DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
NATIONAL INSTITUTES OF HEALTH
NATIONAL CANCER INSTITUTE

15th JOINT MEETING
of the
BOARD OF SCIENTIFIC ADVISORS AND
NATIONAL CANCER ADVISORY BOARD

Summary of Meeting
14–15 June 2023

Conference Room TE406, East Wing, Shady Grove Campus
National Cancer Institute
National Institutes of Health
Bethesda, Maryland

BOARD OF SCIENTIFIC ADVISORS and
NATIONAL CANCER ADVISORY BOARD JOINT MEETING
BETHESDA, MARYLAND
Summary of Meeting
14–15 June 2023

The Board of Scientific Advisors (BSA) of the National Cancer Institute (NCI) and the National Cancer Advisory Board (NCAB) convened for the 15th Joint Meeting on 14–15 June 2023 in Conference Room TE406, East Wing, Shady Grove Campus, NCI, National Institutes of Health (NIH), Bethesda, MD. The meeting was open to the public on Wednesday, 14 June 2023, from 9:00 a.m. to 3:20 p.m., and Thursday, 15 June 2023, from 9:00 a.m. to 11:52 a.m. The meeting was closed to the public on Wednesday, 14 June 2023, from 3:35 p.m. to 4:25 p.m. The NCAB Chair, Dr. John D. Carpten, Professor and Chair, Department of Translational Genomics, Royce and Mary Trotter Chair in Cancer Research, Keck School of Medicine, University of Southern California; and the BSA Chair, Dr. Keith T. Flaherty, Director of Clinical Research, Massachusetts General Hospital Cancer Center, Professor of Medicine, Harvard Medical School, presided during the open sessions. Dr. Carpten presided during the closed session. In the open sessions, the BSA considered new requests for applications (RFAs), cooperative agreements (Coop. Agr.), requests for proposals (RFPs), and program announcements with special receipt, referral, and/or review (PARs) of new and re-issue concepts presented by NCI program staff.

BSA Members

Dr. Keith T. Flaherty (Chair)
Dr. Chandrakanth Are
Mr. Timothy Babich
Dr. Suzanne J. Baker
Dr. Karen M. Basen-Engquist (absent)
Dr. Otis W. Brawley
Dr. Andrew T. Chan
Dr. Nelson J. Chao
Dr. Gloria D. Coronado
Dr. Mark P. Doescher
Dr. Chyke A. Doubeni
Dr. Shelton Earp
Dr. Jennifer R. Grandis
Dr. Dorothy K. Hatsukami
Dr. Trey Ideker
Dr. Karen E. Knudsen
Dr. Michelle M. Le Beau
Dr. Ana Maria Lopez
Dr. Karen M. Mustian
Dr. Lisa A. Newman
Dr. Raymond U. Osarogiagbon
Dr. Sylvia Katina Plevritis
Dr. W. Kimryn Rathmell
Dr. Erle S. Robertson
Dr. Robert D. Schreiber
Dr. David Sidransky
Dr. Cornelia M. Ulrich
Dr. Samuel L. Volchenboum
Dr. Robert H. Vonderheide (absent)
Dr. Richard C. Zellars (absent)

NCAB Members

Dr. John D. Carpten (Chair)
Dr. Francis Ali-Osman
Ms. Margaret Anne Anderson*
Dr. Nilofer S. Azad
Dr. Anna D. Barker
Dr. Richard J. Boxer*
Ms. Ysabel Duron*
Dr. Luis Alberto Diaz, Jr.
Dr. Howard J. Fingert
Dr. Christopher R. Friese
Mr. Lawrence O. Gostin (absent)
Ms. Julie Papanek Grant*
Dr. Andrea A. Hayes Dixon
Dr. Amy B. Heimberger
Dr. Scott W. Hiebert (absent)
Dr. Nikan Khatibi
Dr. Ana Navas-Acien*
Dr. Electra D. Paskett
Dr. Nancy J. Raab-Traub
Dr. Margaret R. Spitz (absent)
Dr. Fred K. Tabung*
Dr. Susan Thomas Vadaparampil
Dr. Ashani T. Weeraratna
Dr. Karen M. Winkfield

President's Cancer Panel

Dr. Elizabeth M. Jaffee (Chair) (absent)
Dr. Mitchel S. Berger
Dr. Carol L. Brown

*Pending appointment

Alternate *Ex Officio* NCAB Members

Dr. John Gordon,CPSC
Dr. Joseph R. Graber, DOE (absent)
Dr. Michelle Heacock, NIEHS
(Alternate for Dr. Gwen W. Collman)
Dr. Michael Kelley, VA
Dr. Richard Pazdur, FDA (absent)
Dr. Tara A. Schwetz, NIH (absent)
Dr. Craig D. Shriver, DoD
Dr. Kerry Souza, NIOSH (absent)

Members, Scientific Program Leaders, National Cancer Institute, NIH

Dr. Monica M. Bertagnolli, Director, National Cancer Institute
Dr. Oliver Bogler, Director, Center for Cancer Training
Dr. Philip E. Castle, Director, Division of Cancer Prevention
Dr. Stephen J. Chanock, Director, Division of Cancer Epidemiology and Genetics
Dr. Henry P. Ciolino, Director, Office of Cancer Centers
Dr. James H. Doroshow, Deputy Director for Clinical and Translational Research
Dr. Dan Gallahan, Director, Division of Cancer Biology
Mr. Peter Garrett, Director, Office of Communications and Public Liaison
Dr. Katrina A.B. Goddard, Director, Division of Cancer Control and Population Sciences
Dr. Satish Gopal, Director, Center for Global Health
Dr. Paulette S. Gray, Director, Division of Extramural Activities
Dr. Ed Harlow, Special Advisor to the NCI Director
Dr. Toby T. Hecht, Deputy Director, Division of Cancer Treatment and Diagnosis
Dr. Tony Kerlavage, Director, Center for Biomedical Informatics and Information Technology
Dr. Kristin Komschlies McConville, Acting Director, Office of Scientific Operations, NCI at Frederick
Dr. Douglas R. Lowy, Principal Deputy Director, National Cancer Institute
Dr. Glenn Merlino, Scientific Director for Basic Research, Center for Cancer Research
Dr. Tom Misteli, Director, Center for Cancer Research
Dr. Meg Mooney, Associate Director, Cancer Therapy Evaluation Program
Dr. Diane Palmieri, Director, Center for Research Strategy
Dr. Henry Rodriguez, Director, Office of Cancer Clinical Proteomics Research
Mr. Jeffrey Shilling, Chief Information Officer and Chief of Infrastructure and Information Technology Services Branch, Center for Biomedical Informatics and Information Technology
Ms. Donna Siegle, Executive Officer and Deputy Director for Management, Office of the Director
Dr. Dinah S. Singer, Deputy Director, Science Strategy and Development
Dr. Sanya A. Springfield, Director, Center to Reduce Cancer Health Disparities
Dr. Louis M. Staudt, Director, Center for Cancer Genomics
Mr. Michael Weingarten, Director, Small Business Innovation Research and Small Business Technology Transfer Programs
Dr. Robert Yarchoan, Director, Office of HIV and AIDS Malignancy
Dr. Maureen Johnson, Executive Secretary, Office of the Director

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WEDNESDAY, 14 JUNE 2023

I. CALL TO ORDER AND OPENING REMARKS—DRS. JOHN D. CARPTEN AND KEITH T. FLAHERTY

Dr. John D. Carpten called to order the 15th Joint Board of Scientific Advisors (BSA) and National Cancer Advisory Board (NCAB) meeting. He welcomed members of the Boards, *ex officio* members, President's Cancer Panel members, liaison representatives, staff, and guests. Members of the public were welcomed and invited to submit to Dr. Paulette S. Gray, Director, Division of Extramural Activities (DEA), National Cancer Institute (NCI), in writing and within 10 days, any comments regarding items discussed during the meeting. Dr. Carpten reviewed the confidentiality and conflict-of-interest practices required of Board members in their deliberations.

Dr. Carpten called Board members' attention to the future meeting dates listed on the agenda, noting that the 2025 NCAB dates will need to be confirmed.

Motion. A motion to approve the 2025 NCAB meeting dates was approved unanimously.

Motion. A motion to accept the minutes of the 9 February 2023 NCAB meeting was approved unanimously.

Motion. A motion to accept the minutes of the 27 March 2023 Special NCAB meeting was approved unanimously.

Motion. A motion to accept the minutes of the 21 March 2023 BSA meeting was approved unanimously.

II. NCI DIRECTOR'S REPORT—DR. MONICA M. BERTAGNOLLI

Dr. Monica M. Bertagnolli, Director, NCI, welcomed members of both the BSA and NCAB to the 15th Joint Meeting of these Boards. Dr. Bertagnolli reviewed the agenda; discussed NCI news and events; and provided updates on the NCI budget, cancer drug shortages, the National Cancer Plan, and recent cancer research advances.

Dr. Bertagnolli next welcomed new NCAB members: **Ms. Margaret Anne Anderson,** Managing Director, Deloitte Consulting LLP; **Dr. Richard J. Boxer,** Clinical Professor, David Geffen School of Medicine, University of California, Los Angeles; **Ms. Ysabel Duron,** Founder and Executive Director, The Latino Cancer Institute; **Ms. Julie Papanek Grant,** General Partner, Canann; **Dr. Ana Navas-Acien**, Professor of Environmental Health Sciences, Department of Environmental Health Sciences, Mailman School of Public Health, Columbia University; and **Dr. Fred K. Tabung,** Assistant Professor, Department of Internal Medicine, College of Medicine and Comprehensive Cancer Care, The Ohio State University.

NCI News and Events. Dr. Bertagnolli reported that the White House recently convened three Cancer Moonshot℠ forums: the Colorectal Cancer Forum on 10 March 2023, Brain Cancers Forum on 25 May 2023, and Smoking Cessation Forum on 1 June 2023. These forums bring together scientists, advocates, and government leaders who speak broadly about achieving progress in cancer research. Additionally, these forums are community-based, far-reaching efforts and are helpful in understanding how to find solutions.

Results from several major Division of Cancer Treatment and Diagnosis (DCTD), Cancer Therapy Evaluation Program (CTEP)-supported trials were presented at the American Society of Clinical Oncology (ASCO) 2023 annual meeting. These trials are clinical practice–changing, are examples of success across the cancer community, and represent the ultimate goal of advancing basic discoveries in

the laboratory to make life better for people with cancer. She remarked on the networks established through the NCI in collaboration with the extramural community that have made these trials possible.

The NCI is committed to generating results faster and addressing bottlenecks across the clinical research enterprise. The Pragmatica–Lung cancer treatment trial (S2302) was designed to be such a model of accelerating results. This registration trial is evaluating two drugs (ramucirumab and pembrolizumab) for advanced non-small cell lung cancer (NSCLC); the comparator arm is the standard of choice selected by the clinician. Because of the toxicity of these drugs, which are well-known and U.S. Food and Drug Administration (FDA)-approved, the data collection is focused on the survival endpoint. The concept of this trial was developed in collaboration with FDA and National Clinical Trials Network (NCTN) leaders in August 2022, and the trial opened in March 2023. The CTEP leadership negotiated with the pharmaceutical companies to use their drugs in the study, which is essential and a significant achievement.

In February 2023, the NCI launched the Clinical Trials Innovation Unit (CTIU), aiming to conduct better, faster, and more accessible cancer clinical trials. The CTIU is a collaboration between the NCI, FDA, and extramural clinical trials leaders (e.g., NCTN group chairs). This team of collaborators is charged with (1) finding innovative new approaches to test and pilot and to propose innovative work (the idea) and (2) determining how to address the operational hurdles (the execution). The first proposal submission deadline was 12 June 2023. Dr. Bertagnolli conveyed that the NCI anticipates great success.

In addition to the Pragmatica–Lung S2302 and the CTIU, which fall under development of effective treatments, she highlighted other examples of NCI's contributions to the shared goals of the National Cancer Plan (NCP). To help eliminate health disparities, the NCI launched the Connecting Underrepresented Populations to Clinical Trials (CUSP2CT) and Telehealth Research Centers of Excellence (TRACE) programs. For engaging every person, NCI's new initiative, Childhood Cancer–Data Integration for Research, Education, Care, and Clinical Trials (CC-DIRECT), brings clinical- and patient-level navigation support to children, adolescents, and young adults with cancer. In addition, the NCI will build on the success of the NCI Community Oncology Research Program (NCORP), which is heavily focused on the community.

NCI Budget. Dr. Bertagnolli reported that debt limit and budget negotiations favor flat funding for the government for the next 2 years. She highlighted the importance of being transparent about how public funding is spent and reviewed NCI's budget expenditures. The Research Project Grant (RPG) pool is the largest investment of NCI funding, at 44 percent of the total budget. Non-RPG activities include the NCI-Designated Cancer Centers (Cancer Centers) and Specialized Programs of Research Excellence (SPOREs) at 8 percent; other research grants (e.g., career development awards) at 9 percent; National Research Service Awards at 1 percent; and research and development contracts at 12 percent, which support the extramural community via the Frederick National Laboratory for Cancer Research (FNLCR). Research and management comprise 7 percent of the NCI budget, and 18 percent supports intramural research.

From fiscal year (FY) 2016 to FY 2023, the NCI appropriations (base and total) steadily increased, amounting to $7 billion (B) in FY 2023 and including funding for the Cancer Moonshot, which is in its final year of 21st Century Cures Act funding; the Cancer Childhood Data Initiative (CCDI); and COVID-19 Serology research, which started in April 2020. During this same period, the NCI increased paylines for early-stage investigators (ESIs) seeking R01s/R37s from the 12th to 16th percentile, and the number of funded awards increased from 84 to 133. For established investigators, the payline was at the 10th percentile in FY 2016, decreased to the 8th percentile in FY 2019, returned to the 11th percentile in FY 2021, and then remained stable. In FY 2003, NCI's budget was $4.5 B, and adjusting for the Biomedical Research and Development Price Index, it had a buying power that was similar to the budget. From FY 2003 to FY 2023, an increasing gap emerged between NCI's buying power and its budget, posing a

challenge. Adjusting for buying power, the difference over 20 years is $1.1 B less than the FY 2021 appropriations.

Cancer Drug Shortages. Dr. Bertagnolli explained that cancer drug (i.e., FDA-approved oncology agents) shortages are making it more difficult to care for cancer patients. The NCI also is concerned about the effect that this may have on research. An estimated 170 government-sponsored cancer clinical trials (from active to trials in review) are potentially affected by these shortages and involve drugs in shortage based on data as of May 2023. It is critical that all people with a cancer diagnosis have access to the drugs that their doctors prescribe. All patients do not have access to newer or more expensive drugs or generic versions (generics). The NCI CTEP is monitoring this situation, but the problem does not appear as though it will be resolved in the near future. Additionally, the resources for opening a trial can be limited but never are in excess. Of the 170 trials, 104 have a shortage of at least one drug on the short list in their protocols, and some have up to four.

National Cancer Plan. Dr. Bertagnolli noted that NCI's approach has always been to work across all of society to achieve goals for cancer patients. The NCP provides a framework that can achieve these goals faster and more efficiently, and collaborations are essential to achieving research advances and societal changes, both of which are needed to truly benefit patients and encourage action from everyone. The NCI has asked the cancer community to read the plan and soon will publish a newsletter describing the collaborations and ways to participate on all levels to work together to combat societal barriers that have led to disparities in cancer research and that also can lead to better results faster for patients. The NCP can be accessed on the NCI website, which includes an NCP Digital Toolkit.

The President's Cancer Panel will be assisting the NCI in executing and implementing the NCP. This process will involve two components: (1) engaging the community in public sessions to discuss contributions and demonstrate progress to the public, and (2) tracking progress over time in annual reporting and in-depth reviews. Dr. Bertagnolli reminded the Boards that President Biden has asked the NCI to reduce mortality by 50 percent in 25 years, and the NCP aligns with this goal. The Panel will commission an in-depth review of the state of two of the eight goals annually, conduct a 4-year in-depth review of all goals, and publish a review in a peer-reviewed journal. She acknowledged the Panel members in attendance at this meeting.

NCI Program Updates. Dr. Bertagnolli reported that the Combination Therapy Platform Trial with Molecular Analysis for Therapy Choice (ComboMATCH) is open, enrolling patients, and is a follow-up trial to NCI-MATCH. ComboMATCH is being coordinated through the ECOG-ACRIN Cancer Research Group and is the largest initiative of its kind to test combinations of cancer drugs; identify promising treatments; and advance them to larger, more definitive trials. ComboMATCH comprises numerous Phase 2 treatment trials, each evaluating a drug combination of either two targeted drugs or a targeted drug plus chemotherapy. The combinations include FDA-approved drugs. Notably, ComboMATCH also includes children with cancer whereas NCI-MATCH focused on adults. Doctors at any of the community hospitals and Cancer Centers participating in the trial refer their patients for additional eligibility screening if the test results show that they are eligible for one of the trials.

The NCI launched the Persistent Poverty Initiative (PPI) to improve cancer outcomes in low-income areas. The goals are to build research capacity, foster cancer prevention research, and promote the implementation of community-based programs. These awards will fund five new Centers for Cancer Control Research in Persistent Poverty Areas ($10 million [M] over 5 years). This is the first major program to address the structural and institutional factors of persistent poverty in the context of cancer.

Cancer Research Advances. Dr. Bertagnolli highlighted the latest progress in NCI-supported research. A recent study showed the potential benefit of incorporating polygenic risk scores for personal biomarkers along with prostate-specific antigen (PSA) screening. The results showed that in men of European ancestry, using a polygenic risk score–adjusted PSA would avoid up to 31 percent of negative

prostate biopsies. Genetically adjusted PSA was more predictive of aggressive prostate cancer than unadjusted PSA.

Another study examining 1.3 million patients diagnosed with cancer in California and Georgia between 2013 and 2019 showed that only 6.8 percent underwent genetic testing. The study found major disparities; Asian, Black/African American, and Hispanic patients underwent testing less often that non-Hispanic Caucasian/White patients.

Lastly, a recent study showed that targeted approaches directed at effective interventions to engage women in rural communities can increase cancer screening.

Dr. Bertagnolli called attention to a request for information (RFI) on RNA-based cancer vaccines. Responses are due by 30 June 2023 and will be used to inform future resource allocation and acquisition strategies that can accelerate the development, availability, and evaluation of such agents.

Questions and Answers

Dr. Gloria D. Coronado, Mitch Greenlick Endowed Scientist in Health Disparities Research, Kaiser Permanente Center for Health Research, asked whether the cancer drug shortage was due to a supply issue. Dr. Bertagnolli explained that this shortage is complicated and the result of how the economics of generic drug production is structured in terms of incentives for companies to produce these drugs, as well as the reimbursements; it is not due to a supply issue. She can direct the Boards to published reviews for further details. The FDA has a mitigation unit that has been working on this issue for some time, and the issue has been raised in congressional hearings. From her perspective, a permanent solution will require a change governing the economics of the production of generics, which will not be an easy fix.

Dr. Nikan Khatibi, Chief Executive Officer and Medical Director, Ahura Healthcare Corporation, asked about how the Boards could engage in the PPI. Dr. Bertagnolli noted that Board members are advisors and partners in NCI's activities and actions. The NCI will provide updates and information as the PPI progresses. On a national level, conquering these issues goes far beyond the NCI. The more partners under the umbrella of the NCP, the better. The NCI is extremely interested in exploring ways to convene any of these partnerships that can achieve these goals.

III. LEGISLATIVE REPORT—MS. M.K. HOLOHAN

Ms. M.K. Holohan, Director, Office of Government and Congressional Relations (OGCR), reported on the Fiscal Responsibility Act of 2023 (FRA), FY 2024 appropriations, and future directions for the NCI. Both Democrats (D) and Republicans (R) have voted to increase the debt ceiling to prevent a default; however, debt limit suspensions frequently become points of leverage for budget negotiations. In April 2023, the House—led by House Speaker Kevin McCarthy (R-California)—passed a bill to raise the U.S. debt limit, which compelled Democrats to negotiate spending priorities. The resulting bipartisan legislation, the FRA, became law on 3 June 2023. Under the new debt ceiling agreement, the President and House Speaker set limits on discretionary federal spending for FY 2024—which will be frozen at 2023 levels—and FY 2025, when discretionary spending growth will be capped at 1 percent. Other key provisions of the legislation include an increase in defense spending for FY 2024, which was funded by canceling $30 B in unobligated COVID-19 spending and rescinding $20 B in Internal Revenue Service funding allocated through the Inflation Reduction Act of 2022; an end to the moratorium on student loan repayments; new work requirements for the Supplemental Nutrition Assistance Program and Temporary Assistance to Needy Families program; the creation of a lead agency to accelerate the review process for energy projects; and a continuing resolution consisting of a penalty that will decrease all FY 2024 government spending by 1 percent if Congress does not pass all 12 appropriations bills associated with the deal by 1 January 2024. The President's budget requested $716 M for the reinvigorated Cancer

Moonshot℠ (a $500 M increase from FY 2023) and $2.5 B for the Advanced Research Projects Agency for Health (ARPA-H) (a $1 B increase from FY 2023). The FRA suspends the debt ceiling until 1 January 2025.

On 12 June 2023, House Appropriations Chairwoman Kay Granger (R-Texas) announced that FY 2024 funding will be cut by Republican appropriators. Allocations—including those from the House Appropriations Subcommittee on Labor, Health and Human Services, Education, and Related Agencies (Labor–HHS), which is responsible for NIH funding—likely will be approved at FY 2022 levels within the week. The disparity between the House and Senate budgets (even with House dispensations for defense and veteran spending) is projected to total $119 B. Chairwoman Granger also announced that she plans to recoup $115 B from unspent funds, adding to the difficulty of predicting final House allocations. The likely outcome of the current budget negotiations is that few significant budget bills will be approved by the House.

On 4 May 2023, the Senate Labor–HHS Subcommittee convened an oversight and allocations hearing to review the President's FY 2024 budget for the NIH, which was attended by Representative Susan Collins (R-Maine), the Vice Chair of the Senate Appropriations Committee, and Principal Deputy Director, NCI, Dr. Douglas R. Lowy, representing the NCI Director. Representatives from the Centers for Disease Control and Prevention (CDC) and U.S. Department of Health and Human Services (HHS) also were present. Representative Tammy Baldwin (D-Wisconsin) was named the new Chair of the Labor–HHS Subcommittee on 15 February 2023, and new Subcommittee members include Representatives John Boozman (R-Arizona) and Katie Britt (R-Alabama). Representative Shelley Moore Capito (R-West Virginia) currently is the ranking member of the Subcommittee.

Ms. Holohan presented a list of "must-pass" legislation that requires approval before the current Congress expires in September. These bills include the FDA Animal Drug User Fee Act and Animal Generic Drug User Fee Act, as well as the Pandemic and All-Hazards Preparedness Act (all three of which expire on 30 September 2023); a new Agricultural Approvement Act, commonly known as the Farm Bill; FY 2024 appropriations; and the National Defense Authorization Act for FY 2024. Ms. Holohan noted that the House is focused on the oversight of federal programs to prevent waste and fraud (with an emphasis on the COVID-19 response). Possible activities for the future include legislation on drug pricing and oversight hearings convened by the Health, Education, Labor and Pensions Committee and Energy and Commerce Committee. Ms. Holohan emphasized the importance of engaging with congressional members and their staffs to promote the value of the work performed by the NIH and NCI.

Questions and Answers

NCAB Chair Dr. Carpten noted that, even after efforts by Chairwoman Granger to recoup $115 B for the FY 2024 budget, a $4 B shortfall would remain. He asked about areas that would be most affected by the budget deficit. Ms. Holohan answered that discretionary funding for causes not supported by Republicans (e.g., environmental) likely would be cut. She noted that NIH funding has bipartisan support and expressed optimism about funding for cancer research.

NCAB Chair Dr. Carpten asked about how the cancer research community could help support NIH funding. Dr. Bertagnolli commented that NCI leadership will advocate for the President's budget and emphasized that the NCI is dependent on input from the Boards when making difficult decisions.

Dr. Khatibi commented that the U.S. Department of Defense (DoD) and Department of Veterans Affairs are supported by nondiscretionary federal funding. He wondered whether those agencies could expand their cancer research efforts. Ms. Holohan pointed out that the DoD awards funding from Congressionally Directed Medical Research Programs (CDMRP) appropriations and that these awards have expanded with time. She noted that defense spending on cancer research possibly can be increased

but that this effort would not be supported by all members of the Congressional Appropriations Subcommittees of Defense.

Concerning NCAB Chair Dr. Carpten's request, Ms. Holohan suggested that cancer research community members engage with the CDMRP and express support for its expansion. She emphasized that cancer researchers should engage robustly with members of Congress (e.g., congressional representatives and their staff members should be invited to events at Cancer Centers). After meeting with a researcher at the Northwestern University Feinberg School of Medicine, Representative Dick Durbin (R-Illinois) publicly commented on advances in penetrating the blood–brain barrier to treat glioblastoma and advocated for sustained funding of medical research. Dr. Lowy, commented that it was not clear to Representative Durbin whether the advances had been supported by the NCI when he spoke; indeed, the blood–brain barrier breakthrough was supported by NCI funding.

In response to a question about the possibility of NCI- or cancer-specific oversight, Ms. Holohan responded that oversight topics are listed when the committees reach out to the NCI. As far as she knows, there is no focus on cancer research. Ms. Holohan noted that most NIH institutes and centers (ICs) have experience with congressional oversight and emphasized that the NCI does not advocate for legislation but rather supports legislation proposed by the President.

Dr. Karen E. Knudsen, Chief Executive Officer, American Cancer Society, Inc. (ACS), American Cancer Society Cancer Action Network, commented that the ACS Cancer Action Network (CAN) lobbies for NCI funding and currently has an active campaign in support of the President's budget. She requested that meeting attendees get involved with ACS CAN.

Dr. Nilofer S. Azad, Professor of Oncology, Co-Director, Developmental Therapeutics Program, Co-Leader, Cancer Genetics and Epigenetics, Sidney Kimmel Comprehensive Cancer Center, Johns Hopkins University, suggested that the NCI engage with patient advocacy organizations in such activities as advocacy training and sharing expertise in legislative affairs.

Dr. Otis W. Brawley, Bloomberg Distinguished Professor of Oncology and Epidemiology, Sidney Kimmel Comprehensive Cancer Center, Johns Hopkins University, commented that to bypass spending cuts imposed by the Balanced Budget and Emergency Deficit Control Act of 1985 (also known as the Gramm–Rudman–Hollings Act), several congressional representatives appropriated funds to the DoD budget for cancer research, with the intention that the funds would be transferred to the NCI. To maintain control of the funds, the DoD created an internal cancer research program.

IV. RECOGNITION OF RETIRING NCAB MEMBERS—DR. MONICA M. BERTAGNOLLI

On behalf of the NCI, Dr. Bertagnolli recognized the contributions made by members of the NCAB whose terms of office have ended. She expressed appreciation for their service and dedication during the course of their terms. Those retiring NCAB members are: **Dr. Francis Ali-Osman,** Margaret Harris and David Silverman Distinguished Professor Emeritus of Neuro-Oncology, Professor Emeritus of Neurosurgery, Duke University Medical Center; **Mr. Lawrence O. Gostin,** University Professor, Faculty Director, Founding Linda D. and Timothy J. O'Neill Professor in Global Health Law, O'Neill Institute for National and Global Health, Georgetown University; **Dr. Scott W. Hiebert,** Hortense B. Ingram Chair in Cancer Research, Professor of Biochemistry, Department of Biochemistry, Vanderbilt University School of Medicine; **Dr. Electra D. Paskett,** Marion N. Rowley Professor of Cancer Research, Director, Division of Cancer Prevention and Control, Department of Internal Medicine, College of Medicine, The Ohio State University; **Dr. Nancy J. Raab-Traub,** Professor, Department of Microbiology and Immunology, School of Medicine, Lineberger Comprehensive Cancer Center, The University of North Carolina at Chapel Hill; and **Dr. Margaret R. Spitz,** Professor Emeritus, Department of Medicine, Dan L. Duncan Cancer Center, Baylor College of Medicine.

V. CANCER RESEARCH COLLABORATIONS WITH THE EUROPEAN UNION—DRS. DOUGLAS R. LOWY, BRIDGETTE C. WIDEMANN, AND NEAL FREEDMAN

Dr. Lowy provided an overview of NCI collaborations with the European Union (E.U.). He noted that Dr. Henry Rodriguez, Founding Director, Office of Cancer Clinical Proteomics Research, Senior Leadership team member, NCI, has led efforts to foster interactions among the NCI, Cancer Moonshot, NCP, and European Union's Beating Cancer Plan. The Cancer Moonshot and Beating Cancer Plan have overlapping goals that include reducing cancer death rates by 50 percent during the next 25 years, overcoming cancer disparities, and ending cancer as we know it. The NCP—a long-term framework for a collaborative, all-of-government, and all-of-society approach to ending cancer—is inclusive of everyone and easily can accommodate the E.U. partners. Dr. Lowy noted that he has attended several meetings with Dr. Rodriguez and recently visited Brussels with HHS Secretary Xavier Becerra to meet with the European Commissioner for Health and Food Safety, Ms. Stella Kyriakides, to discuss joint U.S.–E.U. efforts related to cancer.

Collaboration on Pediatric Rare Cancers. Dr. Brigitte C. Widemann, Chief, Pediatric Oncology Branch (POB), Head, Pharmacological and Experimental Therapeutics Section, Senior Investigator, and Special Advisor to the NCI Director for Childhood Cancer, presented an update on the Coordinated National Effort on Pediatric Rare Cancers by the NCI Childhood Cancer Data Initiative (CCDI) and the opportunity for international collaboration. She noted that rare cancers are most commonly defined as cancers that occur in fewer than 40,000 people per year in the United States. Dr. Widemann pointed out that, according to this definition, rare cancers account for 25 percent of adult cancers and all pediatric cancers. She described the challenges associated with pediatric cancers, which include lack of clinical trials and standards of care, in addition to the inability of patients to receive accurate and timely diagnoses. Dr. Widemann shared the story of a young POB patient whose diagnosis was delayed, in addition to a prognosis that was worsened by this delay and a doctor unfamiliar with her cancer. Such examples underscore the need for improved management of rare cancers.

Dr. Widemann shared promising developments related to pediatric rare cancers. She noted that publications associated with rare tumors or rare cancers have increased exponentially since the early 1980s. Ongoing efforts include NCI-sponsored Children's Oncology Group (COG) conducting interventional clinical trials on treatments for such tumors as retinoblastoma, nasopharyngeal carcinoma, and adrenocortical carcinoma. Several observational studies are ongoing, including the International Pleuropulmonary Blastoma/*DICER1* Registry and the NCI POB's My Pediatric and Adult Rare Tumor Network (MyPART). The European Cooperative Study Group for Pediatric Rare Tumors/Paediatric Rare Tumours Network–European Registry (EXPeRT/PARTNER) Consortium retrospectively reviews rare cancer cases and provides consensus-based treatment recommendations. Dr. Widemann suggested that international collaborations were necessary to overcome limitations associated with rare cancers, including siloed efforts that focus on a limited number of cancers, insufficient patient numbers, and data collection procedures that are not standardized. She acknowledged FDA's recognition of the difficulty of conducting randomized clinical trials for rare cancers. Ongoing FDA efforts in this area include guidance for rare tumor natural history studies (to serve as external controls for clinical trials) and several approvals of treatments for very rare cancers for use in both pediatric and adult patients based on the inclusion of pediatric patients in these trials (e.g., atezolizumab for alveolar soft part sarcoma, larotrectinib for *NTRK* gene fusion cancers).

Dr. Widemann highlighted CCDI's efforts to improve the quality, consistency, and accessibility of pediatric cancer data. She reported on a workshop and symposium that were hosted by the CCDI in recognition of the need to engage multiple advocacy and research partners in discussions regarding rare cancers. She described the Molecular Characterization Initiative (MCI), which is a partnership between the NCI and COG Project:EveryChild. This national collaboration aims to provide participants with a state-of-the-art molecular characterization (to identify cancer subtypes) that is returned within 21 days of

diagnosis, as well as storage of remaining samples in a biobank for future research. Within its first year, the MCI enrolled more than 1,000 participants across multiple U.S. states and other countries.

The CCDI is establishing a task force to test the feasibility of a national observational protocol for very rare pediatric cancers, longitudinally evaluate the disease course of study participants, collect clinical and research molecular characterization data to identify new therapeutic targets, and test the feasibility of national tumor board reviews for rare cancers. Dr. Widemann reviewed the procedures involved with the CCDI Coordinated National Effort on Pediatric Rare Cancers. Patients will be identified through Project:EveryChild, other consortia, hospitals, advocacy, and self-referral. Participants will undergo standardized clinical characterization and receive molecular characterization through the MCI. Clinical and molecular data will be deposited into the CCDI data ecosystem. The goal is to enable patients to navigate to cancer experts and a portable health record to ensure correct and timely diagnoses and effective clinical trials.

Dr. Widemann listed opportunities for E.U. collaboration presented by the CCDI Coordinated National Effort on Pediatric Rare Cancers. These opportunities include data collection efforts (e.g., increasing the number of patients with rare cancers for analysis, establishing external controls for clinical trials, streamlining molecular characterization), molecular tumor boards, evidence-based recommendations for the evaluation and management of rare cancers, and interventional clinical trials. Dr. Ruth Ladenstein, Deputy Director, Children's Cancer Research Institute, is the E.U. co-chair for this collaboration.

Collaboration on Reducing Lung Cancer Mortality. Dr. Neal Freedman, Chief, Tobacco Control Research Branch (TCRB), Division of Cancer Control and Population Sciences (DCCPS), NCI, presented on shared opportunities for reducing lung cancer mortality in the United States and European Union. Lung cancer is the leading cancer-related cause of death in the United States and is responsible for approximately 23 percent of cancer mortality. Dr. Freedman pointed out that—in contrast with mortality associated with other cancers—lung cancer mortality in U.S. women rose sharply between 1970 and 2000 before declining. Identical trends are observed in U.S. men, although the decline in lung cancer mortality in this population began in 1990. Dr. Freedman noted that these patterns reflect the patterns of cigarette consumption in the U.S. population, and cigarette smoking has been estimated to cause between 80 and 90 percent of lung cancer. According to lung cancer data from NCI's Surveillance, Epidemiology, and End Results (SEER) program, incidence rates have declined steadily since 1992, and relative survival rates have increased since 2000, contributing to the recent decline in lung cancer mortality that reflects societal efforts to control tobacco products and reduce cigarette consumption.

Dr. Freedman and TCRB colleagues projected that a continued decline at the current annual rate of 4.7 percent would result in a 50 percent decline in lung cancer mortality by 2037. His group assessed three areas in which progress can be made to further reduce death by lung cancer: prevention, screening, and treatment.

To prevent lung cancer, smoking initiation must be prevented, and cessation must be increased. According to data from the NCI-sponsored Tobacco Use Supplement to the Current Population Survey, the number of "never smokers" in the United States has increased from 50 percent in 1992 to 70 percent in 2019. The FDA's Center for Tobacco Products has announced activities regarding proposed tobacco product standards, including prohibiting menthol in cigarettes and efforts to reduce the nicotine amount content in cigarettes themselves. Dr. Freedman pointed out that smoking causes multiple forms of cancer, more than doubling the risk of cancers of the larynx, pharynx, esophagus, oral cavity, bladder, urethra, renal pelvis, cervix, liver, and pancreas in current smokers when compared to never smokers.

To improve screening, low-dose computed tomography should be implemented for lung cancer screening, and disparities in the use of cigarettes should be reduced. Although continued declines in lung cancer rates are expected as a result of reduced cigarette consumption, many disparities in cigarette

smoking remain. According to 2020 National Health Interview Survey data from the CDC, 21.5 percent of U.S. adults with no high school diploma or General Educational Development (GED) certification and 32 percent of U.S. adults with GED certification smoke cigarettes, compared to 5.6 percent of U.S. adults with a bachelor's degree and 3.5 percent with a graduate degree. Dr. Freedman noted that similar disparities exist between rural and urban populations, racial and ethnic groups, and other population categories.

To improve treatment, disparities in access to more effective treatments should be reduced. NSCLC comprises approximately 75 percent of lung cancer cases in the United States. Therapies targeting oncogenic driver mutations and immune-based therapies have been shown to have contributed to the population-level decline in lung cancer mortality.

Similar to trends in the United States, cancer mortality data from 2020 demonstrates that lung cancer is the deadliest form of cancer in the European Union. In fact, E.U. smoking rates have declined since the 1960s, but approximately 18 percent of people living in the European Union are daily smokers. In individual E.U. countries, the prevalence of daily smokers ranges from approximately 5 percent (Sweden) to almost 30 percent (Bulgaria). Dr. Freedman described efforts to establish a working group on opportunities for collaboration with the European Union on lung cancer. The European co-chair of the group is Dr. Harry de Koning, Professor of Public Health, Erasmus University Medical Centre. The group intends to build on prior efforts, including the White House Cancer Moonshot℠ Smoking Cessation Forum, the National Lung Screening Trial, modeling by the Cancer Intervention and Surveillance Modeling Network Lung Working Group (or CISNET Lung), the Cancer Cessation Initiative (or C3I), the Population-based Research to Optimize the Screening Process (or PROSPR) Lung Research Center, and the Smoking Cessation at Lung Examination (or SCALE) Collaboration.

Questions and Answers

In response to a question from Dr. Coronado about lung cancer associated with vaping and e-cigarettes, Dr. Freedman pointed out that the association between vaping and lung cancer is not yet clear because of lags between tobacco product use and the development of lung cancer, as well as the young age associated with peak use of vape products. He added that this issue is of great future concern and that related research should be funded. Dr. Lowy agreed that vaping and e-cigarettes are a serious issue and added that these products are being addressed by the FDA and other NIH ICs.

Dr. Andrea Hayes Dixon, Dean, Howard University College of Medicine, Vice President of Clinical Affairs, Chair of Surgery, Howard University Hospital, asked about smoking cessation programs intended for pediatric and teenage populations. Dr. Freedman answered that several grant applications to fund smoking cessation efforts in adolescents currently are being reviewed.

Dr. Samuel L. Volchenboum, Associate Professor of Pediatrics, Director, Pediatric Cancer Data Commons, Pritzker School of Medicine, University of Chicago, commented that collaborations between the CCDI and CC-DIRECT initiative should be encouraged (e.g., to promote enrollment in the MCI and the Coordinated National Effort on Pediatric Rare Cancers). Dr. Widemann agreed.

Dr. Ana Maria Lopez, Professor, Medical Oncology and Integrative Medicine (ABIOM) and Nutritional Sciences, Director, Integrative Oncology, Associate Director, Diversity, Equity, and Inclusion, Sidney Kimmel Cancer Center, Thomas Jefferson University, asked about efforts to assess cancer-related issues in other parts of the world (e.g., Asia, Latin America). Dr. Lowy commented that such efforts are not directly part of this initiative, which is focused on the European Union. He added that Dr. Satish Gopal, Director, Center for Global Health, NCI, is leading some efforts related to Latin America and that the World Health Organization has established a tobacco control program.

Dr. Cornelia M. Ulrich, Chief Scientific Officer and Executive Director, Comprehensive Cancer Center, Huntsman Cancer Institute, University of Utah, asked about funding mechanisms to support E.U.–U.S. collaborations in additional areas of cancer research. Dr. Lowy explained that no specific NCI funding for such partnerships currently is available. He added that the E.U.'s Beating Cancer Plan includes €4 B over the next 5 years, most of which is allocated for implementation research.

Dr. Anna D. Barker, Chief Strategy Officer, Ellison Institute for Transformative Medicine, University of Southern California, commented that many NSCLC cases are diagnosed at later stages and account for a large proportion of mortality associated with the disease. She asked whether lung cancer prevention initiatives will cause a decline in late-stage diagnoses. Dr. Freedman responded that this question is difficult to answer given that robust data on the proportion of people who are eligible for lung cancer screening and who actually get tested are not available. He expressed hope that increased screening efforts would help with the stage distribution of lung cancer cases. Dr. Lowy commented that diagnostic blood tests are being developed for use in primary screening for lung cancer.

Dr. Shelton Earp, Director, University of North Carolina (UNC) Lineberger Comprehensive Cancer Center, Director, UNC Cancer Care, UNC at Chapel Hill, commented that policy changes enabling support of smoking cessation efforts by private health insurance companies and the Centers for Medicare & Medicaid Services (CMS) would be beneficial. Dr. Bertagnolli commented on FDA efforts to permit CMS to directly ship smoking cessation medications to people's homes through a reimbursable process.

Dr. Tabung asked for more information about regulatory aspects of E.U.–U.S. collaborations. He noted challenges related to sharing biospecimens. Dr. Widemann commented that the goal of the collaboration is overcome such challenges—for example, with standardized collection procedures. Dr. Rodriguez added that the NCI and NIH are actively engaged with the U.S. National Security Council and U.S. Department of State about data sharing challenges associated with the collaboration. Commissioner Kyriakides is assisting with clarifying the European Union's General Data Protection Regulation. Dr. Lowy suggested the possibility of permitting exceptions for data related to rare cancers.

Dr. Raymond U. Osarogiagbon, Adjunct Research Professor, Department of Medicine, Vanderbilt University, Chief Scientist, Baptist Memorial Health Care Corporation, recommended that the TCRB review a 2023 American Society for Clinical Oncology Annual Meeting informative session on lung cancer screening that reviewed limitations associated current approaches, as well as solutions to these challenges. The NCI should work with national and international organizations to improve eligibility requirements for lung cancer screening and address implantation challenges associated with more widespread screening. Dr. Freedman agreed and added that the European Union would be a beneficial partner in identifying ways to address these issues.

VI. ONGOING AND NEW BUSINESS—DRS. JOHN D. CARPTEN AND KEITH T. FLAHERTY

NCAB *Ad Hoc* Population Science, Epidemiology, and Disparities Subcommittee. Dr. Paskett, Chair of the NCAB *ad hoc* Population Science, Epidemiology, and Disparities Subcommittee, presented the report of the 13 June 2023 meeting. The NCI Director, Dr. Bertagnolli, attended the meeting. During the meeting, Dr. Paskett noted the Subcommittee's purpose and highlighted its activities. The Subcommittee has convened two Working Groups. The first group produced a report on the extramurally supported Cancer Epidemiology Cohort program, and the second group produced a report focused on identifying and evaluating the current status of and barriers to progress on NCI-funded research in various underserved and minority populations. Dr. Paskett explained that the Subcommittee discussed future areas to address and heard a presentation from Dr. Oliver Bogler, Director, Cancer Training Center, NCI, on training opportunities for cancer prevention, disparities, control, and population sciences. Dr. Bogler emphasized that cancer prevention control and population sciences are essential to

the NCI in meeting its goals for the next 25 years and that more ESIs must be recruited and retained. Although training in these areas currently is supported by some NCI mechanisms (e.g., T32, Early K99/R00), opportunities exist to expand the reach of other mechanisms (e.g., F awards, K awards). Dr. Bogler suggested that improved approaches to training, as exemplified by the Center to Reduce Cancer Health Disparities (CRCHD) Continuing Umbrella of Research Experiences (or CURE) program, should be considered to address training needs.

Dr. Paskett shared highlights of the Subcommittee's discussion. These included collecting data on racial and ethnic demographics of award recipients, understanding researchers' difficulties transitioning beyond traditional K99/R00 awards, and collecting information about application rates in underrepresented populations at the institutional level. Following up on previous discussions on investigating the social determinants of health, Dr. Katrina A.B. Goddard, Director, DCCPS, informed the Subcommittee that a cross-NIH Working Group has been undertaking similar efforts and will share its findings shortly. Dr. Paskett noted new suggestions on conducting a clinical trial accrual analysis that implemented terminology and distributions similar to those used for Cancer Center Support Grant (CCSG) analyses and aggregating the subpopulation data related to populations of interest (e.g., Latino/Hispanic, Asian, Tribal). Dr. Paskett announced that the Subcommittee expressed interest in establishing a new *ad hoc* working group to investigate workforce and training issues in population sciences, including cancer control and cancer prevention, which aligns with the NCP. Other suggestions in establishing such a working group were to consider additional funding sources beyond NIH and to develop diversity initiatives that can withstand local and national scrutiny. On behalf of the Subcommittee, Dr. Paskett requested that the NCI work to develop a mission statement for the new Working Group and present it to the NCAB for approval.

Questions and Answers

Dr. Karen M. Winkfield, Executive Director, Meharry–Vanderbilt Alliance, Ingram Professor of Cancer Research, Professor of Radiation Oncology, Vanderbilt University School of Medicine, asked how the new Working Group's efforts would align with Cancer Center efforts to support a more diverse workforce (e.g., gathering information from CCSG reports). Dr. Paskett explained that plans to enhance diversity in CCSG applications were not discussed. The Working Group will be focused solely on workforce training opportunities.

In response to a question from NCAB Chair Dr. Carpten, Dr. Paskett confirmed that the Working Group would incorporate Cancer Research Training and Education Coordination (or CRTEC) programs into its analysis.

Dr. Ulrich asked for additional information about the scope of the new Working Group. Dr. Paskett clarified that the purpose will be to assess and perhaps expand opportunities to increase workforce training within population science.

Dr. Osarogiagbon commented that much of the population science workforce exists within the general population (as opposed to traditional academic environments). Dr. Paskett agreed that the workforce pipeline should extend beyond academia.

Dr. Chyke A. Doubeni, Professor, Department of Family and Community Medicine, Associate Director, Diversity, Equity, and Inclusion, The Ohio State University Comprehensive Cancer Center, Chief Health Equity Officer, Wexner Medical Center, Director, Center for Health Equity, The Ohio State University, requested that the new Working Group assess connections among various activities related to this area, including plans to enhance diversity and other training efforts. The number of these programs has increased, but they often exist in silos and likely would be more effective if connected within the NCI and among other NIH ICs.

Dr. Lisa A. Newman, Professor of Surgery, Chief, Division of Breast Surgery, Weill Cornell Medicine, asked whether the new Working Group will address the need for improved diversity among the clinicians involved with population studies.

Motion. A motion to accept the report of the 13 June 2023 NCAB *ad hoc* Population Science, Epidemiology, and Disparities Subcommittee meeting was approved unanimously.

Motion. A motion to concur with establishing an NCAB Working Group on Workforce and Training in Population Science was approved unanimously.

Other Business. No other business was discussed.

Future Agenda Items. The BSA and NCAB members suggested future presentations on an update from the NCI and FDA on strategies to address cancer drug shortages, a report on the recreational use of cannabis and the modifiable risk factors for reducing lung cancer mortality, an update on the status of implementing the goals and priorities of the reignited Cancer Moonshot℠; a discussion of the impact of AI on cancer disparities and advancing health equity and the implications for treating cancer patients, and a mid-cycle report on the status of the NCI PPI. Members were asked to forward any additional suggestions for potential future agenda items to the respective Board chairs and Dr. Paulette Gray.

VII. RFA/COOP. AGR. AND PAR CONCEPTS—NEW AND RE-ISSUE—NCI PROGRAM STAFF

NCI Comments. Dr. Lowy called attention to the anticipated budget situation and the impacts of having fewer RFAs than in past concept reviews. Dr. Bertagnolli has been cognizant of the possible restrictions on the budget for some time, and the NCI has been fairly stringent in the RFAs being put forward. The NCI would like the Boards' opinions about RFAs, but even if approved by the BSA, because of the budget situation not being totally clear, the NCI might not be able to publish a subset of the RFAs that are approved today and tomorrow. The prioritization will be a strict process if that were to happen. The NCI would like the BSA to be aware of this situation. The NCI had considered the possibility of not putting RFAs forward at this time, but because the process takes time and the BSA is in the early stage of the review process (making a recommendation to approve or not to approve the concept and the RFA to be established), the NCI was concerned that if the BSA did not have the opportunity at this time to approve or disapprove the RFAs, it could be more harmful to the extramural community and its grant application process in the long run. PARs are not affected.

Division of Cancer Control and Population Sciences

Population Approaches to Reducing Alcohol-Related Cancer Risk (Clinical Trial Optional) (New PAR)—Dr. David Berrigan

Dr. David Berrigan, Program Director, DCCPS, NCI, presented a new PAR concept on population approaches to reducing alcohol-related cancer risk. The purpose of the notice of funding opportunity (NOFO) is to fund multilevel research to reduce alcohol-related cancer risk by increasing alcohol/cancer risk awareness, understanding and changing social norms, and developing and/or evaluating alcohol policy measures. The overarching goal is to build an evidence base to support a population shift to lower levels of alcohol consumption for cancer prevention. Alcohol is a known cause of cancer at eight sites: mouth, throat, voice box, esophagus, breast, liver, colon, and rectum, with mixed evidence for cancer at several other sites, as well as protective effects related to kidney cancer. In 2017, the ACS reported that alcohol consumption was responsible for 5.6 percent of cancer cases in the United States in men and women combined. Excess alcohol consumption is the third most important risk factor, with higher major targets for cancer prevention, research, and practice. Despite these findings, alcohol has not been a major target for cancer prevention and control research supported by the NCI.

Recent years have seen a significant increase in new epidemiological evidence regarding alcohol, cardiovascular disease, cancer, and all-cause mortality. Together, these results have suggested that any cardiovascular benefits of alcohol consumption are absent or confined to a smaller subset of the population than originally believed. Canada's Guidance on Alcohol and Health, based on a recent and comprehensive literature review linking alcohol and health outcomes, showed a dramatic reduction in the current U.S. guidelines that recommend no more than one drink a day for women and two drinks or less a day for men. The new Canadian guidance points to low risk from one to two drinks per week and noted three to six drinks per week increased the risk of several types of cancer, notably breast and colorectal cancer.

Evidence is converging to suggest examining alcohol more closely as a target for cancer prevention. Alcohol consumption has been increasing since the mid-1990s. Alcohol-related deaths in the first year of the COVID-19 pandemic sharply increased. Spending on alcohol through 2022 steadily increased. A 2020 study showed that a large portion of the U.S. population consumes alcohol; 59 percent of men and 51 percent of women report past month alcohol consumption, 56 percent of cancer survivors report past-month alcohol consumption, and consumption is increasing among physicians and other subgroups. The awareness of the link between alcohol and cancer risk is low. Only 20 to 30 percent of U.S. adults believe alcohol consumption increases the risk of cancer, and 50 percent more report that they were unaware.

The evidence of alcohol consumption and its link to increased cancer risk provides an opportunity for research-prompted activities across the public health and cancer fields. In 2017, ASCO released "Alcohol and Cancer: A Statement of the American Society of Clinical Oncology." The DCCPS has engaged in promoting this research theme. The signs of changing social norms, such as growing interest in a "dry" January, are more evident. Scientific evidence concerning the harms (e.g., cancer risk) and putative benefits is changing and research needs are evolving. Labeling studies in Canada are in progress. Policy changes in Ireland are forthcoming. This PAR will support studies to increase the NCI research portfolio addressing alcohol and cancer prevention. Only six grants evaluating alcohol and cancer prevention are funded by the NCI: three R01s, two R21s, and one R03. In addition, this research demonstrates NCI's commitment to reducing alcohol-related cancer risk and addresses the lack of cancer focus by the National Institute on Alcohol Abuse and Alcoholism (NIAAA).

Subcommittee Review. Dr. Mark P. Doescher, Professor, Department of Family and Preventive Medicine, College of Medicine, University of Oklahoma Health Sciences Center, expressed the Subcommittee's strong support for the concept, which focuses on an unmet need in cancer research. Dr. Doescher underscored that alcohol is a leading modifiable cause of cancer, but public and health care provider awareness of alcohol-related cancer risk is low. Few NCI grants directly address alcohol consumption and cancer control, emphasizing a demonstrable need for research in this area. The Subcommittee expressed concern that the concept is broad in scope but recognizes that the PAR mechanism is justified to stimulate this research.

Questions and Answers

Dr. Ulrich commented on her experience advocating for alcohol-free beers or wine, which have been successful as healthy beverage choices and could be considered for this concept.

Dr. Erle S. Robertson, Harry P. Schenk Endowed Chair Professor, Vice-Chair, Department of Otorhinolaryngology, University of Pennsylvania School of Medicine, had not observed any causative link between alcohol and cancer and asked whether the relationship is simply an association with cancer. Dr. Berrigan explained that the DCCPS relies heavily on the International Agency for Research on Cancer (IARC) assessments of the evidence for a causal relationship between alcohol and cancer. The IARC reviews, which contain epidemiological and biological evidence, including animal studies, concluded that there is sufficient evidence for a causal relationship between alcohol and cancer. Although no large

randomized controlled trial administering alcohol to people and assessing cancer outcomes was conducted, the IARC reviews, combined with the review processes of the American Institute of Cancer Research, the CDC, and internal NCI considerations, provide strong evidence for alcohol as a cancer risk factor.

Dr. Khatibi asked whether this research will evaluate current, available, and effective treatments. Dr. Berrigan pointed out that this PAR does not address individual-level interventions related to alcohol consumption and noted the reasons. NIAAA has an extremely large portfolio of behavioral interventions addressing alcohol use disorder and risky consumption. The NCI believes that there is a strong need for population-level approaches to reducing the overall levels of consumption to complement that existing body of literature.

Dr. Andrew T. Chan, Chief, Clinical and Translational Epidemiology Unit, Massachusetts General Hospital (MGH), Director of Epidemiology, MGH Cancer Center, Daniel K. Podolsky Professor of Medicine, Harvard Medical School, understands that data are emerging that alcohol is harmful for multiple cancers, but he wonders whether this PAR would address other issues related to alcohol intake that may modify risk, such as time of day or other health and lifestyle factors, or whether the premise is to reduce alcohol use to a minimum. Dr. Berrigan explained that this PAR is focused on a population approach to cancer prevention and control. The NCI is aware of the substantial evidence gaps related to the epidemiology of different patterns of drinking and the epidemiology of the co-use of alcohol and tobacco and anticipates developing funding opportunities in those areas.

Dr. Lopez asked about evaluating risk related to polymorphisms or DNA changes in this PAR and suggested including language on the issues of communication and mistrust. Dr. Berrigan noted that DCCPS investigators currently are working on a project examining the genetics of tobacco and alcohol use, separately and combined, and he anticipates updates in the future.

Dr. Doubeni commented on the evidence base that is predominantly from observational studies, which is challenging to succeed at the policy level. He noted the American Institute for Cancer Research evidence on the seven cancers and the benefit to kidney cancer and asked whether the effects were related to binge drinking. He remarked on the challenge to conduct interventional studies examining alcohol effects because of some federal restrictions on these types of studies. Dr. Berrigan called attention to mechanistic studies linking alcohol and carcinogenesis, notably acetyl aldehyde in head and neck cancers. Although the mechanisms are not well-understood on the relationship between alcohol and cancer at every cancer site, the evidence is strong for several sites involving specific pathways that have been the subject of robust research.

Motion. A motion to approve the DCCPS' new PAR entitled "Population Approaches to Reducing Alcohol-Related Cancer Risk (Clinical Trial Optional)" was approved unanimously.

Division of Cancer Treatment and Diagnosis

Cancer Health Disparities and Minority Health (CHD-MH) SPORE Program (New RFA/Coop. Agr.)—Dr. Leah Hubbard

Dr. Leah Hubbard, Program Director, DCTD, NCI, presented a new RFA concept on establishing the Cancer Health Disparities and Minority Health (CHD-MH) SPORE program, developed in collaboration with the CRCHD. The NCI SPORE program comprises multi-project P50 center grants for translational cancer research, with an emphasis on improving prevention, early detection, diagnosis, and treatment of cancer. SPOREs can be focused on one of three areas: an organ-specific cancer; a group of highly related cancers; or cancers related by a cross-cutting theme, such as pediatric cancers, viral-related cancers, or cancer health disparities.

Addressing cancer health disparities is a high-priority area for the NIH and NCI, as established in the *NIH-Wide Strategic Plan for Fiscal Years 2021–2025*, *NIH Minority Health and Health Disparities Strategic Plan 2021–2025* and NCI's Strategic Planning Objectives (e.g., NCP, NCI Equity and Inclusion Program). Despite these efforts to fund and support research in this area and many applications to the SPORE program, no P50 SPOREs have been awarded that specifically focus on cancer health disparities. To address this gap, the NCI collaborated with CRCHD in 2017 to develop the P20 Cancer Health Disparities (CHD) SPORE RFA, and 12 P20 CHD SPORE 3-year planning grants have been awarded that focus on building the feasibility and infrastructure. This program prepares applicants to apply for a P50 SPORE grant.

The initial P20 CHD SPORE analysis showed that the program was successful in meeting its goals in terms of publications, establishing biorepositories and retrospective cohorts, and funding pilot programs. Even with this P20 initiative, the health disparities funding gap remains in the NCI P50 SPORE portfolio. To assess this problem more broadly, NCI conducted analysis in January 2023 of the NCI-wide cancer health disparities portfolio and found that from FY 2018 to the present, 290 NCI awards with Research, Condition, and Disease Categorization index terms for cancer health disparities were awarded. Of those 290 cancer health disparities awards, only 19 (7 percent), focused on translational research. All 19 grants were from either CRCHD's Partnerships to Advance Cancer Health Equity (PACHE) program or the NCI SPORE P20 SPORE Program. A similar search for minority health showed 87 NCI awards funded in this research area. No NCI minority health awards funded in this 5-year period focused on translational research. Overall, NCI funded only 19 translational research grants during the past 5 years that were specifically related to cancer health disparities. All 19 grants have or will have completed their funding by 2025.

Dr. Hubbard commented that this presents a critical opportunity to expand on current efforts and identify new ways to support competitive applications, particularly to the SPORE program, that are focused specifically on translational research in cancer health disparities in minority health.

To better understand why cancer health disparities applicants have not successfully competed for a full P50 SPORE award, the NCI held a listening session with the P20 grantees and also reviewed the responses to the NCI RFI on Enhancing Cancer Health Disparities Research. The results revealed that the requirements of the SPORE P50 PAR are not able to support the unique needs, methodology, and framework of cancer health disparities translational research because it focuses on the mechanistic aspects of human biology and requires at least one project to include an NIH-defined clinical trial. Cancer health disparities in minority health research requires a multifaceted approach addressing the interplay of social, cultural, and environmental factors with the biology of the disease. The requirement for a trial is a major disadvantage for cancer health disparities for applications and peer review, given the difficulty of prospectively accruing large numbers of patients from populations that are underserved to assess statistically significant differences in patient outcomes.

NCI is proposing this RFA to establish the U54 SPORE CHD-MH program to meet the needs of cancer health disparities and minority health translational research. The CHD-MH program will require significant levels of community outreach and collaborations and does not fit within the scope of a P50 program. The structure of this program will be the same as the current P50 SPORE, with the exception of the inclusion of a Community Outreach and Engagement (COE) core and a community advisory board. CHD-MH SPORE interactions to foster collaborations include attending the monthly SPORE Directors' Teleconference, organ-site–specific calls and annual meetings, and U54 network calls and annual meetings. The scientific aspect will be the cross-cutting theme of cancer health disparities and minority health research, with the option to investigate more than one cancer type in populations that are underserved. This RFA would support six U54 awards over a 5-year project period. The metrics of success will include development of novel interventions, methodologies, and metrics; an increase in research in clinical trial enrollment in populations that are underserved; establishment of COE cores that

integrate and interface with Cancer Center COEs; achievement of proposed human endpoints; and increased publications and citations of the research.

Subcommittee Review. Dr. Brawley expressed the Subcommittee's support for the concept and commended the NCI for this approach. Dr. Brawley emphasized the critical need to fund this RFA despite the budget situation and commented that health disparities and cancer research should remain national priorities. The Subcommittee appreciates the ideas of incorporating genetic ancestry, geographic origin, social determinants of health, and the development of community-based relationships.

The first-year cost is estimated at $8 M for three U54 awards in Year 1 and $16 M for three U54 awards in Years 2–5 over two receipt dates, with a total cost of $80.4 M for 5 years.

Questions and Answers

Dr. Winkfield asked why the Cancer Centers that are already funded and have COEs and why community advisory boards are not responsible for addressing some of this work, as well as how this funding would augment the Cancer Center Support Grants. Dr. Brawley noted that other universities and organizations can apply for this RFA to extend beyond the 72 Cancer Centers, which will be beneficial, as well as establish U54 grants in this area.

Dr. Hubbard confirmed that the RFA allows international global cancer research collaborations on disparities-related topics and that consortium and multi-institutional grants can be considered.

Dr. Karen M. Mustian, Dean's Professor of Oncology and Surgery, Departments of Surgery, Radiation Oncology, and Public Health Sciences, University of Rochester School of Medicine and Dentistry, asked whether the RFA would mandate a funding line item for the community advisory board's involvement. Dr. Hubbard explained that funds are set aside in the P50 SPORES for the advisory boards, which also can be considered for this U54 SPORE.

Dr. Carol Brown, Senior Vice President and Chief Health Equity Officer, Nicholls-Biondi Chair for Health Equity, Memorial Sloan Kettering Cancer Center, suggested clearly defining the terms "underserved" and "minority health" in this RFA.

Motion. A motion to approve DCTD's new RFA/Coop. Agr. entitled "Cancer Health Disparities and Minority Health (CHD-MH) SPORE Program" was approved unanimously.

Division of Cancer Prevention

Mechanisms that Impact Cancer Risk with Use of Incretin Mimetics (New PAR)—Dr. Edward Sauter

Dr. Edward Sauter, Medical and Program Officer, Division of Cancer Prevention (DCP), NCI, presented a new PAR concept addressing the mechanisms that impact cancer risk with use of incretin mimetics. Incretins are gut hormones secreted in response to a meal and consist of two primary types: glucose-dependent insulinotropic polypepide (GIP)-1 and glucagon-like peptide (GLP)-1. Three agent classes are currently FDA-approved to treat type 2 diabetes (T2DM) and to regulate GLP-1 and/or GIP-1 glucose levels. These include GLP-1 receptor agonists (RAs), GIP-1 RAs, and dipeptidyl peptidase (DPP)-4 inhibitors. Clinical data indicate that GLP-1/GIP-1 RAs are more effective and have fewer side effects than DPP-4 inhibitors and will be the focus of this research.

The first approved GLP-1 RA was Exenatide in 2005. Ozempic was approved in 2017, and tirzepatide was recently approved for diabetes and may be approved for obese nondiabetics. The U.S. GLP-1/GIP-1 RA market was valued at $11.3 B in 2019 and is anticipated to grow annually by

6 percent from 2023 to 2027. Compared with lifestyle interventions, RAs are better interventions for people who are obese. They provide more weight loss; show dramatic improvement in T2DM; and have lower risk of heart disease, stroke, and kidney disease. The effect on cancer risk is unclear.

GLP-1/GIP-1 RAs increase insulin and decrease glucagon, but in preclinical studies, mice with dysfunctional GIP-1 receptors are resistant to obesity, and this mechanism is not well-understood. Six agents currently are FDA-approved and with the exception of Semaglutide, are administered subcutaneously daily or weekly. Weight loss across studies ranged from 2 to 20 percent, with tirzepatide linked to the higher weight loss. These agents act on the pancreas and other major organs in the body, resulting in off-target effects; individuals have to eat less for the agents to work.

Preclinically, these agents downregulate inflammation, activate macrophages (an anticancer effect), have antiproliferative effects, improve lipid metabolism, and alter the GI microbiome. Preliminary clinical findings suggest that these agents may increase the overall risk of thyroid cancer and may reduce the risk of prostate cancer and other obesity-associated cancers.

The purpose of this PAR is twofold: promote studies examining the mechanism through which these agents impact cancer risk and attract talented scientists who study obesity and weight loss to investigate the changes that are induced by these RAs that alter cancer risk and outcomes. Program announcements for R21 and R01 applications were suggested.

Subcommittee Review. Dr. Chan expressed the Subcommittee's support for the concept. Dr. Chan remarked on the need to consider the potential cancer harms and cancer benefits of this research and ways the cancer research community can begin to research longer follow-up and outcomes. The Subcommittee encouraged incorporating studies examining the use of incretin mimetics in the context of other lifestyle factors and other behavior, which will be critical to understanding the cancer effects.

Questions and Answers

Dr. Brawley commented that by the end of this decade, there will be more cancer deaths due to a combination of obesity and lack of exercise than tobacco products. Studies supported in the PAR will be critical.

Dr. Coronado suggested expanding the scope of the scientific concept to include epidemiological studies on behavioral and lifestyle factors and leveraging similar NIH programs and/or initiatives. Dr. Sauter noted discussions with the NIDDK Obesity Research Task Force about such studies, but the funding timelines are different than those of the NCI.

Dr. Howard J. Fingert, Vice President, Medical-Oncology, ONO PHARMA USA, INC., noted groups within industry that are dedicated to ensuring these types of studies contribute to public health. He encouraged engaging dissemination and implementation experts who are performing this type of research.

Motion. A motion to approve the DCP's new PAR entitled "Mechanisms That Impact Cancer Risk with Use of Incretin Mimetics" was approved unanimously.

Office of the Director

The NCI Pathway to Independence Award for Outstanding Early-Stage Postdoctoral Researchers (New PAR)—Dr. Sergey Radaev

Dr. Sergey Radaev, Program Director, Center for Cancer Training (CCT), presented a new PAR concept on the pathway to independence awards for outstanding early-stage postdoctoral fellows. The NCI supports training at different career stages, from pre-doctoral to post-doctoral to early-stage principal

investigator. Funding opportunities available to postdoctoral fellows include Career Development (K) awards (K08, K25, K22), Parent K99/R0 awards, and the Ruth L. Kirschstein National Research Service Award for Individual Postdoctoral Fellows (F32). K08 and K25 awards are highly specialized. The K08 award is intended only for U.S. licensed clinician scientists, and applicants apply, on average, 8 years after receiving their doctoral degree. The K25 award is intended for quantitative scientists with little or no experience in biomedical research. The K22 transition award is intended for late-stage postdoctoral fellows with at least 2, but no more than 8, years of postdoctoral research experience. Applicants for the K22 award in their sixth or seventh year of postdoctoral studies have been successful in receiving this award. The Parent K99/R00 award supports 4 years of postdoctoral research experience, but most applicants apply in the third or fourth year of postdoctoral training. The F32 is a congressionally mandated and long-standing program that is intended for early-stage postdocs but has not been as successful as the K awards for establishing independent careers.

The DCCPS analyzed R01s issued from two NOFO cycles in 2017 that focused on data, population, and behavioral scientists receiving a terminal degree in 2005 and found that 50 percent in this group had received tenured track positions 0–2 years into postdoctoral research, but were not competitive for current K awards, which targets individuals with 4 to 8 years of postdoctoral research experience. Also, people receiving tenured positions early have no protected time for teaching, have no assurance of a competitive startup package, and take longer to get a first R01.

In 2018, the BSA and NCI Senior Program Leaders (SPL) approved a pilot RFA for early-stage postdoctoral researchers, the K99/R00 Award, which will expire in 2023. The NCI is proposing to replace this pilot RFA with a new PAR. The objective is to help outstanding postdoctoral researchers complete necessary mentored training and transition to independent tenure-track or equivalent faculty positions in a timely manner. This program is designed for those postdoctoral fellows who do not require extended periods of mentored research training beyond their original doctoral degrees before transitioning to research independence. U.S. citizenship or permanent residency is not required. Individuals on U.S. visas are eligible to apply.

This PAR supports a dual-phase award. The first phase (K99) is a postdoctoral phase and provides up to 2 years of mentored support for postdoctoral training. The second phase (R00) provides up to 3 years of support as an independent scientist. Only postdoctoral fellows with up to 2 years of total aggregate postdoctoral research experience are eligible to apply. Clinical training is not counted toward the eligibility limit. Each candidate must be nominated by an applicant institution. Each institution may nominate up to four candidates per review cycle: one in Cancer Data Science, one in Cancer Control Science, one in Molecular/Precision Cancer Prevention, and one in Other Cancer Research. Dr. Radaev emphasized that the PAR language was developed based on the recommendations from the SPL and colleagues from the DCP and DCCPS.

A portfolio analysis of the pilot K99/R00 RFA showed that close to 80 applications were received in response to the solicitation. The early K99 RFA had three separate scientific fields, and 40 percent of applications represented cancer control science; 30 percent represented data science, and the balance represented other science. Between FY 2020 and FY 2023, the introduction of pilot early K99 RFA did not negatively impact the number of applications received for parent K99.

Subcommittee Review. Dr. W. Kimryn Rathmell, Hugh Jackson Morgan Professor of Medicine and Biochemistry, Chair, Department of Medicine, Physician-in-Chief, Vanderbilt University Medical Center, expressed the Subcommittee's strong support for the concept. Dr. Rathmell remarked on the success of the pilot RFA, demonstrating the value of this program. The Subcommittee appreciated the NCI staff responses to their concerns of the effect on the Parent K99 pool and the rationale for selecting candidates.

Questions and Answers

Dr. Jennifer R. Grandis, Robert K. Werbe Distinguished Professor in Head and Neck Cancer, University of California, San Francisco, encouraged a review of the diversity of the applicant pool, including women and underrepresented individuals both for this program as well as for the parent K99/R00, especially if that is the intent of this funding mechanism. Dr. Radaev noted that the majority of applicants for the pilot K99/R00 RFA were women and that the majority of those who received the award also were women, but he did not have this exact information for the Parent K99/R00.

Dr. Hayes Dixon commented that the PAR language should convey that the recruitment is "inclusive of excellence" for underrepresented minorities and women and not just the typical recruitment.

Dr. Paskett reiterated that the R00 phase is short, especially since transferring to another institution can take 12 or more months before the new award is issued, and suggested expanding the R00 period.

Dr. Radaev confirmed that to transition to an independent phase, a K99 grantee must secure an independent position at another institution. Typically, 80 percent of all CCT K99 grantees transition to independence. He reminded the BSA and NCAB members that the pilot K99/R00 RFA was severely affected by the COVID-19 pandemic, resulting in a lower transition rate than expected.

Dr. Ashani T. Weeraratna, Bloomberg Distinguished Professor of Cancer Biology, E.V. McCollum Chair of Biochemistry and Molecular Biology, Johns Hopkins Bloomberg School of Public Health, Co-Program Leader, Cancer Invasion and Metastasis, Sidney Kimmel Cancer Center, Johns Hopkins School of Medicine, asked whether the criteria for applying for an early-stage K99 would be different from the parent K99, given that it can take more than 2 years to publish research findings. Dr. Radaev reiterated that the review of the early K99 is conducted separately from the parent K99 and that they do not compete. No requirement of publications from postdoctoral training is imposed. Some rules are relaxed regarding the amount of preliminary data necessary to include in the application.

In response to a question from Dr. Mustian, Dr. Paskett confirmed that the new NCAB Working Group on training and workforce development will address some of these issues.

Ms. Duron expressed interest in a report on the demographic information of women applying for these awards to ensure adequate representation among young investigators of communities of color. A consistent report of the percentages and progress also would be helpful. She encouraged adopting a common practice of disaggregation of subpopulations to better understand the communities geographically local to investigators and their research.

Dr. Lopez asked about efforts to proactively increase participation of physician scientists in this funding mechanism. Dr. Radaev noted that 90 percent of applicants are Ph.D.s, with the remaining 10 percent divided between M.D.-Ph.D.s and M.D.s. Compared with the parent K99/R00, a larger number of M.D.-Ph.D.s and M.D.s are applying for the early K99 mechanism. One way to increase participation would be to promote awareness of this opportunity in the research community.

Motion. A motion to approve the Office of the Director's (OD) new PAR entitled "The NCI Pathway to Independence Award for Outstanding Early-Stage Postdoctoral Researchers (K99/R00)" was approved unanimously.

AIDS and Cancer Specimen Resource (ACSR) (Re-issue RFA/Coop. Agr./Limited Comp.)— Dr. Rebecca Huppi

Dr. Rebecca Liddell Huppi, Program Director, Office of HIV and AIDS Malignancy (OHAM), NCI, presented a re-issue RFA concept to support the activities of the AIDS and Cancer Specimen Resource (ACSR). The aim is to provide high-quality specimens from HIV-infected individuals with or at

substantial risk for cancer at little or no cost to qualified investigators and to support biobanking for the AIDS Malignancy Consortium (AMC). NCI is proposing a third component to strategically enrich the existing inventory of rare and difficult-to-obtain specimens through a series of specimen-sparing and optimizing initiatives. The NCI-appropriated AIDS funds, as established by the NIH Office of AIDS Research (OAR), will support this research. This concept has been reviewed by the OAR and deemed AIDS-aligned.

Dr. Huppi noted that the HIV epidemic is ongoing, and no vaccine or cure exists. Most people with HIV reside in low- to- middle income countries (LMICs), with 70 percent living in sub-Saharan Africa. A prominent manifestation of the HIV infection is cancer, which has been observed throughout the epidemic. Cancer is the most common cause of morbidity and mortality in people with HIV in the United States. The ACSR was established in 1994 and the collection contains multiple types of specimens, including peripheral blood mononuclear cells, plasma, and saliva, representing multiple cancer types. Prospective specimen collections follow established standard operating procedures and can typically be linked with high levels of annotation. Special collections include specimens from clinical trials of the AMC, HIV multisite autopsy specimens, and several international collections. Specimens are provided at little or no cost to investigators.

The ACSR structure reflects the two major goals of the RFA. First is support of the five Regional Biospecimen Repositories (RBRs), three domestically and two internationally. The RBRs curate specimens that are available for immediate distribution to the HIV and HIV malignancy research community. Second is support of the four AMC biorepositories, two domestically and two internationally. These serve as cooperative group biobanks for the AMC's clinical trials. Overlap between the BRP and AMC biorepositories is built in to benefit from economy of scale. AMC specimens are not available for distribution until clinical trial embargoes are lifted and specimens that have been appropriately consented for future use move officially to the ACSR. The specimens are made available for general distribution to the HIV-associated malignancy research community.

Activities of the RPRs include managing acquisitions that are strategically focused on obtaining specimens and maintaining general inventory of specimens from people with HIV. These include more than 20,000 tumor tissues and close to 25,000 other sample types. Kaposi sarcoma and non-Hodgkin lymphoma are the most common cancer types. Special collections include cohort and epidemiological studies. These specimens have high amounts of annotation and are the some of the most widely distributed in the ACSR. In this reporting period, the RBRs had 197 investigator interfaces and 64 letters of intent, which led to the distribution of 20,000 specimens, including 298 tissue microarray (TMA) slides representing 10,378 specimens. The most requested and fulfilled material included formalin-fixed paraffin-embedded tissue, nucleic acids, and TMA slides. The ASCR awarded seven Young Investigator Pilot Awards (YIPA), totaling 587 distributions, with hundreds still to be distributed. The YIPA program has had enthusiastic support from the peer reviewers and program evaluation teams.

The AMC biorepository supported 48 domestic and 10 international clinical trial sites, assisting 250 clinical investigators and 24 laboratory investigators. The Anal Cancer high-grade squamous intraepithelial lesions (HSIL) Outcomes Research (ANCHOR) biorepository supports 19 clinical sites and has an inventory of more than 500,000 specimens. Additionally, the ASCR works to develop tools to spare and optimize specimens and manages a TMA program to enable frugal and equitable distribution of rare tissue specimens and a biospecimen science program for optimizing the specimen collections currently available. Activities of the science program include conducting fit-for-purpose studies, performing standardization and optimization of the isolation of liquid biopsy analytes from fresh and frozen plasma, and operating the dried blood spot program.

During this funding cycle, ASCR investigators generated 72 manuscripts; 41 represent the use of ACSR specimens or other resources and 31 reflect AMC clinical trials. The ANCHOR trial made significant contributions and is now closed. A seminal paper reporting the efficacy data was published in

2022 in the *New England Journal of Medicine*. Key contributions to the field of HIV-associated malignancies include two major publications of findings in the HIV Positive Tumor Molecular Characterization Project (HTMCP), which is an NCI-sponsored project. In addition, results from ACSR specimen distributions were reported in two significant publications.

A mid-cycle external evaluation identified several strengths in support of concept reissuance. The evaluation highlighted that the ACSR was unequivocally a valuable resource, has served the community for close to three decades, has provided a vital service as a cooperative group biobank for the AMC and the ANCHOR study, has evolved with the HIV epidemic, and continues to be innovative and address important gaps in science. The evaluation team proposed recommendations for improvements, which the ACSR and NCI program staff began to rapidly address. The ACSR has begun to establish an external advisory board to enhance the strategic planning and evaluation process, completed establishment of a formal ACSR wide disaster recovery plan, reinvigorated collaborations in an interface with other NCI and NIH initiatives post COVID-19, continued investments in marketing efforts to enhance ACSR visibility and use, and continued investments in support of research on LMICs.

The reissue RFA would support the ACSR's continuing to serve as the biorepository for the AMC and ANCHOR trials, enable investigators to conduct AIDS malignancy research using samples from LMICs, and maintain the existing repositories of specimens. A budget increase is proposed to address the activities for accreditation by the College of American Pathologists, support the development of a database management system that better serves the ACSR, and cover the cost of science increases for the RBRs and AMC biorepositories. As in this and previous funding cycles, the budget includes an additional increase of $1 M in years 2 through 5 to support the fiduciary responsibility of the ANCHOR biorepository from the AMC cooperative agreement to the ACSR cooperative agreement as the ANCHOR trial begins to sunset. The ACSR decreased the specimen procurement budget by $100,000, primarily because the group is focusing on sparing and optimizing the existing specimens. The ACSR team and the NCI are requesting a limited competition RFA to maintain the existing complex ACSR infrastructure, both domestic and international; maintain continuity between the ACSR and the AMC biorepository activities; and support a transition of the leadership of the ACSR.

Subcommittee Review. Dr. Coronado expressed the Subcommittee's strong enthusiasm and support for the re-issue concept to continue this international biorepository, focusing on specimens and samples from people with and without HIV. The Subcommittee commended the NCI on this valuable resource that has been vital to investigators internationally and the strong YIPA program that proactively engages young investigators in using the ACSR.

The first-year cost for the one-time re-issuance is estimated at $5.5 M for years 1–2 and $6.6 M for years 3–5 for one UM1 award, with a total cost of $31.3 M for 5 years.

Questions and Answers

Dr. Ulrich suggested reviewing the use of the ACSR in industry and considering increasing the costs of services for these users. Dr. Huppi explained that the ACSR always has been able to attract general cancer researchers to enter the HIV malignancy field. Because the AIDS-associated malignancy research community is small, NCI's aim has been to provide these specimens at low cost to attract more people to the field. Dr. Ulrich added that the NCI could conduct a cost comparison of specimen resources and similar services available commercially.

In response to questions from Dr. Khatibi about the reasons for the budget increases, Dr. Huppi noted the high infrastructure costs to opening and developing RBRs throughout the world. The NCI has two: one in sub-Saharan Africa and one in Latin America. The costs of capacity building in the region and training and accrediting staff who develop the resources also needs to be considered, as does the cost associated with support of clinical trials. Although the infrastructure is in place in the United States, the

costs for including additional specimen types in the ACSR continue to increase.

Dr. Winkfield asked about the data on the demographics regarding race and ethnicity representation in the ACSR, considering that Black/African American women in the United States have the fasting growing rate of HIV. Dr. Huppi described the ACSR collections. With all specimens—HIV negative and HIV positive people—44 percent are Black/African American; 22 percent are Caucasian/White, and 31percent are unknown. In terms of ethnicity, 6 percent are Hispanic, and 80 percent are unknown. With sex as a variable, 67 percent of women are Black/African American, 32 percent are Caucasian/White, and 27 percent are unknown. Representation in men reflects the epidemic: 37 percent are Black/African American, 32 percent are Caucasian/White, and 22 percent are unknown. In response to a question from Dr. Winkfield about direct collaborations with other NIH initiatives or Centers for AIDS Research (CFAR), Dr. Huppi clarified that ACSR investigators collaborate with CFAR and that the ACSR works with other National Institute of Allergy and Infectious Diseases–sponsored initiatives, including the Women's Interagency HIV Study (commonly called WIHS).

Dr. Ali-Osman was surprised by the high number of unknowns in the ACSR and asked about the reasons for these values. Dr. Huppi explained that the ACSR contains archived specimens dating back 30 years, when efforts focused on collecting rare specimens and allowed fewer restrictions on annotation of the associated data. As the repository broadened and collected specimens from prospective studies and standard operating procedures were established, more annotated samples have been accepted into the biorepository. Thus, the ACSR and science both have evolved.

Motion. A motion to concur on the OD's Re-issue RFA/Coop. Agr./Limited Competition (Limited Comp.) entitled "AIDS and Cancer Specimen Resource (ACSR)" was approved with 25 ayes, 0 nays, and 2 abstentions.

Division of Extramural Activities

PAR Re-Issue Concepts—Dr. Shamala Srinivas

Dr. Shamala Srinivas, Associate Director, Office of Referral, Review and Program Coordination, NCI, presented 20 re-issue PARs (29 NOFOs) for BSA consideration and noted that the list and a link to each PAR was made available on the secure BSA-only website prior to the meeting. Dr. Srinivas reminded the BSA of the NIH policy established in 2019 that requires an open forum discussion and acceptance by an Advisory Council or Board for new and re-issue RFAs, RFPs, and PARs. Because of the large volume of PAR re-issues that the NCI receives annually, the BSA will review the re-issues as a group, not individually, and will vote to concur with the re-issuances.

- Research Projects to Enhance Applicability of Mammalian Models for Translational Research (PAR-20-131)
- Exploratory Grants in Cancer Control (R21 Clinical Trial Optional) (PAR-21-341)
- Modular R01s in Cancer Control and Population Sciences (R01 Clinical Trial Optional) (PAR-21-190)
- Secondary Analysis and Integration of Existing Data to Elucidate the Genetic Architecture of Cancer Risk and Related Outcomes (R01 Clinical Trial Not Allowed) (PAR-20-276)
- Secondary Analysis and Integration of Existing Data to Elucidate the Genetic Architecture of Cancer Risk and Related Outcomes (R21 Clinical Trials Not Allowed) (PAR-20-277)
- Cancer Prevention and Control Clinical Trials Program (R01 Clinical Trial Required) (PAR-20-277)

- Specialized Programs of Research Excellence (SPOREs) in Human Cancers for Years 2021, 2022, 2023 (P50 Clinical Trial Required) (PAR-20-305)
- Academic-Industrial Partnerships for Translation of Technologies for Diagnosis and Treatment (R01-Clinical Trial Not Allowed/Optional) (PAR-21-166; PAR-20- 155)
- Innovative Research in Cancer Nanotechnology (IRCN) (PAR-20-284)
- Assay development and screening for discovery of chemical probes or drugs (PAR-20-271)
- National Cancer Institute's Investigator-Initiated Early Phase Clinical Trials for Cancer Treatment and Diagnosis (R01 Clinical Trial Required) (PAR-21-033)
- Assay Validation of High-Quality Markers for Clinical Studies in Cancer (UH2/UH3 Clinical Trial Not Allowed) (PAR-20-313)
- Assay Validation of High-Quality Markers for Clinical Studies in Cancer (UH3 Clinical Trials Not Allowed) (PAR-20-314)
- Revision Applications for Validation of Biomarker Assays Developed Through NIH-Supported Research Grants (R01 Clinical Trial Not Allowed) (PAR-23-088)
- Academic-Industrial Partnerships (AIP) to Translate and Validate *In Vivo* Imaging Systems (R01 Clinical Trial Optional) (PAR-20-155)
- The NCI Transition Career Development Award (Independent Clinical Trial Not Allowed) (PAR-21-128)
- The NCI Transition Career Development Award (K22 Independent Clinical Trial Required) (PAR-21-111)
- The NCI Transition Career Development Award (Independent Basic Experimental Studies with Humans Required) (PAR-21-318)
- Paul Calabresi Career Development Award for Clinical Oncology (K12 Clinical Trial Optional) (PAR-22-136)
- Cancer Research Education Grants Program - Curriculum or Methods Development (R25 Clinical Trial Not Allowed) (PAR-21-065)
- Cancer Research Education Grants Program - Courses for Skills Development (R25 Clinical Trial Not Allowed) (PAR-21-066)
- Cancer Research Education Grants Program - Research Experiences (R25 Clinical Trial Not Allowed) (PAR-21-067)
- Exploratory Grant Award to Promote Workforce Diversity in Basic Cancer Research (R21 Clinical Trial Not Allowed) (PAR-21-061)
- Feasibility Studies to Build Collaborative Partnerships in Cancer Research (P20 Clinical Trial Not Allowed) (PAR-22-239)
- Comprehensive Partnerships to Advance Cancer Health Equity (CPACHE) (U54 Clinical Trial Optional) (PAR-22-249)
- NCI Research Specialist (Laboratory-based Scientist) Award (R50 Clinical Trial Not Allowed) (PAR-22-187)
- NCI Research Specialist (Core-based Scientist) Award (R50 Clinical Trial Not Allowed) (PAR-22-188)

- NCI Research Specialist (Laboratory-based Scientist) Award (R50 Clinical Trial Not Allowed) (PAR-21-285)
- NCI Research Specialist (Core-based Scientist) Award (R50 Clinical Trial Not Allowed) (PAR-21-286)
- NCI Research Specialist (Core-based Scientist) Award (R50 Clinical Trial Not Allowed) (PAR-20-287)
- NCI Research Specialist (Laboratory-based Scientist) Award (R50 Clinical Trial Not Allowed) (PAR-20-288)
- NCI Research Specialist (Clinician Scientist) Award (R50 Clinical Trial Not Allowed) (PAR-21-306)

Questions and Answers

In response to members' questions about educational PAR-21-128 and PAR-21-111, with zero awards, Dr. Paulette Gray explained that those NOFOs were significantly affected by the COVID-19 pandemic. Staffing at the academic institutions was low during that time, and the grants could not be submitted. Although no grants have been issued, NCI has kept those programs active.

Motion. A motion to concur on the 20 re-issue of PARs was approved unanimously.

VIII. ADJOURNMENT OF OPEN SESSION—DRS. JOHN D. CARPTEN AND KEITH T. FLAHERTY

Dr. Carpten adjourned the open session. Only Board members and designated NCI staff remained for the closed session.

IX. NCAB CLOSED SESSION—DR. JOHN D. CARPTEN

This portion of the meeting was closed to the public in accordance with the determination that it was concerned with matters exempt from mandatory disclosure under sections 552b(c)(4) and 552b(c)(6), Title 5 U.S.C., and section 1009(d) of the Federal Advisory Committee Act, as amended (5 U.S.C. §§ 1001-1014).

There was a review of grants and a discussion of personnel and proprietary issues. Members absented themselves from the meeting during discussions for which there was a potential conflict of interest, real or apparent.

The Board was informed that a comprehensive listing of all grant applications to be included in the **en bloc** vote was in the Special Actions package. Those grant applications, as well as those announced during the closed session, could be considered for funding by the institute.

The NCAB **en bloc** motion to concur with IRG recommendations was unanimously approved. During the closed session, a total of 2,586 NCI applications were reviewed requesting direct cost support of $1,179,891,806 and three FDA applications required direct cost support of $633,509.

X. ADJOURNMENT OF NCAB CLOSED SESSION—DR. JOHN D. CARPTEN

Dr. Carpten adjourned the closed session at 4:25 p.m.

THURSDAY, 15 JUNE 2022

XI. CALL TO ORDER AND OPENING REMARKS—DRS. JOHN D. CARPTEN AND KEITH T. FLAHERTY

Dr. Flaherty called Members to order on the final day of the 15th Joint Board Meeting of the BSA and NCAB and welcomed members of the Board, *ex officio* members, President's Cancer Panel members, liaison representatives, staff, and guests.

XII. PROGRESS IN TARGETING KRAS THROUGH THE FREDERICK RAS INITIATIVE—DR. FRANK MCCORMICK

Dr. Frank McCormick, RAS National Program Advisor, FNLCR, David A. Wood Distinguished Professorship of Tumor Biology and Cancer Research, Professor, Helen Diller Family Comprehensive Cancer Center and Department of Cellular and Molecular Pharmacology, University of California, San Francisco, reviewed progress by the NCI/FNLCR RAS Initiative and future program goals. Many cancers are driven by mutations in the *RAS* gene family (i.e., *HRAS*, *KRAS*, *NRAS*), but mutant RAS proteins were deemed undruggable because they lack binding pockets for drug interactions. Former NCI Director Dr. Harold Varmus and the Frederick National Laboratory Advisory Committee (FNLAC) recognized that sufficient drug development progress had been made to warrant revisiting this biological problem and inaugurated the RAS Initiative in 2013. Dr. McCormick explained that the FNLCR is operated by Leidos Biomedical Research, a corporate partner of the NCI. The FNLCR contract with Leidos supports 2,400 employees.

Dr. McCormick reviewed the goals of the RAS Initiative during the next 5 years. These goals include clinically testing direct inhibitors of the active forms of KRAS and RAS–PI3Kα interaction inhibitors; developing molecular descriptions of the activation of rapidly accelerated fibrosarcoma (RAF) kinase by RAS; performing structural analyses of RAS protein complexes to facilitate new approaches to drug discovery; elucidating mechanisms of resistance to RAS and RAS-related inhibitors; developing NRAS inhibitors and inhibitors of other GTPases; identifying RAS proteoforms (i.e., distinct molecular forms of a protein product arising from a single gene); and elucidating the mechanisms that regulate the neurofibromin (NF1) protein, a GTPase-activating protein that functions as a tumor suppressor by turning off RAS signaling.

Dr. McCormick explained that Dr. Varmus intended for the RAS Initiative to serve as a hub in a hub-and-spoke research model. Strategic collaborations with commercial, government, and academic "spoke" organizations are ongoing and essential to the program. Contractor Cooperative Research and Development Agreements (cCRADAs) enable cooperation with one or more partners on jointly conducted research. Intellectual property and other research outcomes are shared among the partners. Current cCRADA partners of the RAS Initiative include Eli Lilly and Company, Sanofi, Evotec SE, and TheRas Therapeutics, Inc. For example, TheRas provides $13 M annually to support 14 full-time RAS Initiative employees. Other partners provide in-kind support for high-throughput screening and medicinal chemistry. The RAS Initiative is committed to community engagement through networking and scientific presentations at RAS Initiative Symposia and the RAS Initiative website, which attracts more than 11,000 visitors each month. The RAS Initiative has distributed high-quality reagents to 623 universities and nonprofit organizations in 43 U.S. states and 45 countries on six continents. Addgene, a nonprofit plasmid repository, has helped distribute 13,127 RAS Initiative plasmids and vectors to the scientific community. The FNLCR has shared 1,503 cell lines generated by the RAS Initiative. RAS-dependent mouse embryonic fibroblast cell lines have been licensed to 23 companies and distributed by 97 academic groups. Farnesylated and fully processed KRAS materials have been licensed to seven companies.

A major goal of the RAS Initiative has been to elucidate the molecular mechanisms of RAF membrane recruitment and activation by RAS. The RAS Initiative has performed biophysical simulations of KRAS–RAF in partnership with the U.S. Department of Energy (DOE) National Laboratories. An area of interest for the RAS Initiative is RAF activation via the low-affinity interaction of RAS with the RAF RAS-binding domain (RBD) and cysteine-rich domain (CRD), whose structures have been solved by Dr. Dhirendra Simanshu, Structural Biology Research Team Lead, FNLCR. The RAS–RAF interface can be targeted by RBDCRD binders that sterically inhibit RAS binding or by compounds that bind to the KRAS–RAF complex and target the entire structure for degradation.

SHOC2 is a regulatory subunit of protein phosphatase 1 (PP1) that acts as an effector of the RAS protein MRAS to activate downstream signaling. PP1C, one of three catalytic subunits of PP1, is responsible for the dephosphorylation of serine and threonine residues, and PPIC becomes active upon binding with MRAS and SHOC2. The SHOC2–MRAS–PP1C (SMP) complex, a potential druggable target, dephosphorylates serine 259 on RAF, a critical component of RAS signaling that is activated in cancers caused by mutant *RAS*. Multiple fitness screens in human cancer cells have suggested selective dependency of *RAS* mutant cells (but not wild-type cells) on RAF activation by the SMP complex. The RAS Initiative and other groups recently have solved high-resolution crystal structures of the SMP complex.

The AI-Driven Multiscale Investigation of the RAS/RAF Activation Lifecycle (or ADMIRRAL) project is part of a series of efforts in the DOE–FNLCR collaboration to elucidate the RAS–RAF activation life cycle through molecular dynamics simulation at multiple scales. Multiscale Machine-learned Modeling Infrastructure (or MuMMI) is being used to study RAS–membrane dynamics. This effort led to the identification of lipid fingerprints associated with RAS clusters that influence RAS orientations and behavior. These findings will be applied to develop models for RAF activation. This project includes a collaboration with Dr. Deborah K. Morrison, Senior Investigator, Chief, Laboratory of Cell and Developmental Signaling, Center for Cancer Research, NCI.

The mutant cysteine in KRAS G12C is a reactive side group that can be exploited to covalently target the mutated form of the protein. This mutant cysteine disrupts the guanine exchange cycle, thereby locking KRAS in an active, GTP-bound form that drives pro-tumorigenic signals. The first generation of KRAS G12C inhibitors decreased RAS affinity for GTP relative to GDP, impairing nucleotide exchange from GDP to GTP and blocking RAS–RAF effector interactions. However, these drugs showed low efficacy in colorectal cancer clinical trials because they preferentially bound the inactive form of KRAS G12C, which is not the most prevalent form of KRAS G12 in mutant cells. Several forms of cancer, including colorectal and pancreatic cancer, primarily are driven by KRAS G12D and G12V mutants, which lack the reactive cysteine residue and can be targeted only by noncovalent inhibitors. Future RAS Initiative efforts will focus on noncovalent KRAS inhibitors that target the active and inactive forms of KRAS G12 mutants (i.e., dual inhibitors) and compounds that inhibit all forms of RAS (i.e., pan-KRAS therapeutics). Dr. McCormick noted that the RAS Initiative was the first group to propose targeting the protein's H95 pocket, which is not conserved in other RAS family members. Compound profiles for KRAS G12C dual inhibitor candidates have been assessed and include detailed biophysical and biochemical characterizations; the path to scalable synthesis and clinical formulation is ongoing. An FDA Investigational New Drug application has been submitted, and clinical trials will begin in late 2023. Drugs targeting active KRAS G12D and G12V currently are being developed.

The interaction between RAS and PI3Kα plays a driving role in oncogenesis, but PI3K signaling is functional in healthy cells that lack RAS. The importance of the RAS–PIK3α interaction has been demonstrated using mouse models. Mice expressing mutant PI3Kα that cannot interact with RAS are highly resistant to KRAS-induced lung tumorigenesis. Inhibition of PI3Kα in human cancer, however, has been limited by side effects related to glucose metabolism, such as hyperglycemia, diarrhea, and rash. Drugs that block the RAS–PI3Kα interaction hopefully will inhibit pathological tumor signaling with

minimal effects on PI3K signaling. Dr. McCormick described successful RAS Initiative efforts to inhibit the RAS–PI3Kα interaction by exploiting a molecular "breaker" compound.

Tumors often develop resistance to drugs used in the clinic. Dr. McCormick summarized anticipated mechanisms of drug resistance for the KRAS G12 ON inhibitors (e.g., point mutations that prevent drug binding, activation of other *RAS* genes and proteins in the RAS pathway, differentiation state changes to escape RAS dependency, activation of alternate signaling pathways) and the RAS–PI3Kα breaker compounds (e.g., point mutations that prevent drug binding, activation of alternate signaling pathways or phosphoinositide kinases, loss of the phosphatase and tensin homolog [PTEN] protein). He concluded by expressing appreciation to colleagues at the RAS Initiative and partner institutes for their contributions.

Questions and Answers

BSA Chair Dr. Flaherty asked for more information about the RAS Initiative team's interest in developing mutant-specific inhibitor compounds versus compounds that inhibit wild-type RAS to some degree. Dr. McCormick pointed out that this issue is highly debated in the RAS community and noted that, in his opinion, a mutant-specific inhibitor of RAS in the active state would serve as a perfect treatment for RAS-related cancer. Compounds that target G12D and G12V mutant alleles likely will target wild-type KRAS as well because the binding pocket is very small. However, evidence from the *KRAS* deletion mouse indicates that HRAS and NRAS can compensate for the complete loss of *KRAS* expression.

Dr. Winkfield asked for additional information related to the RAS Initiative's reagent development pipeline. Dr. McCormick answered that all vectors and cell lines were developed at FNLCR. The preclinical development of therapeutic compounds was funded by cCRADA partners.

In response to a question from NCAB Chair Dr. Carpten, Dr. McCormick confirmed that mechanisms of drug resistance currently are being investigated in preclinical model systems. The RAS Initiative expects to work with clinical partners to identify mutations responsible for drug resistance when the compounds enter clinical trials.

Dr. Navas-Acien asked whether the binding of metal cofactors to the RAF CRD played a role in RAS signaling. Dr. McCormick answered that the CRD indeed is a zinc-binding motif. He added that the role of metal binding to the CRD is unclear but might present an opportunity for therapeutic targeting, possibly via metal chelation.

Dr. Rathmell wondered about the future of RAS research and asked for recommendations related to integrating machine learning (ML) approaches into cancer research. Dr. McCormick expressed hope that highly specific and effective compounds that are safe and orally available will be developed within the next 5 years. The next 10 years likely will involve extensive clinical testing of RAS-related drugs. He added that AI already is revolutionizing drug discovery. Access to computational power and expertise will be the biggest challenge when integrating such approaches.

Ms. Grant asked for best practices and lessons associated with developing medicines (as opposed to screen hits) through effective collaborations with industry partners. Dr. McCormick noted that the RAS Initiative was compelled to partner with private companies because it does not have direct access to medicinal chemistry libraries. He commented that collaborations were initiated via outreach to industry leaders and deepened with time. Drug discovery team efforts were facilitated by frequent virtual meetings.

Dr. Barker asked about efforts to treat additional cancers (e.g., glioblastoma multiforme) with RAS inhibitors. Dr. McCormick answered that *NF1* is mutated in approximately 25 percent of

glioblastomas, and evidence suggests that KRAS is the major RAS protein upregulated by the loss of NF1. Drugs with activity against wild-type KRAS might be useful in treating cancers such as glioblastoma, which are driven by the upregulation of wild-type *KRAS*.

Dr. Bertagnolli commented that National Laboratory efforts are underappreciated and should be publicized more widely. She announced that, after an in-depth review, NCI leadership has decided to fund the RAS Initiative for an additional 5 years.

XIII. RFA/COOP. AGR. AND PAR CONCEPTS—NEW AND RE-ISSUE—NCI PROGRAM STAFF

Division of Cancer Biology

NCI Human Tumor Atlas Network (HTAN) (Re-issue RFA/Coop. Agr./Limited Comp.)—Dr. Shannon Hughes

Dr. Shannon Hughes, Deputy Director, Division of Cancer Biology (DCB), NCI, presented the re-issue concept for HTAN. She explained that HTAN was funded in 2018 in response to a 2016 Cancer Moonshot℠ Blue Ribbon Panel recommendation that directed the construction of human tumor atlases in adult and pediatric cancers to map evolution in space and time. The current HTAN program includes 10 Research Centers, a technology development project, and a Data Coordinating Center (DCC).

Key scientific accomplishments of the HTAN pilot phase include discovery of tumor architecture and recurrent cellular neighborhoods as biomarkers of recurrence, progression, and response to therapy; description of the dynamics of stromal and immune organization in precancer; identification of rare cell states that that predict tumor metastasis or response to therapy; spatial mapping of tumor and microenvironment co-evolution; and development of analysis and visualization tools for HTAN-like data. Since April 2023, the HTAN program has published 12 flagship atlases representing various tumor types. In addition to the 12 main HTAN atlases, HTAN investigators have also contributed to 149 manuscripts. About 40 percent of these manuscripts are focused on developing new single-cell data analysis techniques and integration approaches. All data and resources described by the flagship atlases are available through the HTAN Data Portal, which to date has made data from about 1,300 cases and 4,000 biospecimens available.

The external review panel expressed appreciation for the advances in technologies that enabled the construction of atlases, particularly those pertaining to imaging and computational efforts to quantify cellular neighborhoods and measures of intra- and intertumoral heterogeneity. Recommendations for future HTAN efforts included renewing a focus on analysis of longitudinal samples, especially in the precancer atlas; collecting and harmonizing multiple common data types across atlases; renewing the focus on collection of samples from a diverse patient population; and continuing to lead the community in spatial atlas construction.

The goal of the re-issue RFA is to develop spatial precancer and tumor atlases that inform future development of prevention, interception, diagnosis, and therapy options for patients. The re-issue would support HTAN research projects (U01) to create spatial atlases mapping the dynamic tumor ecosystem, Pre-Cancer Atlas (PCA) Research Centers (U01) to create atlases that comprehensively characterize premalignant lesions, and an HTAN DCC (U24) that is focused on network coordinating and facilitating findability, accessibility, interoperability, and reusability (FAIR) data sharing and reuse. The program would continue to be overseen by the HTAN Steering Committee and HTAN Working Group. Additionally, HTAN staff would continue to engage ESI communities within HTAN and other atlas-building programs and would continue to foster close collaborations with the NCI Cancer Research Data Commons (CRDC) team.

Each U01 awardee will construct one tumor atlas that generates insights poised for translation, include at least two established HTAN data types to facilitate cross-atlas analysis, prioritize funding of projects that include diverse patient samples to increase the impact of atlas-derived insights, and set aside 15 percent of the budget in years 2–5 for collaborative and validation projects. The overall goal of these projects is to guide prevention and interception strategies and map and validate spatial interactions as tumors develop and evolve.

The DCC has enabled community-driven development of HTAN data standards and a clinical data model. Additionally, the DCC has been a collaborator and driving use case for development of the NCI CRDC. DCC's focus for the re-issue would include harmonizing common data analysis pipelines, serving as an exemplar for FAIR sharing and use of spatial omics modalities, and expanding community engagement and education efforts regarding use of HTAN data.

Dr. Hughes emphasized that HTAN contributes to the larger atlas-building and user community. HTAN has collaborated directly with many atlas programs, especially during the development of the HTAN data standard. In the second phase of the program, investigators and program staff will continue to collaborate with other atlas programs. Many of the data sharing tools and infrastructure are being used by other major cancer projects across the United States. Additionally, several new and ongoing efforts at the NCI will benefit directly from HTAN data and resources.

The success of a second phase of HTAN will be evaluated against specific program deliverables and benchmarks, including candidate biomarkers for cancer risk; candidate biomarkers for diagnosis, prognosis, or response to therapy; quantitative maps of large-scale molecular characteristics; easily accessible and analyzable atlas data sets; community use of HTAN atlases; and interoperability of HTAN data sets with other efforts.

The first-year cost of this one-time reissuance is estimated at $17 M for five U01 awards for HTA research projects, five U01 awards for PCA research projects, and a U24 award for the DCC, with a total cost of $85 M for 5 years.

Questions and Answers

Dr. Winkfield suggested standardizing presentations to the NCAB of data on population-based sample collections to include specific parameters, such as race, ethnicity, gender, sex, and geography, as appropriate.

In response to follow-up comments about diversity from Drs. Winkfield and Hayes Dixon, Dr. Hughes explained that approximately 17 percent of HTAN cases are from Black/African American patients, 2 percent are from Asian patients, and 2 percent are from Hispanic/Latino patients. She noted that a significant portion of the ethnicity data are unreported, and the program is working to address this issue through ancestry analysis.

Ms. Duron asked about specific rubrics for increasing diversity of patient samples. Dr. Hughes explained that such a rubric was not implemented during the first phase of the program, and criteria might be tailored to the tumor type. She added that the program is working to collect information to enable the incorporation of race and ethnicity in analyses.

Motion. A motion to concur on the DCB's Re-issue RFA/Coop. Agr./ Limited Comp. entitled "NCI Human Tumor Atlas Network (HTAN)" was approved with 21 ayes, 1 nay, and 2 abstentions.

Division of Cancer Treatment and Diagnosis

NCI's National Clinical Trials Network (NCTN) (Re-issue RFA/Coop. Agr./Limited Comp.)—Dr. Meg Mooney

Dr. Flaherty, BSA Chair, recused himself because of a conflict of interest. Dr. Grandis presided as BSA Chair for the consideration of this concept.

Dr. Meg Mooney, Associate Director, CTEP, Division of Cancer Treatment and Diagnosis (DCTD), NCI, presented the re-issue concept for NCI's National Clinical Trials Network (NCTN). The NCTN was established to harmonize processes and promote collaborations; focus on questions not well supported in a commercial environment; prioritize trials and incorporate innovative science and design; provide large-scale testing of molecularly defined cancers and incorporate precision medicine into the trials portfolio, along with rare tumor trials; and maintain NCI's commitment to conducting trials in diverse and special populations. The current NCTN organizational structure includes six requests for applications: U.S. Group Operations Centers, U.S. Group Statistics/Data Management Centers, Canadian Collaborating Group, Lead Academic Participating Sites, an Imaging/Radiotherapy Core Services Center, and Integrated Translational Science Awards for pilot projects. NCTN Tumor Banks are funded through separate grants for each U.S. NCTN Group by the DCTD Cancer Diagnosis Program. Additionally, centralized contracted services provide programmatic functions across the network. The CTEP CORE for Clinical Trials provides contracted support in information security, administration and logistics, clinical data capture and reporting, regulatory monitoring and reporting, data quality and control, and correlative study data.

The current phase of the NCTN includes a focus on large umbrella and basket trials requiring a national catchment area, multimodality and nondrug trials, combination therapy trials, and special populations and initiatives. Most trials are late phase, with a broad distribution of cancer types. Dr. Mooney noted that special considerations were employed during the COVID-19 pandemic; modifications included allowing more local assessments, appropriate study changes, remote consent and auditing, and shipment of oral agents to patients directly from sites. Additionally, recruitment of non-White patients was sustained during this period. Overall accrual decreased during the pandemic but has since rebounded.

Dr. Mooney highlighted key accomplishments of the NCTN, which include conduct of collaborative trials in special populations (e.g., adolescents and young adults), as well as support for trials that are not well-supported in a commercial environment. Other accomplishments include trials of treatments for high-risk classical Hodgkin lymphoma in children and young adults, acute lymphoblastic leukemia in adults, and recurrent endometrial cancer.

As part of its evaluation, the NCTN surveyed key program participants and found that overall satisfaction increased between December 2016 and August 2022. The external review panel determined that the program conducted many highly significant, practice-changing trials in various cancers; this is considered the best marker of the program's success. Many of the trials would not have been performed by industry alone or without public funding. The panel was highly supportive of other NCTN components.

The panel provided the following key concerns and recommendations. First, increases in funding are critical to continued high-level performance. Second, trials should be designed with challenges for accrual burden on sites in mind, and flexibilities implemented during the COVID-19 pandemic should continue. Third, enrollment of diverse populations needs to be improved and prioritized. Fourth, NCTN groups and the NCI should continue to accelerate trial development. Fifth, collaboration should be enhanced to allow the NCTN to engage in successful initiatives together.

Funding was cited by the extramural community and external review panel as the most critical need. Significant resources are needed to preserve the program, particularly due to rising costs and the loss of health care and research staff. The program has proposed a significant budget increase for the next phase. Most existing program components would be maintained, and increases are proposed for the centers and Lead Academic Participating Sites (commonly called LAPS), as well as capitation for accrual sites. A reduction was proposed for the Integrated Translational Science Awards because other funding opportunities are available.

Subcommittee Review. Dr. Earp expressed the Subcommittee's strong support for the re-issue concept. Dr. Earp remarked that the program has remained flexible and has evolved rapidly in recent years. He underscored the importance of being mindful that the most relevant data are collected from trials and ow trials are adapted to incorporate new technologies. The Subcommittee suggested incorporating a focus on surgical trials and considering the role of AI/ML.

The first-year cost for this one-time reissuance is estimated at $216 M, with a total cost of $1.29 B for 6 years.

Questions and Answers

Dr. Chan suggested conducting trials focused on prevention, as funding in this area has been lacking and outreach with clinicians. Dr. Mooney explained that different NCI Divisions are focused on different aspects of this topic, but the divisions collaborate and share infrastructure as needed.

In response to a comment about data standardization and interoperability from Dr. Volchenboum, Dr. Mooney explained that a common data management system, Medidata Rave®, is in place, but investigations for progress in this area are ongoing. Interoperability is an area of particular interest.

When asked about flexibility during the COVID-19 pandemic, Dr. Mooney clarified that these flexibilities have been continued and expanded. Additionally, strategies for streamlining are being discussed. She also noted that the NCTN has made long-standing efforts to engage rural communities, particularly when considering approaches for streamlining.

Motion. A motion to concur on the DCTD's Re-issue RFA/Coop. Agr./Limited Comp. entitled "NCI National Clinical Trials Network (NCTN)" was approved with 23 ayes, 0 nays, and 1 abstention.

Office of the Director

Innovative Molecular Analysis Technologies (IMAT) Program (Re-issue RFA)—Dr. Kelly Crotty

Dr. Kelly Crotty, Center for Strategic Scientific Initiatives, NCI, presented the re-issue concept for the Innovative Molecular Analysis Technologies (IMAT) Program. She explained that the program supports the early-stage development of technologies for cancer research. IMAT continues to address an area that is unmet by other funding opportunities by focusing support on early-stage development of technologies that could make an impact at any stage of cancer research. Projects supported through IMAT continue to produce high-impact technologies that are being used by the basic, translational, clinical, and epidemiological cancer research communities.

IMAT allows researchers to test novel ideas for new technologies and provide proof of concept. The program uses the R61 and R33 grant mechanisms, as well as competitive revisions. Dr. Crotty explained that IMAT fills a unique role by supporting technology development at the earliest stages; technologies that could make an impact at any point in cancer research; and high-risk, high-reward projects. IMAT has supported sequencing technologies, platforms for proteomics, imaging technologies, and synthetic biology– or immuno-oncology–related tools.

A team from across the NCI cooperatively manages the direction of the program, and a team of research advocates provides patient perspectives. Dr. Crotty emphasized that the program has evolved over the years to meet the needs of the community. Many tools have emerged over time, and others are still in development. IMAT solicits applications using RFAs, which allows the program to focus on technology development proposals. The RFA includes specific review criteria and questions, and all applications are reviewed by special emphasis panels.

The external review panel reported that the IMAT program has a track record of effective technology development. The panel recognized that continued interest in the program exists, based on the number of applications received, and noted the competitive funding rates. The program has been successful in soliciting applications from and funding ESIs, and many IMAT investigators have received funding from other NIH programs or moved into industry to commercialize and continue developing their technologies. Additionally, the program team has been identifying and soliciting applications in specific areas of cancer research where innovation is needed.

Panel recommendations included improving alignment of review panels with the core IMAT mission to fund innovative technologies, enhancing integration of IMAT with other NCI and NIH technology programs, increasing efforts to market the IMAT program, continuing to encourage applications from NIH ESIs, and expanding efforts to identify and focus on technology development areas that would benefit from funding.

Dr. Crotty explained that the RFA mechanism provides assurance of NCI's interest in technology development and allows control over responsiveness and review of applications. Proposed programmatic changes include enhancing focus on innovation, forming a technology interest group, leveraging ongoing activities, and exploring opportunities to support technology development by ESIs.

This RFA request includes re-issue of funding opportunities in the following areas: early-stage innovative molecular and cellular analysis technologies for cancer research, advanced development and validation of emerging molecular and cellular analysis technologies for cancer research, early-stage innovative technologies for cancer-relevant biospecimen science, advanced development and validation of emerging technologies for cancer biospecimen sciences, and competitive revisions.

Subcommittee Review. Dr. Ulrich expressed the Subcommittee's enthusiasm and support for the re-issue concept. She emphasized that the program has led to many new technologies that now are used widely in cancer research. The Subcommittee expressed concerns about silos and noted that opportunities for broader integration might be considered, but these comments have been addressed. Dr. Ulrich noted that innovation remains an important but sometimes overlooked area for funding. Opportunities for coordination with ARPA-H also are present. Program marketing remains an area of importance.

The first-year cost for this one-time reissuance is estimated at $11 M for 21 R61 awards, 12 R33 awards, and 2 competitive revisions, with a total cost of $33 M for 3 years.

Questions and Answers

Dr. Khatibi remarked that technologies developed through IMAT could enable more patients to become involved in clinical trials. Dr. Crotty noted that IMAT is interested in engaging with the NCTN. She emphasized the importance of fostering interactions with other NCI programs.

Motion. A motion to concur on the OD's Re-issue RFA entitled "Innovative Molecular Analysis Technologies Program (IMAT)" was approved with 20 ayes, 0 nays, and 2 abstentions.

Division of Cancer Control and Population Sciences

Improving Care and Outcomes for Cancer Survivors from Sexual and Gender Minority (SGM) Populations (New PAR)—Dr. Chipper Dean

Dr. Chipper Dean, Program Director, DCCPS, NCI, presented the new PAR concept Improving Care and Outcomes for Cancer Survivors from SGM Populations. He noted that multiple calls for SGM-focused cancer research have been published in scientific literature, as well as in response to a recent DCCPS RFI.

The purpose of the proposed PAR is to fund observational and intervention research to further understand and address predictors of disparities experienced by SGM cancer survivors and to support the development, testing, and scaling of innovative, feasible, and effective interventions to address barriers experienced by SGM populations in cancer care. The goal is to fund rigorous research that examines factors influencing cancer care access, and it is designed to improve both proximal and distal outcomes, such as treatment adherence, follow-up screening and care, and mental and physical health outcomes for SGM cancer survivors. Projects must build on a foundation of standardized sexual orientation and gender identity (SOGI) data collection and assess clearly identified endpoints, such as patient–provider communication; psychosocial, behavioral, and functional outcomes; or caregiver engagement.

Incidence and mortality due to cancer among SGM populations is difficult to estimate because of a paucity of epidemiological data, and a consistent national strategy on how to collect SOGI data has not been established. Observational studies, however, indicate that SGM individuals are more likely to receive a cancer diagnosis than non-SGM individuals, and certain cancers have higher rates. SGM individuals are less likely to seek cancer care and have lower rates of access to care. SGM individuals face more challenges related to their cancer care, such as complex treatment needs, inadequate symptom management, and lower adherence to treatment. Further, SGM cancer survivors are more likely to have poorer health outcomes, often due to poorly managed care. SGM-specific concerns in cancer care delivery include fears of disclosing SGM status in cancer care settings, stigmatization and discrimination, intersectionality of multiple minoritized identities, knowledge gaps among providers, and economic strains associated with SGM identity.

Key scientific areas of interest include understanding and/or addressing barriers to cancer treatment and follow-up care for SGM cancer survivors; characterizing and/or developing approaches to address factors that put SGM cancer survivors at higher risk for poorer mental and physical health outcomes; and testing interventions to improve cancer care, particularly focusing on cancer care providers. Sample research topics include barriers faced by SGM cancer survivors; oncology care providers' knowledge gaps related to unique SGM care needs; implementation and testing of training programs for clinicians and their professional organizations to increase sensitivity to those needs; individual- and system-level interventions focused on managing symptoms, functioning, and well-being for SGM survivors that are uniquely tailored to SGM populations; and interactions between gender-affirming care, such as surgery and hormonal therapy, and cancer treatment.

Responsive proposals must explain how the proposed research addresses a pressing need and/or gap in SGM cancer research, include a resource and data sharing plan, describe an existing or planned standardized SOGI data collection process, and include a variety of potential partners (e.g., researchers, SGM community members, providers, health system administrators).

A portfolio analysis in 2020 by the NIH Sexual and Gender Minority Research Office showed that less than 7 percent of the 500 SGM projects funded by NIH in 2020 focused on cancer, representing only 0.2 percent of the total NIH portfolio. Of the 500 SGM-related projects, the NCI funded only 21. Few NCI projects have focused on SGM individuals after their cancer diagnosis or on topics related to SGM cancer care delivery. The NCI has signed onto a current SGM-focused notice of special interest

(NOSI) issued by the National Institute on Minority Health and Health Disparities, but the NOSI addresses broad health areas without a specific cancer emphasis.

Within past year, the NCI awarded 13 Cancer Center Support Grant administrative supplements to conduct SOGI data collection and assess factors associated with implementation, which represents an existing NCI investment in SOGI data collection that can be leveraged in this initiative. The NCI also is currently reviewing submissions for additional administrative supplements to existing grants that are SGM cancer focused. Dr. Dean remarked that taken together, the applications for these supplements indicate a strong interest in and readiness for SGM cancer research support by the NCI in the cancer research community and reflect a strong potential for responses to this PAR.

Currently, the NCI research portfolio is lacking in robust research involving SGM populations. Current funding opportunities do not call for research to improve cancer care and health outcomes for SGM cancer survivors. Dr. Dean commented that this PAR demonstrates NCI's commitment to increasing and accelerating research efforts in SGM populations.

Subcommittee Review. Dr. Coronado expressed the Subcommittee's support for the concept. The Subcommittee appreciated the NCI staff responses to their questions related to the broad scope, defined terminology, intersectionality, defined outcomes, community partner engagement, and policy issues. The Subcommittee also noted the importance of standardized data collection, as well as a policy focus.

Questions and Answers

Ms. Duron commented on the importance of accountability in ensuring inclusion of diverse populations. Dr. Dean noted that the PAR offers an opportunity for specific review criteria to address this matter.

Motion. A motion to approve the DCCPS' new PAR entitled "Improving Care and Outcomes for Cancer Survivors from Sexual and Gender Minority (SGM) Populations (R01, Clinical Trial Optional)" was approved unanimously.

Division of Cancer Treatment and Diagnosis

Pediatric Early Phase Clinical Trials Network (PEP-CTN) (Re-issue RFA/Coop. Agr.)— Dr. Malcolm A. Smith

Dr. Malcolm A. Smith, Associate Branch Chief for Pediatric Oncology, Clinical Investigations Branch, CTEP, DCTD, NCI, presented a re-issue concept for Pediatric Early Phase Clinical Trials Network (PEP-CTN). The purpose of the RFA is to support the PEP-CTN to conduct "first in children" studies (i.e., Phase I often with Phase II expansion cohorts), as well as Phase II and pilot studies of promising agents and regimens; define the pharmacokinetic behavior and key pharmacodynamic effects of novel agents in children; and augment the ability of PEP-CTN to work with pharmaceutical companies by continuing enhancements to its clinical trials infrastructure.

PEP-CTN involves scientific leadership, an operations and biostatistics component, core and non-core member institutions, a pharmacokinetic and biology component, and an imaging component. The NCI will work with PEP-CTN to enhance capabilities. This program builds on years of experience through the Children's Oncology Group (COG) Phase 1/Pilot Consortium and uses NCI-sponsored COG clinical trials infrastructure. The PEP-CTN includes 21 core member institutions, as well as 21 non-core member institutions. The non-core member institutions are added for Phase II components of studies, as well as for pilot studies. Dr. Smith highlighted that geographic distribution has been achieved.

Dr. Smith highlighted clinical trial accomplishments, which include defining activity of nivolumab ± ipilimumab for selected pediatric solid tumors, evaluating trastuzumab deruxtecan in patients with recurrent HER2+ osteosarcoma, completing Phase I clinical trials of pevonedistat with standard-of-care agents for acute myeloid leukemia and for solid tumors, and determining pharmacokinetic behavior for multiple agents. He briefly highlighted examples of PEP-CTN clinical trials.

Support for the Pediatric Cancer Immunotherapy Trials Network (PED-CITN) will end in 2023; two PED-CITN trials are ongoing. Dr. Smith explained that the PEP-CTN will assume responsibility for completing these trials. He also highlighted PEP-CTN clinical trial infrastructure enhancements, which include adding the non-core member sites to increase accrual potential for Phase II trials; incorporating a central review process for all PEP-CTN clinical trials using the Cancer Trials Support Unit (or CTSU) Source Document Portal; and adopting delegation of tasks logs for all PEP-CTN clinical trials and participating in CTEP a protocol deviation integration pilot, with plans to implement in all future trials.

This re-issue RFA will support continuing the PEP-CTN institutions and future infrastructure efforts, including transfer of electronic laboratory data from participating institutions to Medidata Rave. This process involves developing databases, mapping the data extraction process locally and implementing related tools, demonstrating the ability to upload data, comparing data, and assessing the impact of this process on participating sites and the operations centers. Dr. Smith explained the challenges experienced during the first part of the funding period attributed to the COVID-19 pandemic, including interrupted accruals, new protocol development, and enhanced complexity of interactions with pharmaceutical companies, resulting in changes in the regulatory landscape.

In a mid-cycle program review, an external review panel identified PEP-CTN as an important resource that plays a role in pediatric drug development. The panel recommended streamlining processes for agent prioritization while maintaining high standards for moving agents into pediatric testing and enhancing communication strategies with pharmaceutical companies through proactive outreach and committee feedback. The panel also suggested enhancing interactions with COG Disease Committees to facilitate identification of disease-specific early phase clinical trials that can be performed through PEP-CTN, as well as increasing engagement with regulatory agencies to ensure that early phase clinical trials developed by PEP-CTN meet both scientific and regulatory purposes. The NCI is actively addressing these recommendations and is proposing an 8 percent increase in the budget to support the higher costs of research activities and conducting complex clinical trials.

Subcommittee Review. Dr. Baker expressed the Subcommittee's enthusiasm and support for the re-issue concept. Dr. Baker emphasized the importance of engagement with federal and industry partners. The Subcommittee raised the importance of developing novel approaches for collecting standardized data, interacting with existing systems, and ensuring cost effectiveness.

The first-year cost for this one-time reissuance is estimated at $4.5 M, for 1 UM1 award, with a total cost of $22.5 M for 5 years.

Motion. A motion to concur on the DCTD's Re-issue RFA/Coop. Agr. entitled "Pediatric Early Phase Clinical Trials Network (PEP-CTN)" was approved with 22 ayes, 0 nays, and 2 abstentions. (Note – I had noted 20 ayes and 1 abstention.)

XIV. ADJOURNMENT—DRS. JOHN D. CARPTEN AND KEITH T. FLAHERTY

Dr. Carpten thanked all the Board members, as well as the visitors and observers, for attending. There being no further business, the 15th Joint Meeting of the BSA and NCAB was adjourned at 11:52 a.m. on Thursday, 15 June 2023.

Date	Keith T. Flaherty, M.D., Chair, BSA
Date	John D. Carpten, Ph.D., Chair, NCAB
Date	Paulette S. Gray, Ph.D., Executive Secretary