minutes of the 11th Joint Meeting of the National Advisory Council on Alcohol Abuse and Alcoholism, National Advisory Council on Drug Abuse, and National Cancer Advisory Board

May 10, 2023

Members of the National Advisory Council on Alcohol Abuse and Alcoholism (NIAAA), National Advisory Council on Drug Abuse (NIDA), and the National Cancer Advisory Board of the National Cancer Institute (NCI) convened for their 11th joint meeting on May 10, 2023, in hybrid format, i.e., both in-person and online via Zoom. Chaired by George Koob, Ph.D., Director of NIAAA, and Nora Volkow, M.D., Director of NIDA, this open session convened at 10:04 a.m.

National Advisory Council on Alcohol Abuse and Alcoholism Members Present:
Nancy Barnett, Ph.D.
Christopher S. Carpenter, Ph.D.
Christina Chambers, Ph.D.
H. Westley Clark, M.D., J.D.
Beth Kane-Davidson, LCADC, LCPC
David Kareken, Ph.D.
Charles H. Lang, Ph.D.
Mary E. Larimer, Ph.D.
Michael J. Lewis, Ph.D.
Col. Charles S. Milliken, M.D., Ex-Officio
Laura Elena O'Dell, Ph.D.
Katie Witkiewitz, Ph.D.

National Advisory Council on Drug Abuse (NACDA) Members Present:
Arpana Agarwal, Ph.D.
Katherine L. Beebe Devarney, Ph.D.
Charles Chavkin, Ph.D.
Anna Rose Childress, Ph.D.
Dennis Deer, Ph.D.
Amit Etkin, M.D., Ph.D.
Shelley F. Greenfield, M.D.
Paul J. Kenny, Ph.D.
Andrey Ostrovsky, M.D.
Travis N. Rieder, Ph.D.
Rajita Sinha, Ph.D.
Mark E. Von Zastrow, M.D., Ph.D.
Melissa L. Walls, Ph.D.
Sharon L. Walsh, Ph.D.

National Cancer Advisory Board Members Present:
Nilofer S. Azad, M.D.
Christopher R. Friese, Ph.D., R.N
Howard J. Fingert, M.D., F.A.C.P.
Amy B. Heimberger, M.D.
Nikan Khatibi, M.D., M.B.A.

Chairs: George Koob, Ph.D., and Nora Volkow, M.D.

National Institute of Alcohol Abuse and Alcoholism (NIAAA) Director: George Koob, Ph.D.

National Institute on Drug Abuse (NIDA) Director: Nora D. Volkow, M.D.

National Cancer Institute/Behavioral Research Associate Director: William Klein, Ph.D.

Acting NIAAA Deputy Director: Patricia Powell, Ph.D.

NIDA Deputy Director: Wilson Compton, M.P.E., M.D.

NIAAA, Acting Director, Office of Extramural Activities: Phillipe Marmillot, Ph.D.

NIAAA, Acting Executive Secretary: Ranga V. Srinivas, Ph.D.

NIDA, Director, Division of Extramural Research: Susan B. Weiss, Ph.D.

NCI, Director, Division of Extramural Activities: Paulette S. Gray, Ph.D.

NIDA Senior Staff: Gaya Dowling, Ph.D.; Vani Pariyadeh, Ph.D.

NIAAA Senior Staff: Vicki Buckley, M.B.A.; Ralph Hingson, Sc.D.; M. Katherine Jung, Ph.D.; Raye Litten, Ph.D.; David Lovinger, Ph.D.; Antonio Noronha, Ph.D.; and Bridget Williams-Simmons, Ph.D.

NCI Senior Staff: Michele Bloch, M.D., Ph.D.; William Klein, Ph.D.

Additional Participants
Approximately 230 observers joined the meeting, including representatives of constituent groups, liaison organizations, and members of the general public.

Call to Order
Dr. Koob called to order the eleventh meeting of the National Advisory Councils of NIAAA, NIDA, and NCI in open session at 10:04 a.m. on Wednesday, May 10, 2023.

NIAAA Director's Presentation
Dr. Koob began his presentation by announcing the retirement of Dr. Abraham Bautista from his position as the Director of the Office of Extramural Activities (OEA) at NIAAA. Dr. Philippe Marmillot is now Acting OEA Director and Dr. RV Srinivas is Acting Executive Secretary for the NIAAA Advisory Council.

In Memoriam. Dr. Koob announced the death of Dr. Enoch Gordis, NIAAA director from 1986 to 2001.

Alcohol by the Numbers: Scope of the Problem. According to the most recent edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM -5), there are approximately 29 million individuals with alcohol use disorder (AUD) in the United States (10.6 percent of the population). Over 140,000 deaths annually can be attributed to alcohol and the numbers are increasing: Death certificates listing alcohol increased 25.5 percent from 78,927 in 2019 to 99,017 in 2020, the first year of the pandemic. Ten percent more--108,891 deaths—were added in 2021. Further, alcohol was listed in one in six (16 percent) of drug overdose deaths in 2020 and 2021.

Alcohol, Pain, and Opioids. Dr. Koob participated in a panel discussion at the Rx and Illicit Drug Summit in April. Key alcohol-related messages included the following. 1) The opioid crisis overlaps with other public health challenges, such as undertreated chronic pain, mental illness, and AUD. 2) Alcohol misuse contributes to pain (both emotional and physical), and pain contributes to alcohol misuse through drinking to cope. 3) There are overlapping brain mechanisms in chronic pain, AUD, and opioid use disorder (OUD), and understanding this relationship provides an opportunity for preventing and treating these problems. 4) Addressing alcohol misuse in individuals with chronic pain and opioid use disorder may help improve patient outcomes.

NIAAA Efforts to Change the Conversation Around Alcohol. Dr. Koob focused his presentation on the key messages and activities that NIAAA is pursuing this year. These include:

- *Increasing knowledge about the harmful effects of alcohol*. Alcohol misuse is associated with more than 200 diseases and injury-related conditions. Very few Americans are aware of the full range of these diseases, including cancers of the oral cavity, breast, liver, colon, and rectum.
- *Rethinking drinking in U.S. culture.* A "sober curious" movement is emerging, as evidenced by the increased popularity of "dry January" and increased offering of alcohol-free drinks.
- *Promoting screening, brief intervention, and referral to treatment ("SBIRT") as part of routine healthcare.* Although screening among individuals with AUD has increased to almost 70 percent according to a 2021 review, fewer than 6 percent of those identified received treatment. In addition to its importance in preventing and intervening in AUD, screening for alcohol misuse can also help clinicians spot other health-related issues.
- *Supporting research to integrate treatment for alcohol use disorder with treatment for co-occurring conditions.* Alcohol misuse accounts for nearly half of liver disease deaths each year. Alcohol associated liver disease (ALD) is the most common alcohol-related cause of death and the leading cause of liver transplantation. ALD-related deaths increased 47 percent between 2000-2019, and rates are increasing faster for women and young adults ages 25-34. However, there is a paradigm shift underway, led by hepatologists who are promoting integrated treatment of ALD and AUD because it improves patient outcomes. Treating AUD with medications reduces the likelihood of developing ALD and the progression of existing ALD, while behavioral or pharmacotherapy for AUD after discharge from hospitalization for ALD reduces readmission and death. Currently, many U.S. transplant centers require a 6-month period of alcohol abstinence prior to liver transplantation. This policy is not realistic in cases of severe alcohol-associated hepatitis, where a majority (75-90 percent) of patient deaths occur within two months of diagnosis. Data suggests that patients who receive a liver transplant without the 6-month waiting period (early liver transplant) have similar survival outcomes and alcohol relapse rates as patients who receive a transplant after the 6-month waiting period. To build on this research, NIAAA recently issued a Request for Applications (RFA) to encourage studies on factors that influence the selection, management, and outcomes of patients who receive early liver transplantation.

The Addiction Neuroclinical Assessment (ANA) The ANA provides a framework for individualized etiology, prevention, and treatment of addiction by 1) identifying how the three neurofunctional domains in the addiction lifecycle model (incentive salience, negative emotionality, and executive function) influence differences among people diagnosed with AUD which can then be used to guide treatment decisions; and 2) better understanding the differences between individuals with and without AUD.

Validation of Three Neurofunctional Domains in AUD by Deep Behavioral Phenotyping. In a large, diverse clinical sample representing the spectrum of AUD, the three neurobiological domains hypothesized to be critical to the addiction cycle (see above) could be identified through factor analysis. Measures of addiction, personality, cognition, behavior, and exposure to early-life stress were collected in 454 patients. This study (Kwako et al., *American Journal of Psychiatry*, 2019) confirmed the relevance of the three neurofunctional domains to AUD. Using a multiple indicator multiple cause (MIMIC) approach, early life stress and sociodemographic predictors were identified. Other studies have further validated the three addiction domains. some examples follow. 1) Among heavy drinkers, three factors (executive function, incentive salience, and emotionality) were all associated with current AUD, history of AUD, positive family history of AUD, earlier age of first drink, and history of childhood emotional abuse and physical neglect as predictors. 2) Among problem drinkers, four core constructs were identified: incentive salience, negative emotionality, executive function, and negative alcohol-related consequences. 3) In nontreatment-seekers, deep phenotyping combined with factor analytic techniques implicated three intercorrelated neurofunctional domains that mapped on to the proposed ANA domains with methamphetamine use. 4). In another study of non-treatment seekers, functional changes in the nucleus accumbens and amygdala were associated with incentive salience and negative emotionality domains among those undergoing functional MRI after exposure to alcohol cues and negative cues. 5) Among treatment seekers with AUD, the incentive salience domain showed construct validity and demonstrated greater predictive validity for drinking outcomes compared to preexisting scales 6).in another study the negative emotionality domain showed construct validity and demonstrated concurrent associations with more frequent and heavier drinking and drinking to regulate negative affect.

Addiction as a Coping Response: Hyperkatifeia, Deaths of Despair, and COVID-19. Dr. Koob and his colleagues at NIAAA published a paper in the *American Journal of Psychiatry* (2020) about the addition of environmental and epigenetic insults (e.g., COVID pandemic-related isolation and stress) to the three neurofunctional domains. All of these factors contribute to hyperkatifeia, i.e., greater intensity of negative emotional/motivational signs and symptoms during withdrawal from alcohol or other drugs.

Changing the Conversation Around Recovery. Most people with AUD who need treatment receive no treatment of any kind, and little is known about what sustains longer-term recovery. Therefore, NIAAA is expanding its focus on longer-term recovery. NIAAA has defined recovery from AUD based on qualitative feedback from key recovery stakeholders (e.g., researchers, clinicians, and recovery specialists). Recovery is viewed as both a process of behavioral change and an outcome that incorporates time periods for two key components: Remission from DSM-5 AUD and cessation from heavy drinking (a non-abstinent recovery outcome). The NIAAA definition of recovery also emphasizes the importance of biopsychosocial functioning and quality of life in enhancing recovery outcomes.

Research Highlights. Dr. Koob reviewed two recent research articles related to validation of the addiction domains. The first, published by NIAAA Council member Dr. Witkiewitz and colleagues (*Psychology of Addictive Behaviors*, 2023), found that greater relief/negative emotionality at baseline

predicted greater drinking intensity and more frequent heavy drinking, while lower relief/negative emotionality predicted high functioning infrequent drinking during recovery. This study validated the three domains of the 3-stage addiction cycle using measures from Project MATCH and COMBINE, two of the largest multisite alcohol clinical trials ever conducted. At one- year follow up, relief/ negative emotion scores were associated with drinks per day and percent heavy drinking days. The results also support the utility of the domains in predicting AUD treatment outcomes and recovery. The authors noted that the addiction cycle domains were more strongly associated with outcomes than with AUD symptoms. Four latent recovery profiles reflecting differing levels of drinking and functioning were derived based on indicators of alcohol use. Addiction cycle domains were used to predict membership in the high functioning/infrequent drinking profile vs non-recovery profile. The second article (Cho et al., *Psychology of Addictive Behaviors*, 2019) found that negative reinforcement is more strongly associated with alcohol consumption in alcohol dependence (AD) than positive reinforcement. In this study, researchers used longitudinal data in 2,556 young adults to test whether positive and negative reinforcement associated with alcohol consumption differed as a function of AD. The association between positive reinforcement and alcohol consumption did not significantly vary as a function of AD diagnosis. In contrast, the association between negative reinforcement and alcohol consumption increased in the presence of AD diagnosis. Similar effects were observed in males and females.

Disseminating NIAAA Resources. The Healthcare Professional's Core Resource on Alcohol (HPCR) addresses what every healthcare professional should know about alcohol. Organized into 14 concise, practical, user-friendly articles, the HPCR Includes information about clinical impacts of alcohol, including cancer, pain, medication interactions, and co-occurrence with other substance use disorders and mental health disorders. Free continuing education credit up to 10.75 credit hours is available.

NIDA Director's Presentation

Dr. Volkow began her presentation with an observation that more and more people are mixing drugs, especially with alcohol. Thus, the interaction of alcohol and drugs is a critical issue.

NIDA Staff Updates. Dr. Volkow welcomed Dr. Aria Crump as the Director of the Office of Diversity and Health Disparities (ODHD) and the Deputy Director of the Office of Research Training, Diversity and Disparities (ORTDD). She also announced the appointment of Dr. Lorenzo Leggio as Clinical Director of NIDA's intramural research program with a joint appointment with NIAAA.

2022 Monitoring the Future Study. The most recent results of the annual school-based survey of 8^{th,} 10th, and 12th graders indicated that the prevalence of use of most substances remained at or below pre-pandemic levels of use. During the pandemic, teens had many fewer opportunities to interact with one another (and, hence, less peer pressure to use drugs) as well as greater parental oversight. There were few rebounds (except, notably, for alcohol among 12th graders) from last year's unprecedented number of decreases in drug use among youth, a trend since 2005. Among 12th graders, the survey found the substances with the highest prevalence were alcohol (51.9 percent); vaping (mostly tobacco) (32.1 percent); marijuana/hashish (30.7 percent); and vaping marijuana (20.6 percent). The prevalence of teens' prescription drug misuse was 5 percent, down from 11 percent five years ago and 16 percent 15 years ago. During the pandemic, fentanyl--frequently present in illicitly manufactured pills that are less expensive to purchase on the Internet than authentic medications—swept the country, leading to overdose deaths. Among teens 15-19, fentanyl-involved overdose death rates jumped dramatically during the pandemic. Non-fentanyl-involved overdoses remained low but may reflect teens overdosing from alcohol or mixing alcohol with other drugs.

NIDA Research Priorities to Address Teen Drug Use. In response to these trends, NIDA has established the following research priorities: 1) Implementation research of screening interventions for substance misuse and substance use disorder (SUD) in teenagers; 2) Research on interventions to prevent drug misuse in teenagers and in the transition into young adulthood; and 3) Treatment of SUD in teenagers, including mild, moderate and severe OUD. In regard to screening interventions, Dr. Volkow reported that she and Dr. Koob with Dr. Tom McLellan have published a commentary on the idea of preaddiction that has generated some concerns about terminology but is intended to help providers identify those at risk for developing an alcohol or substance use disorder and to create billing codes so that they may be reimbursed for doing do.

Cannabis. Recreational marijuana use is legal in 21 states and the District of Columbia. Medical marijuana use is legal in 38 states and DC. Marijuana use has increased among adults: Between 1992-2020, the number of daily/near-daily users increased 14-fold, while the number of monthly users quadrupled and the number of past-year users tripled. There is also a rising trend in cannabinoid-involved overdose deaths. In 2021, 90 percent of cannabis-involved deaths also involved opioids or stimulants, highlighting the potential dangers of multi-substance use. The increasing number of cannabis-related deaths may reflect the fact that people are consuming increasingly potent doses of marijuana's psychoactive ingredient tetrahydrocannabinol (THC) in a market that is totally unregulated. They may also reflect the availability of synthetic cannabinoids (e.g., spice), which are highly potent and often toxic. The idea that marijuana is safe is not supported by the evidence.

NIDA's Cannabis Research Priorities. To address the challenges of cannabis, NIDA's research priorities include: 1) Cannabis actions at molecular, epigenetic, cellular, neurocircuitry, and behavioral levels; 2) Patterns of cannabis consumption and polysubstance use; 3) Risk factors for cannabis use and cannabis use disorder (CUD); and 4) Consequences of cannabis use in brain, health, and behaviors across the lifespan. There are currently few treatments and no medications for CUD, making the development of such interventions a priority. In addition, NIDA's cannabis research priorities include understanding the impact of different policies on patterns of cannabis consumption and their consequences, as well as the potential of medical cannabis in the management of SUD, HIV, or pain.

Opioid Crisis. Addressing the opioid crisis is a major NIDA priority. Opioids accounted for over 81,000 overdose deaths last year in the United States. Synthetic opioids (excluding methadone) are now linked to almost 90 percent of opioid overdose deaths (over 71,000). The main culprit in opioid-related death by overdose is fentanyl, a drug that is approximately 50 times more potent than heroin and which may be laced into other drugs such as stimulants and counterfeit pills. Fentanyl penetrates the brain more rapidly than heroin and poses a risk of respiratory depression for longer periods, leading to the need for higher and multiple doses of naloxone to reverse the overdose. Further complicating the situation is that fentanyl may be contaminated with xylazine and may be consumed with other drugs. Physical dependence from fentanyl is stronger than for heroin, making treatment initiation with medications for OUD more challenging. Thus, there is a great need to increase understanding of how to prevent and treat those with fentanyl disorder and overdoses.

Fentanyl has changed many of the demographic impacts of drug use. Some people are now vulnerable for overdose deaths who were not in the past. Overdose deaths increased by 50 percent during the pandemic, most dramatically among men, especially Black and American Indian/Alaska Native (AIAN) men. Mortality is highest among those who are 24-44 years-old; men in young middle age are at highest risk. Women ages 35-54 are also at risk. All illicit drugs except marijuana are frequently

contaminated with fentanyl, leading to these demographic shifts. Targeting culturally sensitive interventions to Black and AIAN men will lead to improved outcomes in these groups.

OUD Treatment Research Gaps. Gaps include 1) The need for extended-release medications to treat opioid use disorders (MOUD), particularly extended release methadone; 2) Development of clinically meaningful alternative end points for clinical trials, including patient-reported outcomes; 3) Medications with targets other than μ-opioid receptors (MOR); 4) Repurposed medications (i.e., orexin receptor antagonists such as suvorexant, glucagon-like peptide agonists); 5) Immunotherapies, including vaccines and monoclonal AB; 6) Neuromodulation (e.g., transcranial magnetic stimulation [TMS], peripheral nerve stimulation); 7) fast, high-affinity MOR antagonists with longer duration; and 8) Respiratory stimulating drugs.

CRAN-related NCI Activities and Priorities

William Klein, Ph.D., Associate Director, NCI Behavioral Research Program in the Division of Cancer Control and Population Sciences (DCCPS), reported on CRAN-related activities at NCI. He began his presentation by introducing the new NCI Director Monica M. Bertagnolli, M.D., whom President Biden plans to nominate as NIH Director.

Cancer Moonshot. In 2022, President Biden announced a reignition of Cancer Moonshot^{SM}, highlighting new goals to reduce the cancer death rate by half within 25 years and improve the lives of those affected by cancer. Among many others, cancer prevention priorities include tobacco prevention and increasing knowledge about the cancer-related risks of alcohol.

DCCPS-specific Activities. As part of its science planning, DCCPS identified six cross-cutting areas of focus deserving more attention: health equity, data strategies, modifiable risk factors, climate change, evidence-based policy, and digital health. Within the Behavioral Risk Program (BRP), Dr. Neal Freedman has been named Chief of the Tobacco Control Research Branch, replacing Dr. Michele Bloch who is retiring. In June 2022, the Branch released Tobacco Control Monograph 23, "Treating Smoking in Cancer Patients: An Essential Component of Cancer Care." Tobacco Control Monograph 24 will focus on understanding the effects of alcohol use across the tobacco control continuum.

NCI's Smokefree.gov Initiative (SFGI). SFGI, celebrating its 20th anniversary this year, offers a suite of free web- and mobile-based smoking cessation resources that provide evidence-based information and support to people who use tobacco and want to quit, including new resources to support cessation of menthol tobacco products for African Americans and other groups who disproportionately use these products. Recent accomplishments include a National Text Portal launched in March 2022; a SmokefreeTeen—Next Legends landing page launched in May 2022; and expansion of SmokefreeTeen vaping cessation resources.

FDA Updates. NCI supports the U.S. Food and Drug Administration (FDA) in setting evidence-based tobacco policies. Current issues include: 1) *Menthol in Cigarettes and Cigars.* In April 2022, the FDA issued a news release proposing product standards to prohibit menthol as a characterizing flavor in cigarettes and prohibit all characterizing flavors (other than tobacco) in cigars. More research is needed on cessation from menthol-flavored tobacco products; 2) *Non-Tobacco Nicotine Products*. On March 17, 2023, the FDA issued two notices updating the definition of "tobacco product" in its existing regulations and guidances. These new guidelines amend the April 14, 2022 federal law that was passed in response to the increase of non-tobacco nicotine in popular tobacco products; and 3) *Potential Nicotine Standard*.

The FDA is currently working to develop a proposed product standard that would establish a maximum nicotine level to reduce the addictiveness of cigarettes and certain other combusted tobacco products.

Alcohol and Cancer. Alcohol consumption increases the risk of cancer at seven sites in the body, including mouth, throat, voice box, esophagus, liver, breast and colorectum. It is the third leading modifiable risk factor for cancer morbidity and mortality. NCI alcohol-related research areas include 1) communication and public awareness related to alcohol and cancer risk. (Public awareness of the risks is low. The 2020 Health Information National Trends Survey (HINTS), for example, reported that up to 10% of the US population erroneously believes that alcohol, especially wine, decreases cancer risk); and 2) decision-making processes and evaluation of the effects of warning labels and other communication strategies. A petition has been signed by various professional associations and societies advocating for rotating warning labels that would include alcohol-related cancer risk information. Relevant funding opportunities include Alcohol and Cancer Control (NOT-CA-20-034) and Public Policy Effects on Alcohol-, Cannabis-, Tobacco-, and Other Drug-Related Behaviors and Outcomes (NOT-AA-21-028).

Cannabis. Cannabis may be considered a gateway to tobacco use. Questions related to cannabis will be added to the next wave of the HINTS Survey. Further, the National Academies of Sciences, Engineering, and Medicine (NASEM) is developing a report that will provide an objective and authoritative account of the experiences in states and localities in the United States that permit medical or non-medical (adult use) of cannabis and cannabinoids. The final report is tentatively scheduled for a fall 2024 release.

Funding Opportunity Announcements (FOAs). Dr. Klein announced a new FOA: Advancing Adolescent Tobacco Cessation Intervention Research (RFA-CA-22-042; RFA-CA-22-043) supports research to develop, test, implement, and evaluate behavioral tobacco cessation interventions for adolescents. NIDA is participating with NCI in this FOA, which expires on October 16, 2023. NCI also funded Administrative Supplements to Existing Patterns of Tobacco and Cannabis Use (NOT-CA-22-070*)*, making five awards. Other current CRAN-related funding opportunities may be found on the NCI website within the BRP section.

Resources. NCI supports the Tobacco Use Supplement to the Current Population Survey, as well as HINTS. HINTS will be celebrating its 20th anniversary at a meeting on September 21-22, 2023.

Adolescent Brain and Cognitive Development (ABCD) Study Update

Dr. Volkow introduced Gaya Dowling, Ph.D., Director of the ABCD study, who updated Council members on the status of the study.

NIDA-ABCD Team. Dr. Dowling introduced ABCD staff members Elizabeth Hoffman, Ph.D., and Kim LeBlanc, Ph.D., as well as new additions to the ABCD team: Diana Alkire, Ph.D., Program Analyst, and Lieutenant Commander (LCDR) Traci M. Murray, Scientific Advisor for Justice, Equity, Diversity, and Inclusion (JEDI) for the ABCD and HEALthy Brain and Child Development (HBCD) studies.

Retention Priorities/Strategies. ABCD retention is high, with 97.1 percent of approximately 12,000 youth having been retained or not withdrawn from the study. Investigators are striving to retain a diverse cohort by focusing on retention of low-income families, as there is a greater proportion of families earning less than $50,000/year missing from specific study timepoints. Another area of focus is remote visits, which were popular with families during the pandemic. Now, the ABCD sites are trying to get everyone back in-person, particularly for the collection of biospecimens and imaging. Potential withdrawals are another area of concern: There are 715 families who have not officially withdrawn from

the Study but have not been seen since the two-year follow-up. The Study is stepping up its retention strategies with a data-driven approach that seeks to identify who is most at risk of dropping out and to inform strategies (e.g., compensation and staffing models) to bring them back into the Study. ABCD is also ramping up engagement efforts to reconnect with participants by producing thank you videos and educational resources for youth participants, such as how to leverage their ABCD participation in applying for jobs or college.

Data and Biospecimen Sharing. ABCD Data 5.0 release has been delayed and the data access process has been revamped. Data will continue to be available on the National Institute of Mental Health (NIMH) Data Archive (NDA). Neuroimaging and other file-based data will accessible via the NDA download tool. Tabulated data will be in zip files. ABCD will also host a data dictionary explorer application separate from NDA. For future data releases, a new ABCD Study® Data Sharing Platform will be developed.

ABCD has long sought to make the biospecimens it collects (hair, saliva, teeth, DNA, whole blood, and serum) available to researchers. In November 2022, NIDA published a Notice of Intent to Publish a Funding Opportunity Announcement for NIH Brain Development Cohorts Biospecimen Access (X01 Clinical Trial Not Allowed) (NOT-DA-22-064) to facilitate biospecimen studies consistent with ABCD objectives or which expand the knowledge of adolescent health more broadly. No funds will be provided through this program. A Biospecimen Explorer tool will allow applicants to determine whether the type and quantity of specimens they are interested are available. They will then submit a Biospecimen Availability Request to confirm their availability, which can be used to apply for funding for the analyses. They will then submit an X01 application to request specimens. Specimens from participants who self-identify as American Indian/Alaska Native (AI/AN) will not be included until NIDA's AIAN Collaborative Research Engagement Workgroup (CREW) develops a biospecimen sharing policy that addresses AIAN concerns.

ABCD Study Outcomes. ABCD data has been very popular, with 154 NIH grant awards applying the data in various content areas, including mental health, resting state fMRI, genetics, and cannabis. These grants have been funded by 14 ICs and 6 other funding organizations. Most of these grants are research project grants (RPGs) and training grants. While there are a few FOAs specific to secondary data analysis of ABCD and substance use datasets, many of these grants have been submitted under FOAs unrelated to ABCD, such as those related to the HEAL and BRAIN Initiatives, as well as chronic pain, HIV, and music and health. These grants are using ABCD data in interesting ways. For example, some are developing/validating methods, using ABCD as a comparison group, as a replication sample, or are pooling ABCD data with other datasets. One program project grant is developing animal models relevant to ABCD tasks to better understand mechanisms. As a result, there has been a dramatic increase in the number of published papers based on ABCD data (N-573) from both ABCD and non-ABCD investigators.

Recent Scientific Highlights. *Adverse Childhood Experiences (ACEs) and Alcohol in the ABCD Study***.** Dr. LeBlanc summarized key findings from two recently published papers about the impact of adverse experiences in childhood using ABCD data: "Adverse Childhood Experiences and Sipping Alcohol in U.S. Children: Findings from the Adolescent Brain Cognitive Development Study" (Nagata JM et al. , *Preventive Medicine Reports*) and "Characterizing Alcohol Expectancies in the ABCD Study: Associations with Sociodemographic Factors, the Immediate Social Environment, and Genetic Propensities" (Johnson et al., *Behavior Genetics).* In the ABCD Study, 43 percent of families have experienced household violence and 42 percent household substance abuse. While ACEs are known to impact later substance use and mental health, it isn't clear whether they impact unhealthy behaviors, such as alcohol use, earlier in development.

The ABCD Study has several alcohol-related measures, including alcohol expectancies (AE), that do not require personal experience. Examples of positive AE include “Alcohol helps a person relax, feel happy, feel less tense, and can keep a person's mind off of mistakes at school or work” whereas negative AE include “Alcohol can hurt how well a person gets along with others (makes people mean to others”). In addition, the ABCD study collects information about early alcohol use such as alcohol sipping. Positive AEs have been associated with the initiation and early stages of alcohol use, while alcohol sipping may be useful predictor of future alcohol use and adverse outcomes. The Nagata et al. study examined the relationship between accumulating ACEs (0, 1, 2, 3, or 4+) and alcohol sipping among 9–10-year-old children, while the Johnson et al. study looked at associations between genetic propensities, sociodemographic factors, and ACEs with positive and negative AEs among alcohol-naïve children of the same age. Results across the two studies demonstrated that a larger number of ACEs was associated with a greater likelihood of positive AEs in non-sipping youth; having four or more ACEs was associated with 1.27 times the risk of sipping alcohol; and, for ACEs subtypes, household violence and household alcohol abuse were significant. Thus, ACEs play a significant role in early alcohol behaviors. The longitudinal nature of the ABCD Study presents opportunities to investigate future alcohol drinking in these participants as well. Finally, ACEs--along with other sociodemographic and environmental variables-- may inform predictive models for early prevention and intervention strategies.

Racial Disparities in Adversity Underlie Brain Differences. Dr. Hoffman summarized a recent study using ABCD data that reported on “Racial Disparities in Adversity during Childhood and the False Appearance of Race-related Differences in Brain Structure (Dumornay, et al., *American Journal of Psychiatry*, 2023). Previous research had shown that Black youth in the United States are disproportionately burdened with adversity, including neighborhood disadvantage, material hardship, and trauma. Early adversity is associated with structural brain differences in regions involved in emotion regulation (amygdala, prefrontal cortex [PFC], hippocampus). Previous work had also shown lower neural response to threat within these regions in Black compared to White young adults. Durmornay et al. examined if early disparities in exposure to adversity contribute to youth race-related differences in brain volume as well as how contextual factors may impact neurocircuitry. Their study assessed group differences in exposure to adversity among a sample of approximately 7,500 white youth and 1,800 Black youth at their ABCD baseline visit (age 9-10). They ran mixed-effects models to assess race-related differences in gray matter volume (GMV); each model included all indices of adversity (neighborhood disadvantage, family conflict, material hardship, trauma, and low socio-economic status) as potential mediators with brain region as the dependent variable. Black youth in the study experienced more adversity and parents/caregivers of Black youth had lower educational attainment, lower income, and more unemployment compared with those of white youth. Black youth also had lower brain volume in the amygdala, hippocampus, and PFC compared with white youth. These brain volume differences varied with adversity metrics, with family income as the most frequent predictor. Disparities in adversity exposure partially mediated some of these brain differences; however, the models didn’t include other socioenvironmental disparities (e.g., perceived discrimination, school context, census-based measures of systemic inequities) that may further explain some of these differences. These findings highlight potential systemic contributors to disparate rates of psychiatric disease among Black and White individuals in the U.S., many of which are modifiable.

The article generated multiple press accounts of the nuanced findings. Thus, it provides a nice example of how ABCD data should be used, interpreted, editorialized, and reported on in the press. The findings also lead to new questions and opportunities, e.g., how might brain volume differences between groups change across development? Because the investigators excluded many other constructs available in

ABCD data, Dr. Hoffman highlighted this important concern: Should we avoid framing this kind of work in the context of race differences in brain or behavior and instead focus directly on social determinants of health (SDOH), recognizing that Black youth in our country face a greater burden of SDOH?

Justice, Equity, Diversity, and Inclusion. LCDR Murray provided an update on ABCD's JEDI initiative. She reported that there are now three full-time positions supporting JEDI, including her own role as Scientific Advisor, as well as a JEDI Associate Director and administrative support within the Coordinating Center. JEDI is guided by an Advisory Council that oversees three working groups on equitable and inclusive methods, diversity and inclusion in ABCD, and responsible use of ABCD Study data. Most recently, the Initiative commissioned an external consultant report that provided recommendations on how to enhance ABCD's JEDI efforts. As a result, the ABCD leadership is undergoing efforts to reset, restructure, and re-engage the consortium by expanding efforts beyond racial discrimination and improving transparency and accountability; broadening Advisory Council membership; and instituting quarterly JEDI All Hands meetings, short trainings during staff meetings, and more integration and collaboration with non-JEDI working groups. Finally, ABCD's START program finished its first year, in which START scholars have produced interesting results using ABCD data, some of which will be presented at a session at the upcoming American Psychological Association meeting on the "*Impact of the Environment on Adolescent Development: Findings From BIPOC Scholars in the ABCD Study START Program."*

Research Dissemination. Dr. Dowling highlighted a paper that came out the preceding week that illustrates how research using the ABCD dataset can influence programs and policies. "Antipoverty Programs Associated with Reduced Disparities in Brain Development and Mental Health," published in *Nature Communications*, presented an analysis of ABCD data from more than 10,000 youth across 17 states that differ in their cost of living and anti-poverty policies. It reported that the disparity in brain structure between children from high- versus low-income households was more than a third lower in high cost-of-living states with greater cash assistance than in those offering less, and the disparity in mental health symptoms was reduced by nearly half. In less than one week, 337 news stories highlighting an actionable policy to improve people's lives were published, potentially reaching over 776.6 million people.

Screentime Infographic and Webinar. ABCD is seeking to engage families by showing them what they have contributed to science. The first step was the development of an infographic on the popular topic of screen time that distilled key findings into actionable messages written in language that everyone can understand. It was disseminated to families, as well as to organizations such as AASA, The School Superintendents Association, that distributed it to its 30,000 members. The information was also presented in a webinar on May 4, 2023, that featured researchers whose work was highlighted on the infographic; the webinar was viewed by 254 people, most of whom were ABCD participants and their caregivers. Future efforts are planned on other topics.

Paulette Gray

Discussion. Dr. Sinha recommended development of an addiction prevention framework based on the ABCD data. She also inquired about how trauma is being assessed, i.e., have assessments of trauma been broadened in study protocols? Dr. Dowling responded that assessments have been broadened in that information was primarily obtained from caregivers in the early years when the child participants were very young. Now that these participants are older, researchers can obtain more information directly from the youth themselves, e.g., in the post-traumatic stress disorder (PTSD) module about specific life events that youth may have experienced. ABCD investigators have also been incorporating data (e.g., on pollution, crime exposure) from other datasets to enhance ABCD data without

overburdening the respondents. Dr. Greenfield inquired about what ABCD researchers are learning about sex differences. Dr. Dowling responded that many researchers are using ABCD data to study sex differences. Data is disaggregated by sex. In addition, there is a work group specifically looking at sexual identity and health. Dr. Ostrovsky recommended sharing the data presented at this meeting with the Child Health Insurance Program (CHIP) staff at the U.S. Centers for Medicare and Medicaid Services (CMS) as well as with the National Association of State Medical Directors, as the findings are very relevant to policy. Dr. Clark pointed out that other Federal agencies, such as the Administration for Children and Families, could also benefit from ABCD research. To influence state policies, he suggested outreach to the Bipartisan Policy Center. He encouraged ABCD to continue to translate its findings from the academy to the community. Dr. Ostrovsky asked if ABCD data is available to non-researchers, such as entrepreneurs, so that it can inform the design of new care models. Dr. Hoffman replied that the data are available to anyone who has authorized use, i.e., affiliated with an institution identified by NIH. Dr. Ostrovsky asked how non-academic researchers can gain access to the data so that more creative products and services can be developed. Dr. Dowling suggested that they follow-up to discuss this issue in greater detail.

Dr. Kareken applauded the idea of the infographics and suggested they be displayed in pediatricians' offices and similar venues, so that the research is widely disseminated. Dr. Dowling, noting the availability of the screen time infographic on the ABCD website, responded that the Study will coordinate with the Office of Science Policy and Communications to more widely distribute them. Dr. Agrawal wondered to what extent researchers will find out how participation in a longitudinal study will impact children's behaviors. Dr. Dowling responded that the impact of participation has been an issue of concern since the beginning of the study, but no one knows yet what kind of impact it will have.

HEALthy Brain and Child Development (HBCD) Update

Dr. Volkow introduced Dr. Michelle Freund, Director of the HBCD Study at NIDA. HBCD is a prospective longitudinal study recruiting 7,500 mother-child dyads from women in the 2nd trimester of pregnancy and following the child through early childhood. It includes multi-modal assessments of the brain as well as cognitive and emotional development. One goal is to characterize neurodevelopmental trajectories and determine how substance exposure and other environmental factors affect these trajectories. The resulting dataset will be broadly shared with annual releases for secondary analyses and biospecimens will be made available to researchers via a biorepository.

The ongoing opioid crisis brings an urgency to develop a better understanding of the factors that influence developmental outcomes, but there is also a paucity of normative data to inform scientists and healthcare providers about typical neurodevelopment. The HBCD study will establish an invaluable dataset on brain development and health in children for use as benchmarks by pediatricians and neurologists. Because these data are so important and cut across the mission of many ICs at NIH, this project is being supported through a partnership with the Helping to End Addiction Long-term (HEAL) Initiative and 11 Institutes, Centers and Offices, including NIDA.

HBCD has a number of aims, including:

- What are typical neurodevelopmental trajectories and what is the normal range of variability in brain development from birth through childhood?
- How do biological and other environmental exposures affect these developmental trajectories?
- How do genetic influences interact with environmental factors to influence neurodevelopment and cognitive, emotional, and social behavior?

- How does early life exposure to opioids, other substances, and/or other adverse environmental circumstances affect developmental trajectories?
- Are there key developmental windows during which the impact of adverse environmental exposures (e.g., stress, COVID-19) influence later neurodevelopmental outcomes?
- Are there key developmental windows during which ameliorating influences (e.g, substance use disorder treatment; social/economic support) are protective against the potential neurodevelopmental insults of early adverse exposures?
- What is the impact of early parent/caretaker interactions with their children on later health and other outcomes?

Sampling Design. The Study's sampling design is intended to achieve both external and internal validity. Because of the relatively low prevalence of opioid and other substance use in pregnancy in the general population, substance-using participants are being purposefully oversampled. Therefore, the sampling goals for HBCD are to: 1) recruit 7,500 pregnant women (300 women in each of the 25 sites); 2) recruit 25 percent (1,875 total or 75 per site) of participants who report or have biomarkers indicative of substance use during pregnancy; 3) recruit a study population that reflects birthing women ages 15-49 in the U.S.; and 4) recruit women similar to those who used substances during pregnancy to ensure a reasonable balance of potential confounders and improve the internal validity for scientific questions of substance use during pregnancy and child development.

Visits and Timeline. HBCD has designed a schedule of in-person and remote visits that will enable accomplishment of the Study aims while at the same time not placing an undue burden upon participants. Visits 1 (prenatal), 2 (0-1 month), 3 (3-9 months), 4 (9-15 months), and 6 (15-48 months) will be conducted in-person, while visits 5 (10-17 months), 7 (16-50 months) and 8 (36-60 months) will be conducted remotely. MRIs will be completed at V2, V3, V4 and V6 and child and parent biospecimens will also be collected. Wearable biosensors (an ankle sensor worn for 72 hours to monitor movement and a arm band to measure heart rate and sleep) are provided at Visits 2 and 3.

Current Study Status. HBCD currently has enrolled 345 parents and 244 children for pilot testing. The race/ethnicity distribution of these pilot participants is fairly close to the Study's targets. Assessments were piloted at the beginning of the year. MRIs have been completed for some participants, but imaging is not yet complete at all sites. EEG data and biospecimens have been piloted and wearable technology has been distributed. Preliminary analysis of the pilot urine samples revealed a positivity rate for exposure to substances similar to that of the general population. The full HBCD Study will launch on July 1, 2023.

Discussion. Dr. Singh inquired if nutrition data is being collected; Dr. Freund responded that it is being collected through questionnaires. Dr. Ostrovsky asked if insurance information is being collected. Dr. Freund replied that there is a wide array of demographic questions. Dr. Lewis inquired about how long HBCD will remain in touch with participants. Dr. Freund noted that the Study is 10 years in length with many touchpoints built in. Dr. Agrawal congratulated NIDA on the amazing effort, noting that tracking so many participants is a lot of work but that the project will yield a treasure trove of information. Dr. Barnett commented that she was pleased that the rates of substance use in the pilot reflected the proportion in the general population and that self-reports and biospecimen data were consistent. She asked how HBCD managed to accomplish this. Dr. Freund explained that one of the unique characteristics of HBCD is that it includes study navigators with lived experience at each site whose job is to make participants feel comfortable; the navigators are often peer recovery specialists. Dr. Volkow interjected that HBCD faces more challenges than ABCD because pregnant women who use drugs are

criminalized in some states. She worries about retention because the women and their children are quite vulnerable.

Deciding Bidirectional Interactions between Alcohol and Pain

Dr. Koob introduced Jeff Boissoneault, Ph.D., Director, Minnesota Alcohol and Pain Lab (MAPL), University of Minnesota, who reported that about one in five (20.4 percent) of U.S. adults have chronic pain, with 8 percent reporting high-impact chronic pain that limits activities on most days. Older adults, women, veterans, and those living in poverty are more likely to live with chronic pain. The overall cost of chronic pain to the U.S. economy is more than $600 billion annually. Unfortunately, front line treatments have poor efficacy and significant side effects.

Riley and King (*Journal of Pain*, 2009) surveyed 4,321 individuals with tooth, jaw, or arthritis pain. They found that, across conditions, approximately 25 percent of individuals endorsed the use of alcohol to manage pain. NIAAA reports that self-medication of pain with alcohol likely results in hazardous drinking, as well as a risk of developing painful alcohol-related neuropathy. Relief of pain provides additional negative reinforcement for alcohol use, increasing the risk of developing AUD or a return to use for those in recovery. Further, alcohol withdrawal increases pain severity and sensitivity.

Dr. Boissoneault presented a schematic that illustrated the bidirectional interactions between substance use and pain. Substance use affects pain by producing acute analgesia, abstinence-induced hyperalgesia, and risks for chronic pain. Pain, in turn, affects substance use by serving as a motivator to use, providing a way to cope with pain, being a barrier to cessation, and increasing risks for developing a substance-related disorder. This vicious cycle contributes to the maintenance and progression of both chronic pain and addiction and there is a need for research to disentangle these interactions. To that end, Dr. Boissoneault and his colleagues developed the Catastrophizing, Anxiety, Negative Urgency, and Expectancy (CANUE) model to define a testable paradigm of pain and substance use. The model posits that pain leads to negative affect, influenced by pain attitudes. Negative affect leads to substance use, influenced by negative urgency. Pain itself leads to substance use, influenced by substance-related expectancies. The model identifies some non-modifiable factors, including race and ethnicity, sex, SES, substance and mental health history, and pain characteristics (e.g., duration, severity, among others).

Pain as an Antecedent for Alcohol Use. There is substantial evidence that pain is a potent predisposing factor for heavy drinking and alcohol-related consequences. Greater pain severity has been associated with greater odds of a return to drinking both during and after treatment. Reductions in pain severity during residential treatment predicted increased abstinence, self-efficacy, and quality of life, as well as reduced craving. Experimentally induced pain increased the urge and intention to drink in healthy young adults. With this background in mind, the MAPL research team undertook a Strength Training and Alcohol Consumption (STAC) Study with 53 individuals, of whom 30 were women. Participants were randomized to vigorous eccentric exercise expected to result within 48 hours in delayed onset muscle soreness (DOMS) in the elbow flexors or low-intensity concentric bicep exercise (Sham DOMS). The investigators hypothesized that the DOMS exercise would lead to a greater increase in alcohol demand, as measured by the Alcohol Purchase Task administered before and 48 hours after exercise, and that the effect would be greater among men. Results showed that men in the DOMS group increased in demand intensity (number of drinks consumed when drinks are free) and breakpoint (price when consumption reaches zero) from pre to post test, but not women or men in the Sham DOMS group. However, breakpoint (price when consumption reaches zero) and essential value (EV) (inversely proportional to elasticity, which is the point at which demand becomes sensitive to changes in price) significantly decreased in women in the DOMS group.

In another study, the researchers looked at the effect of pain on drinking topography (the microstructure of drinking behavior during an episode of alcohol consumption). In the Pain and Alcohol in Virtual Reality (PAVR) Study, 20 individuals (including 11 women) completed two alcohol self-administration sessions in a virtual reality (VR) bar setting. In each session, participants were exposed to either painful heat (44°C) or non-noxious warmth (38°C). Sip interval (seconds) and sip volume (grams) were measured. Results showed that painful heat significantly increased sip interval in men, but not in women. No effect of pain on sip volume was found. Analyses indicated that the effect of the painful heat condition was stronger in those with higher levels of greater negative urgency, independent of sex. Thus, people with greater negative urgency may be at elevated risk for hazardous drinking when experiencing pain.

Acute Analgesic Effects of Alcohol. There are both anecdotal and clinical reports of alcohol's analgesic effects that date back as far as 1513, as well as consistent laboratory evidence that alcohol increases the pain threshold and decreases pain intensity in healthy individuals. However, studies have often been limited to men and people without chronic pain. MAPL researchers examined the analgesic effects of alcohol on chronic jaw pain. In their experiment, 48 individuals (36 women, 19 people with chronic pain) completed two double-blind testing sessions in a counterbalanced order: alcohol (target BrAC = 0.08 g/dl) and placebo (0 g/dL target BrAC). In each, pressure algometry was performed at the insertion of the masseter muscle in the face and jaw. Pain threshold, pain intensity, and perceived pain relief were assessed. Significant increases in pain threshold and pain relief, as well as reductions in pain unpleasantness and pain intensity were found under the alcohol condition. Chronic pain participants demonstrated lower pain thresholds and greater pain intensity and pain unpleasantness ratings than controls. No interactive effects of alcohol and pain conditions were found on any pain measure. Expectancy also played a role. In the alcohol condition, those who were expecting more pain relief did, in fact, experience greater pain relief.

Dr. Boissoneault and his colleagues have also investigated functional connectivity of the mesocorticolimbic system as a factor in alcohol and pain. In one study, they focused on the effects of acute alcohol intake on connectivity of the circuit between the nucleus accumbens and the medial prefrontal cortex, selecting these structures because they've been shown to modulate pain as well as to contribute to the development of chronic pain. Those with chronic low back pain tend to have higher connectivity between these structures. Those who can better modulate pain have lower connectivity. The researchers found that alcohol tended to decrease the connectivity between the structures acutely. This finding was consistent with the possibility that changing connectivity in this circuit may be one way alcohol affects the pain experience for people who are self-managing. MAPL researchers have also been interested in developing more novel metrics related to brain function. One of those is regional signal variability (RSV), the standard deviation of signal intensity over time. Greater RSV is associated with improved cognitive performance and better pain modulation, thus reflecting greater functional capacity of a brain region. In a study with 26 individuals, they have found that alcohol is acutely reducing signal variability in a variety of cortical areas, but not in the sub-cortex. More recently, they have re-run these analyses with data from their full sample and largely replicated their findings. Interestingly, they have found some evidence of increasing variability in sub-cortical areas such as the brainstem and thalamus.

Summary and Future Directions. MAPL studies have provided further evidence that pain increases the motivation to use alcohol, reinforces efficacy of alcohol, and alters the drinking topography. These effects appear to be especially strong among men and individuals with higher negative urgency. Further, alcohol acutely increases an individual's pain threshold and perceived pain relief and decreases pain

intensity. To deepen understanding of the bidirectional nature of pain and alcohol, there is a need to more fully characterize pain as an antecedent for alcohol use and/or a return to use as a function of putative risk factors, with systematic inclusion of individuals at higher risk for alcohol-related consequences, such as older adults, historically excluded and marginalized groups, individuals with chronic pain, people in AUD recovery, and an adequately powered sample to test predictions of the CANUE model. Further research is also needed on the impact of sex and family history on the analgesic effects of alcohol and functional neural correlates, as well as on the mechanisms underlying the negative reinforcing effects of alcohol intake in the context of pain. There is also a need to develop and evaluate interventions to reduce the risk of alcohol-related consequences in people with pain, and vice versa.

ARPA-H: The Mission

Dr. Volkow introduced Susan Monarez, Ph.D., Deputy Director of the Advanced Research Projects Agency for Health (ARPA-H), who introduced the recently established agency.

Working with NIH. Dr. Monarez described ARPA-H as NIH's newest partner that takes on high risk, high reward programs that extend how NIH thinks about approaching a health problem. ARPA-H is part of NIH but is an independent agency that collaborates across the entire project lifecycle, including: 1) *Program design* (ARPA-H staff will work with NIH subject matter experts [SMEs] to validate well-defined problems in health); 2) *Team building* (ARPA-H provides a program manager; NIH SMEs may share opportunities with their R&D networks, support proposal evaluation); 3) *Program execution* (as appropriate, ARPA-H may invite NIH stakeholders to Principal Investigator meetings for awareness of a program's approach from Day 1); 4) *Learning and growing* (NIH colleagues may be transition partners for programs, and remain stakeholders for the duration of the program); and 5) *Commercialization and transition* (engaging NIH stakeholders who may be appropriate for technology transition as users or funders; can formally position NIH as transition partner).

To date, ARPA-H leadership has met with 11 IC Directors to share its mission and explore working together and has addressed the Advisory Committee to the NIH Director and the National Cancer Advisory Board, among others. Future collaborative efforts include meeting with all IC Directors and their teams at NIH by Summer 2023 and coordinating small team brainstorming sessions to identify well-defined problems in health that ARPA-H might pursue. More activity at the Program Officer level is anticipated as additional ARPA-H Program Managers come onboard.

Initial Focus Areas. ARPA-H seeks to solve the greatest challenges in the healthcare ecosystem by addressing four major focus areas: 1) *Health science futures*: Developing approaches that bring radically new insights and paradigms. These innovative tools, technologies, and platforms can apply to a broad range of diseases that affect large populations, rare diseases, or diseases with limited treatment options; 2) *Scalable solutions*: Addressing challenges that include geography, distribution, manufacturing, data and information, and economies of scale to create programs that improve healthcare access and affordability; 3) *Proactive health*: Creating new capabilities to identify and characterize disease risk, reduce comorbidities, and promote treatments and behaviors to improve health and wellness reducing the likelihood of medical intervention or accelerating recovery and regeneration capabilities; and 4) *Resilient systems*: Creating capabilities, developing mechanisms, and accelerating system integrations to enhance stability and reliability to weather crises — from the molecular to the societal — such as pandemics, social disruption, climate change, molecular disturbances, and economic instability. Additional topics of interest include quantitative measurements of health outcomes, human-centered design for health innovations, participatory research, and advances in Ethical, Legal, and Societal Implications (ELSI) of new technologies. Dr. Monarez provided a

theoretical example of how the agency will approach its work using digital histopathology capability as a model. She identified a notional national program problem: Current histopathology practice is manual, requires an expert in the loop, is costly, and data is not accessible to share broad insights to improve patient care. Therefore, ARPA-H might address technical issues, such as designing and developing novel multi-omic histopath assays; applying artificial intelligence, machine learning, and data technology for automated diagnostics and 3D tissue characterization; and then integrate data into care pathways and digital advocacy.

ARPA-H Mission and Business Model. ARPA-H's promise is to accelerate better health outcomes for everyone who has a health condition. ARPA-H is a Federal R&D Funding Agency with an initial $2.5 billion in funding and is an independent agency of HHS within NIH: The ARPA-H Director reports directly to the Secretary of HHS. The agency maintains no internal research labs and is disease agnostic. Its priorities are bottom-up Program Manager-driven ideas and decision-making, emphasizing high risk/high impact research. ARPA-H's work is not grant-based, but will instead focus on cooperative agreements, "other transactions authority" (OTAs), and contracts. It also has prize authority. Thus, ARPA-H operates in an ecosystem in which NIH, other Federal agencies, and private investors constitute stakeholders; academia, industry, and non-governmental organizations function as "performers;" and healthcare providers and patient groups serve as customers.

Established in March 2022, ARPA-H is "open for business." It published its first Agency-wide Open Broad Agency Announcement (BAA) seeking proposals for breakthrough research to improve health outcomes across patient populations, communities, diseases, and health conditions. ARPA-H is also seeking to establish sites in three geographic locations across the United States through the pursuit of a hub-and-spoke strategy. ARPA-H will solicit respondents to identify the geographic locations of sites for Hubs No. 2 and 3, issuing a draft Request for Consortium Agreement (RCA). The ARPA-H Dash to Accelerate Health Outcomes, or "ARPA-H Dash," is a collaborative online competition open to bold thinkers across health and scientific communities and provides a simple, engaging, and impactful way to solicit the best ideas in the country to enhance the ARPA-H mission. It is currently being launched.

Round Table Discussion

Dr. Koob moderated the round table discussion. Dr. Volkow asked Dr. Monarez how ARPA-H will select projects to work on. Dr. Monarez responded that the agency is Program Manager-driven: Program Managers propose an idea for a program they want to get funded. These program ideas are reviewed and validated by internal experts before being approved by the Director. Dr. Ostrovsky asked Dr. Monarez how ARPA-H will avoid duplicating what's already on the market, and how will it attract partners who can help the agency scale up or commercialize. Dr. Monarez responded that ARPA-H is using a three-pronged approach to avoid duplication. First, the agency plans to conduct a landscape research assessment to incorporate everything in the public domain with private efforts into a dataset. Second, ARPA-H will bring in technical expertise from NIH and other sources to ensure broad inputs before launching a program. Finally, ARPA-H's BAAs are designed to be as broad as possible, and the agency hopes to hear from those working on a technology or within a domain. Regarding the venture community, ARPA-H is launching a venture hub, as well as an investor hub, to engage those who can help pull a new technology through the commercial pipeline. ARPA-H does not intend to be long-term funder but will encourage help from other sources. Dr. Ostrovsoky offered to help connect ARPA-H with certain investor sources. Dr. Volkow followed up with a question: How will ARPA-H establish the value of a program, i.e., how will the agency determine how much money to invest in a project and what an appropriate timeline will look like? How will the agency apply prediction modeling early on so ARPA-H can learn what are successes and what are not? Dr. Monarez responded that ARPA-H is adopting a

bottoms-up approach driven by its Program Managers. Internal vetting of their proposals will raise questions about whether an alternative approach would be more beneficial. Time horizons are very compressed, as Program Managers are hired for three years only, then can re-up for three more. Programs are designed to be completed within two to four years, with go/no go intervals at 24 months. The agency will package investors and other supports together around a program. This has been a successful model for the Defense Advanced Research Projects Agency (DARPA) and ARPA-H is confident it will work.

Dr. Koob posed a question to Dr. Boissoneault, noting that it may have ARPA-H implications: Can emotional pain be measured? Is it a covariate that can explain some of the variance? Dr. Boissoneault responded affirmatively, explaining that all pain stimuli have an emotional component and negative emotionality (anxiety, depression, fear, etc.) can be measured well. In the CANUE model and others, negative emotion is moderating the relationship between pain and substance use. While pain is one source of emotional distress or pain, other sources include trauma, socio-economic problems, etc., that might have a similar relationship. Dr. Powell posed a question for Dr. Monarez in the chat about ARPA-H's potential interest in pain management, given that 20 percent of the population has chronic pain. Dr. Monarez responded that ARPA-H is waiting for a Program Manager who is interested in that topic and would need an assessment of what would be a scalable effective intervention for the broadest population. Dr. Koob asked Dr. Boissoneault to comment on this issue. He responded that the challenges are in pain management and relevant strategies. There is a lack of crosstalk between clinical and basic researchers and a need to back-translate what is observed in humans to animals. Dr. Powell followed up on her question, noting that she was struck during Dr. Boissoneault's presentation about the difference between perceived pain relief and pain intensity. She asked if that might lead ARPA-H to endeavor not to relieve pain intensity but to focus on the perception of pain. Dr. Monarez replied affirmatively, noting that ARPA-H would ask: What would it take to move from the original conceptualization to translation to patients and are there any limitations in the benefit that patients would derive? The agency seeks to have a pipeline of programs that will benefit patients within four years. Dominique Lorang-Leins, Ph.D., NIAAA Program Officer, asked Dr. Monarez if ARPA-H would support development of non-invasive sensing technologies that can be used to objectively assess the level of physical and/or emotional pain. Dr. Monarez speculated that the agency might support a wearable biosensor to determine when someone is feeling stress or pain so that pain assessment moves from a perception based on individual self-report to a deployable technology that can be trusted by physicians. Thus, ARPA-H might launch a program based on how important and prevalent pain is, but it would also have to assess if the resulting technology could successfully make its way through the regulatory process and be used in the clinic.

Dr. Milliken responded to data presented by Dr. Volkow about drug screening in adolescents. He noted that the Department of Defense (DoD) conducted a large anonymous survey of military members who had used opioids. Among those who endorsed opioid use, 45 percent tested positive for alcohol-related problems on the Alcohol Use Disorders Identification Test (AUDIT-C). This suggests that in a clinical setting, it may be more acceptable to ask teens about alcohol use to see how many are also using marijuana. Dr. Volkow agreed that there is data that asking about legal drugs first helps focus on those using illegal drugs. If the respondent replies negatively to a question about legal drug use, it is unlikely that he or she is using illegal drugs. This is important because practitioners are not likely to do lengthy assessments. Dr. Greenfield observed that digital screening for substance use usually evokes more honest responses than other types of screening, but that there's little point in doctors screening if they can't treat. She recommended creating an interface that would allow treatment follow-up after digital screening.

Dr. Greenfield also addressed Drs. Koob and Volkow with this question: How do we do universal screening and interventions within the medical system and then, when administering treatments, how do we tailor them to specific situations? She noted there is a tension between the two and that further research is needed on both. This is especially true for addressing those in the early stages of addiction. She also suggested that NIAAA piggyback on the U.S. Preventive Task Force recommendation that breast cancer screening begin at age 40 by highlighting the risk between alcohol use and breast cancer. Dr. Greenfield also posed a question about the HPCR, asking if it is linked to all medical societies and what incentives are in place to encourage physicians to use this and other resources. Dr. Williams-Simmons responded that NIAAA is working hard to disseminate the HPCR to medical societies.

Dr. Walls asked what synergies might be created or already exist across ICs to address the inequities and health disparities that exist. How can this be done in a way that balances pragmatism with revolution? What will produce the "biggest bang for the buck?" She noted that the current approach of discussing approaches that work within the existing system and using measures developed for the mainstream population is not working. It's one thing to include more American Indians in large scale studies, but how do we engage them? Journals publish articles on the root causes of biological differences, but really the differences reflect racism. The field knows little about strength-oriented approaches to healing as demonstrated in research based on Alaska Natives. Small studies have shown that benevolent childhood experiences outweigh adverse ones, but these positive experiences are not being measured. By not measuring them, the field may be perpetuating stigma although calling it structural racism. Dr. Volkow responded that NIH creates synergies across ICs. She acknowledged that research to reduce health disparities needs to empower groups to come up with their own solutions, especially among Native Americans. A major focus is how to train researchers from non-mainstream cultures to preserve strengths and bolster resiliency. She noted there is now an opportunity to partner with ARPA-H to build bold solutions to these issues. Dr. Koob reiterated the value of Dr. Stacy Rasmus' work in Alaska using cultural approaches to prevention. He asked Dr. Boissoneault if he has noted any differences in pain across sub-groups. Dr. Boissoneault responded that his group has focused more on gender differences than on racial/ethnic differences. One of his students looked at race as a potential predictor of pain and substance use, finding similar results between Black and White respondents.

Dr. Chambers asked if pain varies across the menstrual cycle for women. Dr. Boissoneault responded that there are some small effects of the menstrual cycle on pain perceptions, but it is currently unknown about their relationship with alcohol use. His group has the data that would allow them to examine this issue. Another question addressed research on individuals with migraine or chronic headaches. Dr. Boissoneault responded that his group has not recruited research participants with headache pain. Dr. Volkow asked Dr. Boissoneault if his team had done tests on replicability of their findings and on the effects of circadian variability on pain perception. Dr. Boissoneault replied that lack of sleep is associated with increased sensitivity to pain and that alcohol interferes with sleep. These factors could help explain the differences in pain among races, as sleep time is generally shorter among Blacks, possibly as a result of stress from low income. He also commented that MAPL researchers have not directly manipulated circadian periods, mostly administering alcohol around noon to 1 p.m. They have not assessed "night before" sleep but do get an overall assessment of sleep, finding a strong association between sleep quality and pain. Dr. Volkow recommended a deeper look at circadian variability and pain.

Dr. Fingert inquired about how ARPA-H considers major changes that have occurred within the past three years to 1) the R&D community that has experienced limitations (e.g., reduced qualified R&D staffing that limits trial enrollment) that challenge Phase I and II studies to succeed within the patent domain and therefore to attract larger companies to commercialize their research; and 2) the regulatory

community where accelerated programs are now under challenge because many have not been successful in moving on to Phase III studies within designated timeframes. Dr. Monarez acknowledged that these are huge issues. One of ARPA-H's goal for its investor hub and spoke model is to have it help develop clinical trial networks and assure they have equity and diversity included. In terms of the regulatory process, the agency understands it is a challenge. When Congress created ARPA-H, it gave the agency the authority to work directly with the FDA to understand how to strengthen the regulatory process of ARPA-H programs. ARPA-H has also issued an RFI about how the agency should approach its relationship with FDA and regulation in general. These are tough challenges in the ecosystem, but the agency is trying to think about how to address them.

Dr. Milliken commented that DoD hopes to avoid cannabis legalization and lauded Dr. Compton's study on cannabis and psychosis.

Adjournment

Dr. Volkow adjourned the meeting at 3:31 p.m.

CERTIFICATION

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

For NIAAA:

/s/

George Koob, Ph.D.
Director
National Institute on Alcohol Abuse and Alcoholism
and
Chairperson
National Advisory Council on Alcohol Abuse and Alcoholism

/s/

Ranga V. Srinivas, Ph.D.
Executive Secretary (Acting)
National Advisory Council on Alcohol Abuse and Alcoholism
National Institute on Alcohol Abuse and Alcoholism

For NIDA:

/s/

Nora Volkow, M.D.
Director
National Institute on Drug Abuse
and
Chairperson
National Advisory Council on Drug Abuse

/s/

Susan Weiss, Ph.D.
Executive Secretary
National Advisory Council on Alcohol Abuse
National Institute on Drug Abuse

For NCI:

/s/

Christopher R. Friese, Ph.D., R.N.
Acting Chair
National Cancer Advisory Board
National Cancer Institute

/s/

Paulette S. Gray, Ph.D.
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