DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
NATIONAL INSTITUTES OF HEALTH
NATIONAL CANCER INSTITUTE
14th VIRTUAL NATIONAL CANCER ADVISORY BOARD

Summary of Meeting
February 11, 2021

Virtual Meeting
National Cancer Institute
National Institutes of Health
Bethesda, Maryland

NATIONAL CANCER ADVISORY BOARD
BETHESDA, MARYLAND
Summary of Meeting
11 February 2021

The National Cancer Advisory Board (NCAB) convened for its 14th virtual regular meeting on 11 February 2021. The meeting was open to the public on Thursday, 11 February 2021, from 1:15 p.m. to 3:55 p.m., and closed to the public from 4:20 p.m. to 5:10 p.m. The NCAB Acting Chair, Dr. Scott W. Hiebert, Hortense B. Ingram Chair in Cancer Research, Professor of Biochemistry, Department of Biochemistry, Vanderbilt University School of Medicine, presided during both the open and closed sessions.

NCAB Members

Dr. Scott W. Hiebert (Acting Chair)
Dr. Peter C. Adamson
Dr. Francis Ali-Osman
Dr. Anna D. Barker
Dr. Deborah Watkins Bruner
Dr. Yuan Chang
Dr. Howard J. Fingert
Mr. Lawrence O. Gostin (absent)
Dr. Andrea A. Hayes-Jordan
Dr. Nikan Khatibi
Dr. Timothy J. Ley
Dr. Electra D. Paskett
Dr. Nancy J. Raab-Traub (absent)
Dr. Margaret R. Spitz
Dr. Susan Thomas Vadaparampil
Dr. Max S. Wicha

Alternate Ex Officio NCAB Members

Dr. Michael A. Babich, CPSC
Dr. Joseph R. Graber, DOE
Dr. Michael Kelley, VA (absent)
Dr. Aubrey Miller, NIEHS
Dr. Richard Pazdur, FDA (absent)
Dr. Craig D. Shriver, DoD (absent)
Dr. Kerry Souza, NIOSH (absent)
Dr. Lawrence A. Tabak, NIH (absent)
Dr. Aaron Tustin, OSHA

Members, Scientific Program Leaders, National Cancer Institute, NIH

Dr. Norman E. Sharpless, Director, National Cancer Institute
Dr. L. Michelle Bennett, Director, Center for Research Strategy
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. Robert Croyle, Director, Division of Cancer Control and Population Sciences
Dr. William Dahut, Scientific Director for Clinical Research, Center for Cancer Research
Dr. James H. Doroshow, Deputy Director for Clinical and Translational Research
Dr. Dan Gallahan, Acting Director, Division of Cancer Biology
Mr. Peter Garrett, Director, Office of Communications and Public Liaison
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. Sara Hook, Director, Office of Scientific Operations, NCI at Frederick
Dr. Tony Kerlavage, Director, Center for Biomedical Informatics and Information Technology
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. Margaret Mooney, Associate Director, Cancer Therapy Evaluation Program
Dr. Henry Rodriguez, Acting Deputy Director, Center for Strategic Scientific Initiatives
Mr. Jeff Shilling, Chief Information Officer and Chief of Infrastructure and Information Technology Services Branch, Center for Bioinformatics and Information Technology
Ms. Donna Siegle, Executive Officer and Deputy Director for Management, Office of the Director
Dr. Dinah Singer, Deputy Director, Science Strategy and Development
Dr. Sanya 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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THURSDAY, 11 FEBRUARY 2021

I. CALL TO ORDER AND OPENING REMARKS—DR. SCOTT W. HIEBERT

Dr. Scott W. Hiebert called to order the 14th virtual National Cancer Advisory Board (NCAB) meeting. He welcomed members of the Board, 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. Hiebert reviewed the confidentiality and conflict-of-interest practices required of Board members in their deliberations.

Motion. A motion to accept the minutes of the 1–2 December 2020 Joint Meeting of the Board of Scientific Advisors (BSA) and the NCAB was approved unanimously.

II. FUTURE BOARD MEETING DATES—DR. SCOTT W. HIEBERT

Dr. Hiebert called Board members' attention to the future meeting dates listed on the agenda.

III. NCI DIRECTOR'S REPORT—DR. NORMAN E. SHARPLESS

Dr. Norman E. Sharpless, Director, NCI, welcomed NCAB members and attendees to the 14th virtual meeting and provided an update on the 50th anniversary of the National Cancer Act (NCA) of 1971, Cancer Moonshot℠ midpoint, NCI appropriations and paylines, coronavirus disease 2019 (COVID-19) impacts and activities, cancer research highlights, and NCI Equity and Inclusion Program.

On 3 February 2021, the First Lady, Dr. Jill Biden, visited the NCI (virtually) to express appreciation to the NCI staff for their work on behalf of cancer researchers and patients. Three speakers and presentations were featured for the First Lady's virtual visit: Dr. Worta McCaskill-Stevens, Chief, Community Oncology and Prevention Trials Research Group, Division of Cancer Prevention (DCP), who described the success and reach of the NCI Community Oncology Research Program (NCORP) in minority accruals for clinical trials; Dr. Stephanie L. Goff, Associate Research Physician, Surgery Branch, Center for Cancer Research (CCR), who discussed cutting-edge treatments at the National Institutes of Health (NIH) Clinical Center; and Dr. Ligia Pinto, Director, Vaccine, Immunity and Cancer Program, Frederick National Laboratory for Cancer Research (FNLCR), who discussed the serology efforts in response to the COVID-19 pandemic. Dr. Sharpless noted that Dr. Biden conveyed that cancer, along with education and support for military families, is one of her top three areas of focus as First Lady. The NCI is confident the current Administration will be a significant partner in cancer research and health care for patients.

50th Anniversary of the NCA of 1971. Dr. Sharpless announced that on 8 February 2021, the NCI launched NCA-50, "Nothing Will Stop Us," campaign in commemoration of the 50th Anniversary of the NCA of 1971. NCA-50 is an opportunity to ignite and inspire the next generation of cancer researchers and supporters of cancer research. The NCI is excited about the potential of the NCA-50 activities to spotlight the progress for cancer patients across the Nation and how these efforts have (and remain) dependent on basic science for translational research, including research services and survivorship research. In all these activities, the NCI is working in concert to improve the lives of patients with cancer. NCAB members were encouraged to view the commemorative video, accessible from the NCA-50 webpage.

Cancer Moonshot℠ Midpoint. Dr. Sharpless reminded NCAB members that the Cancer Moonshot℠ was approved in the 21 Century Cures Act with a 7-year funding allotment beginning in fiscal year (FY) 2017. The initiative is at its midpoint and the progress remains impressive. The

240 research projects and initiatives funded from FY 2017 to FY 2020 span the research continuum extending from fundamental understanding of the drivers of childhood cancer to genetic counseling and screening of individuals with inherited predispositions to cancers to direct engagement with patients. Although it will take years to translate the projects into clinical benefit (e.g., diagnostics and treatments), the investments already are resulting in new national resources. Further details on progress can be accessed from the NCI website via the *Cancer Currents: An NCI Cancer Research* blog. Dr. Sharpless and Dr. Dinah Singer, Deputy Director, Science Strategy and Development, NCI, soon will publish a midpoint progress update. The NCI is planning for future projects beyond the end on the 7-year funding period in FY 2023 and ways to transition those efforts into existing programs. To address the concerns in the cancer research community that only NCI established and long-time investigators were receiving Cancer Moonshot℠ funding, the NCI Center for Research Strategy (CRS) analyzed the extramural awards (excluding grant supplements). The data revealed that 12 percent of the established extramural principal investigators had no prior NCI funding and 25 percent were new investigators. Of the 25 percent, 5 percent were early-stage investigators (ESIs). These data demonstrate that the Cancer Moonshot℠ is meeting its key goal of increasing the pool and diversity of ideas about cancer research at the NCI.

NCI Appropriations and Paylines. Dr. Sharpless reported that the FY 2021 NIH budget includes an annual appropriations of $42.9 billion (B), which is an increase of $1.25 B above the FY 2020 enacted budget; $6.56 B to the NCI, which is an increase of $119 million (M). The NCI regular appropriations include $195 M for the Cancer Moonshot℠ and $50 M for the Childhood Cancer Data Initiative (CCDI). The FY 2021 budget also designates $37.5 M to the NCI to (1) prioritize competing grants (e.g., Type 2) and (2) sustain the commitments in continuing grants (i.e., Noncompeting Continuation [Type 5] awards). In FY 2020, the fourth COVID-19 emergency bill allotted the NCI $306 M for serology research. The NCI is actively implementing those efforts.

Dr. Sharpless discussed the NCI paylines for FY 2021. In its *Annual Plan and Budget Proposal for Fiscal Year 2022* the NCI proposed a "5 in '25" plan to increase funding for the Research Project Grant (RPG) pool, gradually reaching a 15th percentile payline for R01 grants for established investigators by FY 2025. The continued support and commitment from Congress has enabled the NCI to reach the 11th percentile for established investigators in FY 2020, a rate that is an increase of 35 percent for 2 consecutive years. Grants for ESIs are at the 16th percentile and at the 9th percentile for exploratory grants (R21). Noncompeting Continuation Type 5 awards will be funded at 100 percent. The NCI is well on its way to achieving this aspirational and resource-intensive goal by FY 2025 without making cuts to major programs (e.g., NCI-Designated Cancer Centers) outside of the RPG pool. Further details have been provided on the NCI blog, *NCI Bottom Line: A Blog About Grants and More*.

COVID-19 Impacts and Activities. Dr. Sharpless remarked on ways that the NCI has contributed to the nation's response to the COVID-19 pandemic, all while maintaining focus on the central mission—cancer research and ensuring progress for patients with cancer. The NCI COVID-19 in Cancer Patients Study (NCCAPS) plan to enroll 2,000 patients in the United States across 1,000 trial sites was rapidly launched on 21 May 2020, just 5 weeks from conception. As of 10 February 2021, 873 trial sites have been activated across the NCI National Clinical Trials Network (NCTN) and NCORP in all 50 states; Washington, D.C.; Puerto Rico; and Canada. A total of 994 patients have been screened and 894 enrolled in NCCAPS, and the trial is now open to pediatric cancer patients. The NCCAPS data set will be important to understanding the natural history of COVID-19 in specific populations and long-term sequalae in cancer patients. He remarked that COVID-19 vaccinations are well underway in the United States and many places globally. Campaigns, he recognizes, will be successful only as the confidence among populations in the benefits of such campaigns is addressed.

A recent NIH report, *COVID-19 Vaccination Communication: Applying Behavioral and Social Science to Address Vaccine Hesitancy and Foster Vaccine Confidence*—an effort led by the NCI Health

Communications and Informatics Research Branch (HCIRB), Division of Cancer Control and Population Sciences (DCCPS) and NIH Office of Behavioral and Social Sciences Research (OBSSR)—focuses on the NCI research on vaccine hesitancy. For the past 2 years the HCIRB has been dedicated to setting a research agenda to better understand and address health-related misinformation contained online. The health topic of vaccines remains among those most affected by misinformation. The NCI joined the OBSSR in establishing a trans-NIH working group on COVID-19 vaccine communication, which is available to provide expert advice as needed. This report—which has been widely shared across the U.S. Department of Health and Human Services (HHS), National Science Foundation, and other public health agencies—makes a strong case for evidence-based communication adaptable to real-time changes in vaccine research.

The FNLCR led efforts to develop a U.S. human SARS-CoV-2 serology standard (i.e., assay calibrator) to harmonize assays that measure anti-SARS-CoV-2 antibodies to increase comparability of results across studies, including candidate vaccine trials. The aliquoted, calibrated, and validated U.S. serology standard, pooled plasma from four blood donors with SARS-CoV-2 antibodies, is obtainable through the FNLCR and will be calibrated to the World Health Organization International Standard when it becomes available.

NCI Research Highlights. Dr. Sharpless highlighted two publications that feature recent cancer research progress related to prostate and melanoma cancers with links to the NCI Intramural Research Program (IRP). Results from a large-scale international trans-ancestry genome-wide association meta-analysis of prostate cancer, funded in part by the DCCPS, was published in the 4 January 2021 issue of *Nature Genetics*. The 230 authors, including Division of Cancer Epidemiology and Genetics (DCEG) investigators, examined diverse ancestries in men of European, African, East Asian, and Hispanic descent and identified 86 new genetic risk variants that independently associate with prostate cancer risk. This study demonstrates an improved ability to conduct personalized risk prediction, all using a polygenic risk model. IRP investigators collaborated with University of Pittsburgh Medical Center Hillman Cancer Center to treat immunotherapy-refractory melanoma patients using fecal microbiota transplant (FMT). This first-of-a-kind FMT study, reported in the 3 February 2021 issue of *Science*, revealed that FMT promotes an improved response in these patients treated with a challenged dose of an immune checkpoint inhibitor, suggesting that the composition of the colonic microbiome can augment the efficacy of these immunotherapy agents.

Regarding progress in other recent initiatives, the NCI partnered with Cancer Research United Kingdom (UK) to sponsor the Cancer Grand Challenges (CGC) to award grants to international multidisciplinary research teams seeking to address cancer research problems. Nine CGC were published in October 2020 and can be accessed from the NCI website. The first stage of the competition, expressions of interest from the teams, will be accepted through April 2021. The CGC leverages the NCI Provocative Questions (PQ) Initiative, will use the PQ Initiative funds every other year, and is supported by Cancer Research UK funds. Dr. Sharpless informed the Board that the NCI is taking this opportunity to pause and conduct an internal program evaluation of the PQ Initiative, commencing in FY 2021.

In November 2020, the NCI released a request for information (RFI) to solicit ideas on new national programs appropriate for the FNLCR. The NCI is seeking input from the cancer research community on the most important needs and promising opportunities in cancer research that are difficult to address on an individual level or by any single research network. This RFI will close on 19 February 2021.

In FY 2020, Congress appropriated $50 M to the NCI to initiate the CCDI, and a detailed report on the program structure and years ahead was provided in the December 2020 Joint BSA and NCAB meeting. The CCDI governance structure consists of four working groups to manage building the CCDI components and overseeing implementation. The Childhood Cancer Data Platform Working Group is

developing an infrastructure for and enhancing sharing of new and existing data from children's cancer institutions and community-based and NCI-supported sources. The National Childhood Cancer Cohort Working Group is gathering data from every child diagnosed with cancer in the United States. The Childhood Molecular Characterization Protocol Working Group is developing a national strategy to provide clinical and molecular characterization for every child diagnosed with cancer in the United States. A CCDI Coordination Center Working Group is developing guidelines and approaches to address cutting-edge issues. A CCDI Steering Committee will oversee the activities of the four working groups and will be informed by a CCDI Engagement Committee to involve the wider childhood cancer community in the CCDI. The NCI is finalizing the member rosters of the working groups and committees and will include NCI and extramural experts, patient advocates, and caregivers. The first Steering Committee meeting is planned for late February 2021.

NCI Equity and Inclusion Program. Dr. Sharpless updated the NCAB members that the NCI Equity and Inclusion program consists of an NCI Equity Council, which he chairs, and Dr. Gray, who serves as vice-chair. It comprises five working groups, three of which will address the program content represented in three broad aspects of inclusion: Working Group 1, enhancing research to address cancer health disparities; Working Group 2, ensuring diversity of thought and background in the cancer research workforce; and Working Group 3, promoting an inclusive and equitable community at the NCI. Working Groups 4 and 5 will address crosscutting themes on equity activities, including systemic tracking and evaluation and community and outreach, respectively. Working Group 1 began its activities using the analytic capabilities from the CRS to perform an in-depth portfolio analysis of the NCI cancer health disparities–related research and training conducted from FY 2010 to FY 2020. The data show steady increases in NCI investments (annually) and significant growth, particularly since FY 2015 and primarily within the DCCPS. A significant and world leader in funding health disparities research, the NCI and its investments complement and exceed the budget of the National Institute of Minority Health Disparities by $350 M.

Questions and Answers

Dr. Sharpless posed a question that has been prevalent in the extramural cancer research community about the flexibility of extending deadlines of training programs, given the disruptions caused by the COVID-19 pandemic. Dr. Oliver Bogler, Director, Center for Cancer Training (CCT), explained that the NIH Office of the Director released a notice (OD-21-052) that summarizes the flexibilities, including no-cost extensions and deadlines for transition awards (e.g., F and K awards). He encouraged the training grant principal investigators to contact the program officers for case-by-case assistance, noting that the CCT had successfully responded to and accommodated several similar requests within the past 18 months.

NCAB Acting Chair Dr. Hiebert inquired about the extending window of eligibility for Career Transition Award (K99) postdoctoral fellows, which involves only extra time and no cost allowances. Although the grant submission deadlines will remain unchanged, Dr. Bolger clarified that applicants will not be disqualified because of COVID-19-related delays.

Dr. Andrea A. Hayes-Jordan, Byah Thompson Doxey Distinguished Professor of Surgery, Division Chief, Pediatric Surgery, Surgeon-in-Chief, The University of North Carolina Children's Hospital, asked about addressing access to care for impoverished and underserved populations within the focus areas of the NCI Equity Inclusion program and issues on providing care (e.g., telehealth) across state lines. Dr. Sharpless commented that access to care will reside in the focus areas of Working Group 1 in reviewing the NCI health disparities research portfolio and then ensuring these issues are addressed, researched, and funded. He elaborated on the rules governing care across state lines and how related questions provide an opportunity for future research in this area at the NCI.

Dr. Susan Thomas Vadaparampil, Associate Center Director, Community Outreach, Engagement, and Equity, Moffitt Cancer Center, inquired about special provisions for institutional training grant (T-32) appointments, especially for trainees delayed in securing faculty positions. Dr. Bolger pointed out that the CCT will work with institutions in retaining trainees for longer periods of time to enable easier career transitions, but noted that the number of allotted T-32 positions on a particular grant could not be changed.

Dr. Anna D. Barker, Chief Strategy Officer, Ellison Institute for Transformative Medicine, University of Southern California, remarked on the NCA-50 campaign and asked about plans for engaging the broader cancer research community, including the NCI-Designated Cancer Centers (Cancer Centers) and the public in the messaging. Dr. Sharpless noted that the materials, tagline, and logo commemorating the NCA-50 are not NCI-branded and can be widely disseminated and used by any groups or individuals interested in cancer research. Many of the Cancer Centers are developing campaigns specific to their own accomplishments in cancer care within the past 50 years. He continued that NCA of 1971, a remarkable vision, has led to many benefits for patients and has created long-standing research capabilities.

Dr. Peter C. Adamson, Global Head, Oncology Development and Pediatric Innovation, Sanofi, commended the NCI for expanding the breadth of the CCDI and sought clarity on whether the molecular characterization of every child with cancer included treatment-relapsed, refractory patients. Dr. Sharpless clarified that the goal is to establish a base of molecular analyses for every child with cancer, regardless of disease stage (e.g., new diagnoses, relapse, or refractory).

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

Ms. M.K. Holohan, Director, Office of Government and Congressional Relations (OGCR), reported on the new Administration, 117th Congress, COVID-19 funding, and FY 2022 appropriations. On 7 December 2020, then President-Elect Joseph R. Biden, Jr., nominated Xavier Becerra, California Attorney General and former 12-term Member of the House of Representatives, as Secretary of HHS. Mr. Becerra's nomination has been referred to the Senate Finance Committee and a hearing date is to be announced. As of 11 February 2021, the Senate Health, Education, Labor and Pensions Committee has confirmed 7 of 23 of President Biden's cabinet nominees. Two of the remaining nominees, Dr. Miguel Cardona for Secretary of Education and Marty Walsh for Secretary of the Department of Labor, have had favorable votes out of Senate committees. President Biden has elevated the Director, White House Office of Science and Technology Policy (OSTP), to a Cabinet-level position, the first in the history of the OSTP. Dr. Eric Lander (geneticist) has been nominated to fill this position and is currently advisor to the Administration.

In the 117th Congress, the House has 221 Democrats (D), 211 Republicans (R), and three vacancies. The Senate has 50 Republicans and 50 Democrats; and the two new senators from Georgia will be up for re-election in 2022. A sitting President's party loses seats during midterm elections, almost always in the House, except for two occasions. The 117th is the most racially and ethnically diverse Congress in history, with 23 percent representation in the voting members and 27 percent of seats held by women. The new Congress established Senate leadership and committee changes. Sen. Chuck Schumer (D-NY) is Senate Majority Leader, and Sen. Dick Durbin (D-IL) is Senate Majority Whip. Sen. Mitch McConnell (R-KY) is Senate Minority Leader and Sen. John Thune (R-SD) is Senate Minority Whip. The House leadership remains unchanged for both parties.

Ms. Holohan called attention to the leadership changes of the committees that authorize NIH funding. For the House Energy and Commerce Committee and Health Subcommittee, Rep. Cathy McMorris Rodgers (R-WA) is Full Committee Ranking Member and Rep. Brett Guthrie (R-KY) is Health Committee Ranking Member. In the Senate Health, Education, Labor and Pensions Committee,

Sen. Patty Murray (D-WA) is Committee Chair and Sen. Richard Burr (R-NC) is Committee Ranking Member. These committees authorize the NIH annual appropriations to fund specific programs, which may have specific directions attached.

Regarding the appropriations committees, Rep. Rosa DeLauro (D-CT) is Chair of the House Appropriations Committee and Chair of the House Appropriations Subcommittee on Labor, Health and Human Services, Education, and Related Agencies (L-HHS), which allots NCI's appropriations. No changes were made to the ranking members of the House Appropriations Committee and L-HHS Appropriations Subcommittee. Sen. Patrick Leahy (D-VT) is Chair of the Senate Appropriations Committee, Sen. Richard Shelby (R-AL) is the Committee Ranking Member, and Sen. Roy Blunt is L-HHS Appropriations Subcommittee ranking member. The Senate Chair of the L-HHS Appropriations Subcommittee is to be determined. Ms. Holohan pointed out that these legislators are not new to Congress; they have long-standing relationships with each other, and many have a vested interest in cancer research.

In January 2021, President Biden announced the next COVID-19 bill, the American Rescue Plan. This $1.9 trillion authorizing (i.e., not supplemental) bill includes extensions for unemployment benefits and housing and food assistance programs and provisions for individual stimulus checks. The House majority is using the reconciliation process established by the Congressional Budget and Impoundment Control Act of 1974, allowing expedited approval of this bill without Senate filibuster. After a 15-hour deliberation "vote-a-rama" on 5 February 2021, the budget resolution passed out of the House committees. Legislation is being drafted in 12 authorizing subcommittees, and bill markups are anticipated later this week. The goal is to have the resolution bill signed by the President prior to 14 March 2021. Recognizing that the COVID-19 pandemic has affected biomedical research, resulting in loss of productivity across laboratories, members of Congress reintroduced the Research Investments to Spark the Economy (RISE) Act on 5 February 2021. The RISE Act authorizes nearly $25 B of support to U.S. researchers affected by the pandemic and includes $10 B for the NIH. Prior efforts to include funding for lost productivity and restart costs during the 116th Congress either did not become law or were not included in the final appropriation.

The NIH/NCI FY 2022 budget appropriations process presents with several complications, including the timing for the President's Budget Request, ongoing focus on the $1.9 trillion COVID bill, and expiration of the debt limit suspension on 31 July 2021. In addition, the U.S. election years have affected the completion of the NIH appropriations process, with delays in FYs 2013 and 2017 and approvals of long-term continuing resolutions.

V. ANNUAL DELEGATIONS OF AUTHORITY—DR. PAULETTE S. GRAY

Dr. Paulette S. Gray, Director, DEA, requested concurrence by the NCAB on two Delegations of Authority to the Director of the NCI. She described the delegations and provisions in the Statement of Understanding. Delegation A allows the Director to obtain the services of not more than 151 special experts or consultants who have scientific or professional qualifications. Dr. Gray also explained that Delegation B specifies that the NCAB delegates authority to the NCI Director to appoint one or more advisory committees composed of private citizens and officials of federal, state, and local governments to advise the Director with respect to his or her functions.

The Statement of Understanding with NCI Staff on Operating Principles in Extramural Grants also falls within the Delegations of Authority to the Director, NCI. NCAB operations are conducted in accordance with management and review procedures described in the NIH Manual Issuance 4513. Concurrence of the NCAB with recommendations of initial review groups will be required, except for the following: (1) Training grants and fellowships and other non-research grant applications are not subject to NCAB review and approval and, without other concerns, may be awarded without presentation to the

NCAB for concurrence, with the exception of Ruth L. Kirschstein National Research Service Awards. (2) Applications above the 20th percentile will not have summary statements presented to the NCAB unless the Institute is considering an award of such an application, or other special consideration is requested or required by NCI or NIH policy, or for special consideration by an appointed member of the Board. (3) For applications assigned raw scores that are not percentiled, the cutoff will be a priority impact score of 50 for all mechanisms except R41, R42, R43, and R44 awards; for the latter, all scored applications will be included.

Expedited Concurrence: (1) For R01 and R21 applications with percentiled or raw scores that fall within the NCI paylines for that mechanism, a process of expedited concurrence will be used and (2) the Executive Secretary will alert Board members with responsibility for expedited concurrence when review outcomes for eligible applications are available on the Electronic Expedited Concurrence portion of the Electronic Council Book.

Administrative Adjustments: (1) Permission is delegated to the Director, NCI, to allow staff to negotiate appropriate adjustments in dollars or other terms and conditions of grant and cooperative agreement awards. (2) Administrative requests for increases in direct costs that are the result of marked expansion or significant change in the scientific content of a program after formal peer review will be referred to the Board for advice and recommendation. (3) Actions not requiring Board review or advice—such as change of institution, change of principal investigator (PI), phase-out of interim support, or additional support—need not be reported to the Board. (4) NCI staff may restore requested time and support that were deleted by the initial review group when justified by the PI in an appeal letter or when restoration is in the best interest of the NCI and the project is of high NCI programmatic relevance.

To continue responsible stewardship of public funds, the NIH has instituted a policy of Special Council Review of applications from well-funded investigators. Applications from PIs who have $1 M or more in direct costs from active NIH RPGs must be given additional consideration.

Motion. A motion to approve the NCI Annual Delegations of Authority was approved unanimously.

VI. PHASE III TRIAL OF STANDARD ADJUVANT ENDOCRINE THERAPY +/− CHEMOTHERAPY IN PATIENTS WITH 1–3 POSITIVE NODES, HORMONE RECEPTOR-POSITIVE (HR+) AND HER2–NEGATIVE: SWOG S1007—DR. KEVIN KALINSKY

Dr. Kevin Kalinsky, Acting Associate Professor of Medicine, Emory University School of Medicine; Director, Glenn Family Breast Center; Director, Breast Medical Oncology, Winship Cancer Institute of Emory University, presented results of the SWOG (formerly the Southwest Oncology Group) Cancer Research Network S1007 trial, referred to as the Rx for Positive Node, Endocrine Responsive Breast Cancer (RxPONDER) trial. He also reviewed data from the Trial Assigning IndividuaLized Options for Treatment (Rx) (TAILORx) and provided an update on the NCTN Late Recurrence Project. Dr. Kalinsky reminded the NCAB members of the strategic priorities of the NCI Breast Cancer Steering Committee, which are to decrease the toxicity, treatment, and costs associated with therapy with negligible clinically meaningful benefit and to understand and translate the biology into diagnostic and therapeutic strategies.

The aim of the TAILORx and RxPONDER trials was to evaluate the benefit of adjuvant chemotherapy in patients with HR+/human epidermal growth factor receptor 2–negative (HER2−) breast cancer using the Oncotype DX Breast Recurrence Score® (RS), a 21-gene panel assay. TAILORx is coordinated by the Eastern Cooperative Oncology Group American College of Radiology Imaging Network Cancer Research Network. This trial enrolled, registered, and randomized HR+/ HER2−/lymph

node− patients with mid-range RS (11–25) to either the experimental (i.e., endocrine therapy alone) or standard treatment (i.e., endocrine therapy plus chemotherapy) arms. Patients with low RS (0–10) were assigned to experimental treatment, and patients with high RS (25–100) were assigned to standard treatment (i.e., chemotherapy followed by endocrine therapy) arms. Overall, patients with RS 11-25 did not benefit from the addition of chemotherapy. Exploratory analysis in patients aged 50 or less, with mid-range RS (11–25), showed some benefit with chemotherapy if RS 16-25. Further evaluations integrating genomic and pathologic features using the RSClin™ tool in a subset of these patients further individualized risk and potential absolute chemotherapy benefit.

The RxPONDER trial, of which Dr. Kalinsky is principal investigator and study chair, evaluated the role of genomic assays for risk determination and chemotherapy benefit in patients with HR+/HER2−/1–3 node+ breast cancers, leveraging the SWOG S8814 trial. Eligible patients ages 18 and older—who did not have distant metastasis, were able to receive adjuvant taxane- and/or anthracycline-based chemotherapy, and had RS between 0 and 25—were enrolled and randomized to treatment. The primary objective was to determine the effect of chemotherapy on invasive disease-free survival (IDFS) in patients with 1–3 node+ breast cancer and a RS less than 25 and to assess whether the effect depends on the RS. Dr. Kalinsky and colleagues hypothesized that chemotherapy benefit would increase as the RS increases from 0 to 25, in an intent-to-treat analysis.

Dr. Kalinsky detailed the study results. Of the patients randomized to chemotherapy, 50 percent received the taxotere and cytoxan, and 16 percent of patients in the experimental arm and 3 percent in the standard treatment arm had ovarian function suppression 6 months post-randomization. A pre-specified interim analysis for IDFS in 2020 revealed statistically significant differences in chemotherapy benefit for IDFS, dependent upon menopausal status. Regarding baseline characteristics across treatment arms, the majority of patients were White/Caucasian, one-third were premenopausal, 57 percent had RS of 14–25, 67 percent had one positive node, and the majority had intermediate grade tumors. In the overall study population, the 5-year IDFS improved significantly with the addition of chemotherapy. Stratified by menopausal status, the 5-year IDFS was statistically significant in the premenopausal group but not in the postmenopausal group.

The RxPONDER study concluded that postmenopausal women with one to three positive nodes and RS 0–25 likely can safely forego adjuvant chemotherapy without compromising IDFS. Premenopausal women with positive nodes and RS 0–25 likely will benefit significantly from chemotherapy. Future directions in HR+ breast cancer research will be to determine whether the benefit of chemotherapy observed in TAILORx and RxPONDER in premenopausal patients is due to chemotherapy or ovarian suppression and to explore additional opportunities to intervene in high-risk patients to prevent late recurrence of HR+ breast cancer.

To address late recurrence, a working group composed of representatives of the NCTN groups discussed opening an NCTN Late Recurrence Trial. The group deliberated on a Phase III trial design for capturing late recurrence in HR+/HER2− breast cancer patients who had completed 4–6 years of endocrine therapy. Clinical risk assessments, blood-based biomarker testing, and cooperative randomization according to risk would be included in the design schema. Low clinical and biomarker–risk patients would be de-escalated to an observational cohort, and high biomarker or high clinical–risk patients would be randomized to an intervention. To conduct a Phase III trial of this scale, several questions on the role of blood-based biomarker detection in early-stage breast cancer and the best therapeutic intervention remain to be addressed. An NCTN Late Recurrence Phase II trial (i.e., treatment phase) has been designed that considers these questions and will inform a Phase III trial.

Dr. Kalinsky concluded that the TAILORx and RxPONDER trials enabled significant progress in chemotherapy regarding de-escalation. Premenopausal patients can assist in identifying de-escalation

strategies to prevent recurrence. For late recurrence, assessments using predictors and potential interventions remain critical.

Questions and Answers

Dr. Max S. Wicha, Madeline and Sidney Forbes Professor of Oncology; Director, Forbes Institute for Cancer Discovery; Founding Director Emeritus, University of Michigan Rogel Cancer Center; Professor, Internal Medicine, Division of Hematology and Oncology, University of Michigan, inquired about the rationale of not including patients with more than three positive nodes in the RxPONDER trial, given that patients with several positive nodes could have low RS but still require chemotherapy. Dr. Wicha also called attention to one clinical problem in breast cancer that a trial such as RxPONDER could address—understanding of the biology of tumor dormancy in bone marrow cells. Dr. Kalinsky explained that RxPONDER modeled the SWOG S8814 study, which contained only a small subset of patients with more than three positive nodes. The stronger supporting evidence led to selecting patients with three or fewer positive nodes for this current study. In terms of investigating markers of tumor dormancy, he called attention to the RxPONDER sub-study, recently submitted for approval, that will allow collecting additional samples, including circulating tumor cells and cell-free DNA in patients randomized to treatments.

In response to a query from Dr. Barker on whether not recommending chemotherapy would pose issues for clinicians, Dr. Kalinsky commented that RSClin has been helpful in discussions with clinicians on individualizing risk and chemotherapy in breast cancer patients. The anticipation is that final results from the RxPONDER trial will provide compelling evidence for de-escalating chemotherapy in postmenopausal patients and begin to address questions on why the chemotherapy benefit is selective for premenopausal patients.

VII. STRUCTURE AND FUNCTION OF MAMMALIAN SW1/SNF CHROMATIN REMODELING COMPLEXES IN HUMAN CANCER—DR. CIGALL KADOCH

Dr. Cigall Kadoch, Associate Professor of Pediatric Oncology, Dana–Farber Cancer Institute, provided an overview of the mammalian switch/sucrose-nonfermentable (mSWI/SNF) chromatin-remodeling complexes (also called BRG1-associated factors [BAF] complexes) in human cancer. Dr. Kadoch focused her presentation on her Cancer Moonshot℠–funded research project addressing fusion oncoproteins in chromatin-bound protein complexes and related pathways in childhood cancers. In terms of background, sequencing efforts like The Cancer Genome Atlas (TCGA) have revealed that chromatin regulatory processes are frequently mutated in human cancer. Mutations in the ATP-dependent chromatin modeling complexes are common, of which, the mSWI/SNF complexes are the most well studied. It is well known that 29 genes associate with these complexes, resulting in several hundred possible combinations. Dr. Kadoch, and her laboratory, has conducted studies revealing three distinct final forms of mSWI/SNF complexes—canonical BAF (cBAF), polybromo-associated BAF (PBAF), and noncanonical BAF (ncBAF)—with specific subunits in human cells. The mSWI/SNF complexes are mutated in 20 percent of human cancers, and the most frequently mutated across tumor types in TCGA data is the AT-rich interaction domain-containing protein, ARID1A.

Rare cancers driven by mSWI/SNF complex perturbations include such pediatric cancers as synovial sarcoma and pediatric chordoma. Dr. Kadoch noted key themes from the published data about mSWI/SNF complexes: Specific subunits are mutated in specific malignancies; other subunits mutated across a wider range of cancers suggest defining commonalities in terms of function; frequently mutated subunits are not always required for *in vitro* modeling; and mutations can be heterozygous, implicating gene dosage effects. Over the past 5–6 years, Dr. Kadoch and her laboratory have investigated rare diseases driven by the mSWI/SNF complex and its components in loss-of-function studies, identified the

biochemical and modular organization and three-dimensional structure of this complex, used systems biology approaches to identify functional modules, and examined interactions with transcription factors.

Recent efforts have focused on an mSWI/SNF gain-of-function mutation found in 100 percent of synovial sarcomas characterized by the synovial sarcoma (SS)-specific fusion protein, SS18 SSX. Using genomic approaches (e.g., chromatin immunoprecipitation) to determine the global effect of targeting BAF complexes in synovial sarcoma cell lines (e.g., Aska-SS) revealed distinct chromatin sites where SS18-SSX is uniquely located. Further evaluations found that SS18-SSX-bound BAF complexes co-target with polycomb repressive complex 1 (PRC1) more strongly than wild-type (WT)-BAF complexes. The next step was to determine the mechanism associated with site-specific targeting and chromatin interaction properties of SS complexes. A signature 78 amino acid tail appears to be central to these interactions. Dr. Kadoch emphasized that uncovering this mechanism will improve understanding of cancer-specific synthetic lethal dependencies in SS and inform new therapeutic approaches. Using in-house purified SS18-SSX-bound BAF complexes, the Kadoch laboratory found that these complexes bind tightly to chromatin, specifically the histone core octamer and enriching for members of the BAF complex, all relative to WT BAF complexes. Chromatin binding was corroborated in Aska-SS cell lines derived from primary SS tumors containing the SS18-SSX protein.

Additional experiments showed that isolated SSX protein containing the 78 signature amino acids is sufficient to bind nucleosomes and targets repressed chromatin. Further evaluations of the last 34 of the 78 amino acid tail revealed two conserved regions (basic and acidic amino acids) on the SSX C-terminus required for nucleosome binding. Perturbations in the basic region in the 34 amino acids disrupt nucleosome binding. Using Aska SS cell lines, the Kadoch laboratory demonstrated that both conserved regions of SSX are required for oncogenic targeting, which they confirmed using point mutations, arginine (R) 169 alanine (A) and R171A, of the SSX 34 amino acid tail. Dr. Kadoch collaborated with Dr. Thomas William Muir and his laboratory at Princeton University on cross-linking studies to determine the specific SSX binding region. The results reveal direct SSX binding to the nucleosome histone 2A (H2A) glutamic acid (E)56 and H2B E113 in the acidic patch.

Dr. Kadoch and her laboratory next evaluated the role of SWI/SNF-related matrix-associated actin-dependent regulator of chromatin subfamily B member 1 (SMARCB1), an mSWI/SNF gene mutated in SS that disrupts nucleosome binding. TCGA data identified a major hotspot for mutations responsible for nucleosome disruption, which Dr. Kadoch confirmed using structural biology and homology modeling. Further evaluations showed that the SSX-acidic patch interaction displaces the SMARCB1 C-terminus domain (CTD)-acidic patch, suggesting a role in destabilizing SS. In earlier studies, Dr. Kadoch observed strong BAF47 (or SMARCB1) downregulation at the protein level in SS cell lines. Efforts next focused on understanding the process involving SS18-SSX-CTD-bound BAF complexes selectively targeting repressed regions of chromatin. Dependency screen data showed that the main dependencies of SS tumor types are members of the PRC1 family, specifically Ring finger protein 1/2 (or RING1A/B), all showing preferential binding to the H2A ubiquitinated nucleosome. Collectively, these data led Dr. Kadoch to develop a working model of SS18-SSX-containing BAF complexes and their engagement with chromatin.

Questions and Answers

Given the heterogeneity and uneven expression of PRC1 in cells, Dr. Wicha asked whether binding varied by cell differentiation state and whether the complexes work together at the chromatin bivalent mark. Dr. Kadoch explained that PRC1 levels correlate with the level of SS18-SSX-bound BAF complexes, vary in differentiation, and show enrichment at the bivalent mark.

Dr. Barker asked whether the idea is that chromatin remodeling would be unique to a specific cancer or present as pattens that replicate across a number of cancers. Dr. Kadoch called attention to

efforts in TCGA, the Catalogue Of Somatic Mutations In Cancer (COSMIC) and other sequencing databases to define the signatures of deletion and remarked on the opportunity to link structure of mSWI/SNF complexes to human genetics.

In response to a query from Dr. Adamson on the future directions, Dr. Kadoch noted two therapeutic approaches her laboratory plans to investigate: ncBAF degraders in SS and small molecule inhibitors of the SS18-SSX nucleosomes chromatin interaction.

VIII. ONGOING AND NEW BUSINESS—DR. SCOTT W. HIEBERT

Dr. Hiebert invited the Subcommittee Chairs to present their respective reports.

NCAB *ad hoc* Subcommittee on Experimental Therapeutics. Dr. Timothy J. Ley, Professor of Medicine and Genetics, Division of Oncology, Department of Medicine, Washington University School of Medicine in St. Louis, Chair of the NCAB *Ad Hoc* Subcommittee on Experimental Therapeutics, presented the report of the 11 February 2021 meeting. The NCI Director, Dr. Sharpless, attended the meeting. The Subcommittee members met to consider the first two topics to explore: cell-based therapies and smart drug design. Dr. Rosemarie (Rose) Aurigemma of the Division of Cancer Treatment and Diagnosis and Subcommittee Executive Secretary, summarized two recent NCI workshops on cellular therapies, highlighting the opportunities and challenges. Dr. Aurigemma also provided an executive summary, which Dr. Ley noted that the Subcommittee members will need to carefully review prior to making recommendations to the NCI. The group will reconvene and further discuss this topic and draft formal recommendations parallel to the June 2021 Joint BSA and NCAB meeting.

Motion. A motion to accept the report of the 11 February 2021 NCAB *Ad Hoc* Subcommittee on Experimental Therapeutics meeting was approved unanimously.

NCAB Planning and Budget Subcommittee. Dr. Barker, Chair of the NCAB Planning and Budget Subcommittee, presented the report of the 11 February 2021 meeting. The NCI Director, Dr. Sharpless attended the meeting. The Subcommittee discussed the NCI budgets and the timing and uncertainty of the transition between presidential administrations. It was noted that the FY 2021 budget appropriations have continued the trend of steady increases, enabling the NCI to raise funding paylines and implement other initiatives, but the appropriations do not include provisions for costs associated with research losses due to the COVID-19 pandemic. The Subcommittee was provided an overview of the FY 2021 budget—including trends—by Mr. Patrick McGarey, Associate Director for Finance and Legislation, and Subcommittee Executive Secretary. Dr. Barker summarized Mr. McGarey's overview. Dr. Barker conveyed that members shared their input on future budget needs, with discussions calling attention to the effect of COVID-19-related disruptions on new researchers and training. The Subcommittee members remain optimistic about the prospects of the FY 2022 budget and additional COVID-19 funding.

Motion. A motion to accept the report of the 11 February 2021 NCAB Planning and Budget Subcommittee meeting was approved unanimously.

Future Agenda Items. The NCAB members were asked to forward any suggestions for potential future agenda items to Drs. Hiebert and Gray.

Other Items. Dr. Hiebert asked about any remaining topics to discuss.

Dr. Barker recommended formally commending the NCI for the "Nothing Will Stop Us" campaign commemorating the 50th anniversary of the NCA of 1971 and requested a motion to that effect. Dr. Hiebert suggested drafting a formal resolution that the NCAB could approve at the next meeting.

Motion. A motion to commend the NCI for the "Nothing Will Stop Us" campaign commemorating the 50th anniversary of the NCA of 1971 campaign was approved unanimously.

Dr. Ley reflected on the lives and careers of three iconic figures in cancer research who made significant contributions to the NCI and the mission of cancer throughout the country. He expressed the NCAB's condolences on the passing of Dr. Joseph V. Simone, who was known for his discoveries in childhood leukemia therapies; Dr. Emil J. Freireich, who developed groundbreaking therapies for childhood leukemia and was recognized as a founding father of modern clinical cancer research; and Dr. Arthur Nienhuis, gene therapy pioneer.

IX. ADJOURNMENT OF OPEN SESSION—DR. SCOTT W. HIEBERT

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

X. CLOSED SESSION—DR. SCOTT W. HIEBERT

"This portion of the meeting was closed to the public in accordance with the provisions set forth in Sections 552b(c)(4), 552b(c)(6), Title 5 U.S. code, and 10(d) of the Federal Advisory Committee Act, as amended (5 U.S.C. appendix 2)."

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 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 2,587 NCI applications were reviewed requesting direct cost support of $974,866,322 and one FDA application requesting direct cost support of $127,820.

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XI. ADJOURNMENT— DR. SCOTT W. HIEBERT

Dr. Hiebert thanked all the Board members, as well as the visitors and observers, for attending.

There being no further business, the 14th virtual meeting of the NCAB was adjourned at 3:55 p.m. on Thursday, 11 February 2021.

Date	Scott W. Hiebert, Ph.D., Acting Chair, NCAB
Date	Paulette S. Gray, Ph.D., Executive Secretary