

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

**12th JOINT MEETING
of the
BOARD OF SCIENTIFIC ADVISORS AND
NATIONAL CANCER ADVISORY BOARD**

**Summary of Meeting
December 4, 2018**

**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
December 4, 2018**

The Board of Scientific Advisors (BSA) and the National Cancer Advisory Board (NCAB) convened for the 12th Joint Meeting on December 4, 2018, in Conference Room TE406, East Wing, Shady Grove Campus, National Cancer Institute (NCI), National Institutes of Health (NIH), Bethesda, MD. The meeting was open to the public on Tuesday, December 4, 2018, from 9:00 a.m. to 5:42 p.m. and closed to the public Tuesday, December 4, 2018, from 8:00 a.m. to 8:54 a.m. The NCAB Chair, Dr. Elizabeth M. Jaffee, Deputy Director, The Sidney Kimmel Comprehensive Cancer Center, Co-Director, Skip Viragh Center for Pancreas Cancer, The Dana and Albert “Cubby” Broccoli Professor of Oncology, Johns Hopkins University, and BSA Chair, Dr. Dafna Bar-Sagi, Vice Dean for Science, Senior Vice President and Chief Scientific Officer, Professor, Department of Biochemistry and Molecular Pharmacology and Medicine, New York University (NYU) Langone Health, NYU School of Medicine, presided during the open session. Dr. Jaffee presided during the closed session.

BSA Members

Dr. Dafna Bar-Sagi (Chair)
Dr. Kenneth C. Anderson (absent)
Dr. Michael John Becich
Dr. Mary C. Beckerle*
Dr. Melissa L. Bondy
Dr. Otis W. Brawley*
Dr. Graham A. Colditz
Dr. Christopher M. Counter
Dr. Carol E. Ferrans
Dr. Keith T. Flaherty*
Dr. Karen E. Knudsen*
Dr. James V. Lacey
Dr. Michelle M. Le Beau* (absent)
Dr. Sylvia Katina Plevritis
Ms. Diane Zipursky Quale
Dr. W. Kimryn Rathmell*
Dr. Leslie L. Robison*
Dr. Martine F. (Sheer) Roussel
Dr. Robert D. Schreiber (absent)
Dr. Victoria L. Seewaldt
Dr. Kevin M. Shannon (absent)
Dr. Padmanee Sharma* (absent)
Dr. David Sidransky* (absent)
Dr. Alexis A. Thompson* (absent)
Dr. Ian M. Thompson, Jr. (absent)
Dr. David A. Tuveson
Dr. Robert H. Vonderheide* (absent)
Dr. Eileen P. White
Dr. Kevin P. White
Dr. Cheryl L. Willman

*pending appointment

NCAB Members

Dr. Elizabeth M. Jaffee (Chair)
Dr. Peter C. Adamson
Dr. Francis Ali-Osman
Dr. Deborah Watkins Bruner
Dr. Yuan Chang
Dr. David C. Christiani
Dr. Judy E. Garber
Mr. Lawrence O. Gostin
Dr. Scott W. Hiebert (absent)
Dr. Beth Y. Karlan
Dr. Timothy J. Ley
Dr. Electra D. Paskett
Dr. Nancy J. Raab-Traub
Dr. Mack Roach III
Dr. Charles L. Sawyers (absent)
Dr. Margaret R. Spitz
Dr. Max S. Wicha

Alternate Ex Officio NCAB Members

Dr. Robert T. Anderson, DOE (absent)
Dr. Michael A. Babich, CPSC
Dr. Vincent J. Cogliano, EPA (absent)
Dr. Michael Kelley, VA (absent)
Dr. Aubrey Miller, NIEHS
Dr. Richard Pazdur, FDA (absent)
Dr. Craig D. Shriver, DoD
Dr. Kerry Souza, NIOSH (absent)
Dr. Lawrence A. Tabak, NIH (absent)
Dr. Richard J. Thomas, DOL

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. 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 and Interim Director, Center for Global Health
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, Deputy Director, Division of Cancer Biology
Mr. Peter Garrett, Director, Office of Communications and Public Liaison
Dr. Paulette S. Gray, Director, Division of Extramural Activities
Dr. Ed Harlow, Special Advisor to the Director
Dr. Toby T. Hecht, Deputy Director, Division of Cancer Treatment and Diagnosis
Dr. Tony Kerlavage, Acting Director, Center for Biomedical Informatics and Information Technology
Dr. Kristin Komschlies, Acting Director, Office of Scientific Operations, NCI Campus at Frederick
Dr. Barry Kramer, Director, Division of Cancer Prevention
Dr. Douglas R. Lowy, 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. Henry Rodriguez, Acting Associate Director, Center for Strategic Scientific Initiatives
Mr. Jeff Shilling, Acting 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
Dr. Dinah Singer, Acting Deputy Director and Director, Division of Cancer Biology
Dr. Sanya Springfield, Director, Center to Reduce Cancer Health Disparities
Dr. Louis M. Staudt, Director, Center for Cancer Genomics
Dr. Edward L. Trimble, Director, Center for Global Health
Mr. Michael Weingarten, Director, Small Business Innovation Research and Small Business Technology Transfer Programs
Dr. Jonathan Wiest, Director, Center for Cancer Training
Dr. Robert Yarchoan, Director, Office of HIV and AIDS Malignancy
Dr. Maureen Johnson, Executive Secretary, Office of the Director

Liaison Representatives

Ms. Carolyn Aldige, Prevent Cancer Foundation
Dr. Carol Brown, Society of Gynecologic Oncologists
Dr. Margaret Foti, American Association for Cancer Research
Dr. Leo Giambaresi, American Urological Association
Dr. Francis Giardiello, American Gastroenterological Association
Dr. Mary Gullatte, Oncology Nursing Society
Dr. Ruth Hoffman, American Childhood Cancer Organization
Dr. Steven L. Klein, National Science Foundation
Ms. Laura Levit, American Society of Clinical Oncology
Ms. Maria Lopez, Kidney Cancer Association
Dr. W. Marston Linehan, Society of Urologic Oncology
Ms. Margo Michaels, Education Network to Advance Cancer Clinical Trials
Dr. Patricia Mullan, American Association for Cancer Education
Ms. Shelly Fuld Nasso, National Cancer Institute, Council of Research Advocates

Ms. Nancy O'Reilly, American College of Obstetricians and Gynecologists
Ms. Leah Ralph, Association of Community Cancer Centers
Ms. Susan Silver, National Coalition for Cancer Survivorship
Ms. Christy Schmidt, American Cancer Society
Ms. Barbara Duffy Stewart, Association of American Cancer Institutes
Dr. Johannes Vieweg, American Urological Association
Dr. Pamela A. Wilcox, American College of Radiology
COL. (Ret.) James E. Williams, Jr., Intercultural Cancer Council

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TUESDAY, DECEMBER 4, 2018

**I. NATIONAL CANCER ADVISORY BOARD (NCAB) CLOSED SESSION—
DR. ELIZABETH M. JAFFEE**

“This portion of the meeting was closed to the public in accordance with the provisions set forth in Sections 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 intramural site visits 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.

**II. CALL TO ORDER AND OPENING REMARKS—DRS. ELIZABETH M. JAFFEE AND
DAFNA BAR-SAGI**

Dr. Elizabeth Jaffee called to order the 12th Joint Board of Scientific Advisors (BSA) and NCAB meeting and welcomed members of the Boards, *ex officio* 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. Drs. Jaffee and Dafna Bar-Sagi reviewed the confidentiality and conflict-of-interest practices required of Board members in their deliberations.

Motion. A motion to approve the minutes of the August 14, 2018 NCAB meeting was approved unanimously.

**III. FUTURE BOARD MEETING DATES—DRS. ELIZABETH M. JAFFEE AND DAFNA
BAR-SAGI**

Dr. Jaffee called Board members’ attention to future meeting dates listed on the agenda and in the Board book.

IV. NCI DIRECTOR’S REPORT—DR. NORMAN E. SHARPLESS

Dr. Norman E. Sharpless, Director, NCI, welcomed members of both the BSA and NCAB to the 12th joint meeting of these boards. Dr. Sharpless thanked everyone for their willingness to accommodate the last-minute changes to the agenda due to the December 5, 2018, state funeral services for former President George H. W. Bush, a dedicated civil servant, friend to the NIH, and champion for cancer research. Dr. Sharpless provided an update on the budget, notable highlights of fiscal year (FY) 2018, and other NCI activities.

Dr. Sharpless acknowledged members new to the BSA and introduced those present: Dr. Mary C. Beckerle, Jon M. Huntsman Presidential Endowed Chair, Distinguished Professor of Biology, Chief Executive Officer, Huntsman Cancer Institute, Associate Vice President of Cancer Affairs, The University of Utah; Dr. Otis W. Brawley, Chief Medical and Scientific Officer, American Cancer Society, Professor, Department of Hematology and Oncology, Professor, Department of Medicine, School of Medicine, Professor, Department of Epidemiology, Rollins School of Public Health, Emory University; Dr. Keith T. Flaherty, Director, Henri and Belinda Termeer Center for Target Therapy, Director of Clinical Research, Massachusetts General Hospital Cancer Center; Dr. Karen E. Knudsen, Hilary Koprowski Endowed Professor, Chair, Department of Cancer Biology, Director, Sidney Kimmel Cancer Center, Thomas Jefferson University; Dr. W. Kimryn Rathmell, Cornelius A. Craig Professor,

Department of Medicine, Director, Division of Hematology and Oncology, Vanderbilt University Medical Center; and Dr. Leslie L. Robison, Chairman, Department of Epidemiology and Cancer Control, St. Jude Children's Research Hospital, Associate Director, St. Jude Comprehensive Cancer Center. Other new members not present at this meeting will be introduced at a future meeting. Because the new BSA and NCAB members' orientation session had to be postponed, Dr. Sharpless called members' attention to the public meeting forum and its guidelines. The NCI Director welcomed the perspective and scientific opinions of all BSA and NCAB members and looked forward to forthright and valuable discussions.

NCI Budget and Appropriations. Dr. Sharpless reported that the NCI regular appropriations have steadily increased since FY 2015, resulting in an increase in funding to the NCI of more than \$1 billion (B), including the Cancer MoonshotSM appropriations. Dr. Sharpless informed the BSA and NCAB members that the Cancer MoonshotSM appropriation of \$400 million (M) for FY 2019 will be the highest of the \$1.8 B, 7-year funding period for the program. Beginning in FY 2020, the annual allotments will decrease by \$200 M per year. Dr. Sharpless explained that the FY 2019 budget, which was enacted on September 28, 2018, prior to the beginning of FY 2019 on October 1, includes a total increase of \$179 M to the NCI, \$79 M of which is regular appropriations and \$100 M of which is Cancer MoonshotSM funding. This early decision on the budget is allowing NCI a full year to plan and appropriate funds for new and ongoing initiatives.

The strong bipartisan support from Congress for the NIH/NCI and cancer and biomedical research has resulted in several successes. The NCI was able to provide the Research Project Grant (RPG) Pool—which supports investigator-initiated research (e.g., R01s, P01s, R21s)—its largest increase since 2003. The NCI was successful in increasing the number of early stage investigator (ESI) R01s by 25 percent in FY 2018, which aligns with the objectives of the 21st Century Cures Act. In FY 2018, the total new RPG awards had significantly increased over FY 2017. Despite the NCI budget increases and progress made, the FY 2019 appropriation increases are less than FY 2018 increases and less than what is needed to support the expenses of the RPG Pool. In addition, costs are rising for rent and utilities, and mandatory assessments and transfers to the NIH and U.S. Department of Health and Human Services (HHS) are ongoing. Furthermore, increases to National Research Service Award (NRSA) stipends, R01/R21 award sizes, and commitments to non-competing awards in the RPG Pool are budgeted items that also must be considered.

Since FY 2013, the competing (Type 2) R01 applications to the NCI have increased by 50 percent compared to the total NIH R01s, which have increased by only 10 percent. The increase in the applications has led to increases in R01 awards, but not at the same pace. Therefore, the paylines are lower than desired and are expected to be even lower in FY 2019. Factors that have sparked new enthusiasm in cancer research and in grant applications to the NCI are the influx of new scientists and new ideas about cancer, the excitement of the Cancer MoonshotSM, and the influence of the NCI-designated Cancer Centers (Cancer Centers) in recruiting new NCI-supported investigators. This speaks to the success of the NCI Cancer Center Program in providing the infrastructure and necessary environment that is inclusive and supportive of junior faculty.

Dr. Sharpless remarked that the NCI leadership's three guiding principles for FY 2019 budget decisions are (1) preserve the RPG Pool, (2) stay true to the Cancer MoonshotSM vision, and (3) continue to prioritize ESI funding. Dr. Sharpless announced changes to the NCI funding structure and policy for RPG awards for FY 2019. There will be a 5 percent across-the-board reduction in funding for NCI Divisions, Offices, and Centers; operating costs will not be affected. There will be a 3 percent decrease in Non-Competing Continuation (Type 5) awards in the RPG Pool, except for Cancer MoonshotSM grants, Cancer Center Support Grants (CCSGs), and NRSA training awards.

Highlights of the Past Year. Dr. Sharpless called attention to the 2018 *Annual Report to the Nation on the Status of Cancer*—a collaborative effort between the NCI, Centers for Disease Control and Prevention (CDC), American Cancer Society, and the North American Association of Central Cancer Registries—which shows a decline in the incidence and mortality of cancer in the United States from 1999 to 2015. Although this progress is significant for some cancers, including lung and colon cancers, progress has not been distributed evenly across all cancers. For example, the incidence and mortality of obesity-associated cancers are increasing. The NCI is tasked with making progress against all forms of cancer. The NCI released its *Annual Plan and Budget Proposal for Fiscal Year 2020*, which complies with the National Cancer Act and describes the priorities of the NCI 1 fiscal year in advance. A copy of the budget proposal was provided in the Boards' meeting books.

Dr. Sharpless remarked on the advancements in cancer immunotherapy in the intramural and extramural communities. Dr. Steven A. Rosenberg, Center for Cancer Research (CCR), reported on the success of using immunotherapy to treat solid tumors and metastatic breast cancer. Dr. Rosenberg and two other NCI-supported researchers—Dr. James P. Allison, MD Anderson Cancer Center, and Dr. Carl H. June, Abramson Cancer Center—are co-recipients of the 2018 Albany Medical Center Prize in Medicine and Biomedical Research. Dr. Allison also was awarded the 2018 Nobel Prize in Physiology for his milestone achievements in immunotherapy. Results from immunotherapy clinical trials are being reported at a rapid pace primarily due to the success of combination therapies, such as checkpoint inhibitors. The NCI will need to focus efforts on ways to advance these highly research-based therapies to the broader cancer research community.

Dr. Sharpless reported that the NCI Intramural Research Program (IRP) contributed to the FDA approval of moxetumomab, a cluster of differentiation-22 (CD22) receptor inhibitor, for hairy cell leukemia, which reflects decades of work by CCR investigator Dr. Ira Pastan and colleagues. The NCI–National Institute on Aging study Aspirin in Reducing Events in the Elderly (known as ASPREE), which is being conducted in Australia and the United States, revealed that the use of daily doses of aspirin for no prior indication in healthy adults ages 70 years and older resulted in an increase in all-cause mortality without any benefit to cancer prevention or survival. These data align with other studies published in the October 18, 2018 issue of the *New England Journal of Medicine* focusing on this topic and prior NCI studies. NCI is carefully considering its investments in chemo-prevention and targeted trials in high-risk populations.

Dr. Sharpless conveyed NCI's excitement about the FDA approval of larotrectinib, a tropomyosin kinase inhibitor, for pediatric and adult cancers expressing neurotropic receptor kinase gene fusions. Larotrectinib, which was first discovered in the IRP and the Frederick National Laboratory for Cancer Research (FNLCR), is currently a therapy arm in the Adult NCI-Molecular Analysis for Therapy Choice (MATCH) and NCI Children's Oncology Group Pediatric MATCH trials. Dr. Sharpless highlighted NCI's activities at the American Society of Hematology 2018 Annual Meeting. The NCI presented data on chronic lymphocytic leukemia clinical trials, which showed superior progression-free survival and minimal toxicity with chemotherapy-free agents ibrutinib and/or ibrutinib/rituximab.

NCI Ongoing Activities. Dr. Sharpless reported that the NCI is 3 years into the Cancer MoonshotSM initiative, and results from large-scale funding efforts and networks are being reported. The NCAB Blue Ribbon Panel recently was updated on the progress to date. Dr. Sharpless reminded BSA and NCAB members that the appropriation structure of the Cancer MoonshotSM funding is not tied to a specific FY and provides flexibility in managing out-year costs, especially with the variable allotments. Dr. Sharpless called attention to the Specialized Programs of Research Excellence (SPORE) Program Evaluation Working Group Report that recommended the NCI convene thought leaders to discuss specific translational opportunities for the NCI portfolio. In response to the recommendations, two Clinical Trials

and Translational Research Advisory Committee *ad hoc* Working Groups, Glioblastoma and Radiation Oncology, recently have been established.

Dr. Sharpless noted NCI's ongoing recruitment for Directors for the Center for Global Health (CGH), Center for Biomedical Informatics and Information Technology (CBIIT), and Cancer Therapy Evaluation Program (CTEP) and for the Associate Director of the FNLCR. The NCI will soon be recruiting a Division of Cancer Prevention (DCP) Director to replace Dr. Barnett Kramer, who is retiring in January 2019. Dr. Sharpless expressed appreciation to Dr. Kramer for his service, leadership, and vision for cancer prevention.

Questions and Answers

Dr. Nancy J. Raab-Traub, Professor, Department of Microbiology and Immunology, School of Medicine, Lineberger Comprehensive Cancer Center, The University of North Carolina (UNC) at Chapel Hill, wondered how the paylines for other NIH Institutes and Centers (ICs), especially the National Institute of Allergy and Infectious Diseases (NIAID), compare to the NCI. Dr. Sharpless explained that most of the ICs, including NIAID, are experiencing a 10 to 15 percent increase in R01 submissions; the NCI is an outlier by a factor of two. He noted that success rates may be different in the NCI because of the use of select-pay rather than score-based (e.g., paylines) criteria, for a portion of the applications they receive to ensure that innovative science is not overlooked in heavily compressed scoring situations and to maintain a diverse NCI cancer research portfolio that spans disease states.

In response to a query by NCAB Chair Dr. Elizabeth Jaffee on the paylines for ESIs and the effects of funding cuts, Dr. Sharpless replied that the NCI will again prioritize funding for the ESIs in FY 2019 above the FY 2018 levels, which he anticipates will translate into a substantial increase in ESI paylines.

Dr. Knudsen asked whether the policy changes for establishing Cancer Center focus areas could impact the increase in R01 grant submissions. Dr. Sharpless pointed out that most grants are reviewed by the NIH Center for Scientific Review and then are referred to the ICs relevant to the topic area. Abstracts containing the word "cancer" are referred to the NCI. There are no changes to this process that could lead to an increase in applications. Dr. Cheryl L. Willman, The Maurice and Margaret Liberman Distinguished Endowed Chair in Cancer Research, University of New Mexico (UNM) Distinguished Professor of Pathology, UNM School of Medicine, Director and CEO, UNM Comprehensive Cancer Center, UNM, added that the new guidelines have prompted culture changes at the Cancer Centers such that investigators are more apt to apply for NCI funding.

Dr. Robison asked about the plans for extending funding to the ESIs beyond the first and possibly the second R01 renewal. Dr. Sharpless noted NCI's data, which showed that the success rate of an R01 renewal for early but established investigators was the same regardless of the number of times the grant had been renewed. The NCI is extending this priority to investigators meeting the ESI status requirements; the definition of these requirements still is being reviewed by the NIH, and recommendations are forthcoming. Dr. Sharpless also mentioned the NCI use of the Method to Extend Research in Time (MERIT) Award (R37) as a mechanism to increase and extend funding to ESIs, which was implemented in FY 2018 and is expected to continue in FY 2019.

V. PRESIDENT'S CANCER PANEL REPORT—DR. BARBARA K. RIMER

Dr. Barbara K. Rimer, Dean, Gillings School of Global Public Health, Alumni Distinguished Professor of Health Behavior and Health Education, University of North Carolina (UNC) at Chapel Hill, provided an update on the duties and activities of the President's Cancer Panel (Panel), which she chairs.

The BSA and NCAB members were reminded that the Panel, which is authorized by the Public Health Service Act, is required to monitor the development and execution of the activities of the National Cancer Program and report directly to the President of the United States any barriers to the progress of that program. Dr. Rimer explained that the Panel—which until recently consisted of three members, including herself; Mr. Hill Harper, cancer survivor, actor, and philanthropist; and Dr. Owen N. Witte, Clinical Scientist, University of California, Los Angeles—decided to focus efforts on topics that had potential to lead to actionable recommendations and engage NCI leadership, including then-Director Dr. Harold E. Varmus and Deputy Director Dr. Douglas R. Lowy, in the discussions. In its early days, the Panel devoted its time to generating succinct reports that could clearly convey the intended message. Since the 2012 appointments of Drs. Rimer and Witte and Mr. Harper, the Panel’s work has resulted in four Reports to the President, including a report entitled “Accelerating Human Papillomavirus (HPV) Vaccine Uptake: Urgency for Action to Prevent Cancer,” which was released in 2012–2013, and a report entitled “Improving Cancer-Related Outcomes with Connected Health” in 2016. Two other reports were released in 2018 and were discussed later in the presentation. Dr. Rimer credits the NCI, especially Division, Office, and Center directors and NCI leadership, in helping the Panel develop high-quality reports.

The Panel’s first 2018 report to the President, “Promoting Value, Affordability and Innovation in Cancer Drug Treatment,” was released in March 2018. This report was motivated by the fact that drug costs are a burden for many cancer patients and can contribute to financial toxicity—the harmful effects of care costs on patients’ well-being, which can affect patients’ quality of life, interfere with the delivery of quality care, and even can affect survival. While patients are expressing a desire to discuss the costs of cancer drugs and care with their doctors, barely more than a quarter of cancer patients report having these discussions. In its report, the Panel recommended promoting value-based pricing and use; enabling communication about treatment, options, and cost; minimizing the contributions of drug costs to financial toxicity; stimulating generic and biosimilar markets; ensuring adequate resources for the FDA; and investing in biomedical research. Dr. Rimer summarized the key conclusions. Rising cancer drug costs are a significant problem that cannot be ignored because the consequences to patients, families, and society are too great. Today and beyond, affordable access to drugs will be the difference between life and death for cancer patients. There are three principles that should guide actions moving forward. First, cancer drug prices should be aligned with the value to patients. Second, all patients should have affordable access to appropriate cancer drugs. Third, investments in science are essential to drive future innovation.

The Panel’s second 2018 report to the President, “HPV Vaccination for Cancer Prevention: Progress, Opportunities, and a Renewed Call to Action,” was released in November 2018. This report revisits the message of the 2012–2013 HPV report by examining the current landscape of HPV cancers and HPV vaccination and identifying strategies for building on recent progress and overcoming persistent barriers to vaccine uptake. Dr. Rimer acknowledged the report’s many contributors, including vaccine experts Drs. Lowy, NCI, and Noel Brewer, UNC at Chapel Hill, and additional representatives from the ACS, CDC, HHS, and NCI. Since the initial Panel report on HPV vaccination, there have been changes to the 3-dose vaccine regimen based on new research and approval of the vaccine for expanded age ranges. In 2016, the CDC Advisory Committee on Immunization Practices recommended a 2-dose schedule with the 9-valent HPV vaccine for adolescents who initiate the vaccine series before 15 years of age. Very recently, the FDA approved the 9-valent HPV vaccine for adults up to age 45 years.

HPV-associated cancers are more prevalent worldwide than in the United States. Although cervical cancer is the predominant HPV-associated cancer worldwide, incidences of other HPV-associated cancers are increasing. Reports on HPV vaccine uptake among U.S. adolescents ages 13–17 from 2006 to 2017 show that on average, the percentage of adolescents who started the regimen increased by 5 percentage points each year and was more pronounced in males compared to females. Geographical

differences in vaccine uptake vary by state. The reasons for these differences are not well understood, and are more complex than simply comparing urban and rural areas.

Dr. Rimer detailed the continuing challenges of U.S. HPV vaccine uptake and reviewed the goals and opportunities to increase uptake and the progress to date. HPV vaccination coverage in the United States remains lower than that of other adolescent vaccines and lower than in other countries. The HPV vaccine uptake rate varies across the United States and coverage differs by state; the lowest level of uptake is in Mississippi, at 29 percent, and the District of Columbia has the highest uptake at 78 percent. In its 2012–2013 report, the Panel concluded that the underuse of HPV vaccines was a serious but correctable threat and outlined goals to improve uptake. The 2018 report confirms these goals are still relevant and describes priorities and strategies to achieve these goals. The key conclusions were that provider and systems-level changes hold the greatest potential to increase U.S. HPV vaccination rates, and partnerships and collaborations are essential. The 2018 renewed call to action recognizes the progress and momentum built over the past 5 years to increase HPV vaccine uptake further and reduce the burden of HPV-associated cancers. Broadly, cancer and immunization stakeholders worldwide must renew their collective commitment to achieving HPV vaccination targets. In closing, Dr. Rimer expressed appreciation for the NCI, Panel staff, and contractors for their support. As her term ended, she encouraged the new Panel to consider adopting the necessary practices to ensure reports continue to remain meaningful.

Questions and Answers

Dr. Sharpless, BSA, and NCAB members expressed appreciation for Dr. Rimer and the outgoing Panel for their efforts.

In response to a query by Dr. Willman on the low frequency of HPV-associated cancers in the United States compared to frequencies worldwide and whether the lack of screening could be a factor, Dr. Lowy called attention to the recent workshop hosted by the NCI Division of Cancer Epidemiology and Genetics that addressed this question. He speculated that the regions assessed have low incidences of oropharyngeal cancer; the reason why is unclear, and the trajectory remains to be seen. The data sources for low- to middle-income countries are not as robust as those from high-income countries, and measuring prevalence at one point in time for HPV-associated cancer is less informative than a study that measures outcomes over time.

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, asked whether the CDC recommendations on including HPV vaccinations in the requirements for school entry for youth had been considered. Dr. Rimer agreed that having the HPV vaccination integrated into the school vaccination program would have significant impact, although parents could choose not to participate (i.e., opt out) and there would be other, numerous challenges to implementation. The Panel's updated 2018 HPV report has reframed the emphasis to vaccination for cancer prevention rather than focusing on sexual behavior.

Dr. Jaffee asked about the status of educating pediatricians and increasing pharmacy access. Dr. Rimer replied that the CDC has addressed HPV vaccination as routine health care through initiatives and funding sources, refined the language used, and made recommendations to the pediatricians and other physicians. Discussions on pharmacy regulations and access, which are governed by the individual states, are ongoing.

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, added that a prescription is required for the vaccination. A change in the cultural authoritative model (e.g., norms) suggesting that HPV vaccination is just addressing the incidences and mortality of cervical cancer is necessary. Discussions at the national level are needed because the precancerous occurrences are significant. The NCI could consider whether a report to the President is the best option to convey the truth about HPV vaccination and cancer. Dr. Rimer commented that HPV-associated cervical cancer is preventable and prevention is within the United States' expertise and control.

Dr. Beth Y. Karlan, Director, Women's Cancer Program, Samuel Oschin Comprehensive Cancer Institute, Director of Gynecologic Oncology, Department of Obstetrics and Gynecology, Cedars-Sinai Medical Center, and Professor, Obstetrics and Gynecology, David Geffen School of Medicine, University of California, Los Angeles, wondered whether the Panel had considered efforts to address legislation for school entry requirements at the state level as one way to address pharmacy requirements. Dr. Rimer emphasized the limitations of the Panel and its staff to address aspects of any recommendations and suggested that various cancer groups (e.g., American Society of Clinical Oncology [ASCO]) could consider addressing this issue in the future.

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

Ms. M. K. Holohan, Director, Office of Government and Congressional Relations (OGCR), reported on the 2018 midterm elections and committee changes, budget and appropriations, congressional hearings and visits, and other legislation of interest. She called attention to the detailed legislative report contained in the Board meeting book. Ms. Holohan pointed out that historically, a sitting President's party loses seats during midterm elections, almost always in the House and often in the Senate. In the 2018 midterms, the Democratic (D) party regained the House after 8 years in the minority. In the Senate, the Republicans (R) increased their majority. Ms. Holohan announced the anticipated Appropriations Committee changes in the House of the 116th Congress. Representative Nita Lowey of New York is expected to become Chair of the House Appropriations Committee, with Representative Kay Granger of Texas as the ranking member. Representative Rosa DeLauro of Connecticut is expected to become Chair of House Appropriations Subcommittee on Labor, Health and Human Services, and Education (Labor-HHS), and Representative Tom Cole of Oklahoma is expected to become the ranking member of the subcommittee.

Congressional appropriators packaged the FY 2019 Defense and FY 2019 Labor-HHS spending bills, and this package was passed by Congress and signed into law on September 28, 2018. The Labor-HHS bill includes a \$2 B increase for the NIH, a \$79.3 M increase for the NCI, and \$400 M for the Cancer MoonshotSM. Of the 12 FY 2019 appropriations bills, five had passed and signed into law as of December 4, 2018, leaving seven still in progress. The five enacted bills together fund 75 percent of the government. The unfunded agencies began operating under a continuing resolution (CR) set to expire on December 7, 2018, with plans to extend the CR to December 21, 2018.

Regarding budget caps and the debt ceiling, the debt ceiling will be reinstated in March 2019, and the budget caps will return in October 2019. Congress will need to decide on a \$50 B reduction in overall allocation, government-wide, or pass legislation to extend the deadlines.

Dr. Sharpless joined Dr. Francis S. Collins, Director, NIH; Dr. Stephanie Devaney, Deputy Director, *All of Us*SM Research Program; and Dr. Scott Gottlieb, Commissioner, FDA, to testify at the House Energy and Commerce Subcommittee on Health hearing on July 25, 2018. Implementation of the 21st Century Cures Act at the NIH and the FDA was discussed. Dr. Sharpless also joined Dr. Collins and other IC Directors to testify at the Senate Health, Education, Labor and Pensions hearing on August 28, 2018, to discuss the topic "Prioritizing Cures: Science and Stewardship at the NIH."

Ms. Holohan provided an update on congressional visits. On September 25, 2018, Kansas Representative Kevin Yoder (R) visited the NCI Pediatric Oncology Branch, CCR. On September 26, 2018, Dr. Sharpless visited with North Carolina Representative G. K. Butterfield (D).

Ms. Holohan noted other legislation of interest to the NCI. The Research to Accelerate Cures and Equality (RACE) for Children Act was signed into law in August 2017. The FDA—after consulting with the NCI and soliciting input from other stakeholders—recently released lists of molecular targets that are relevant and non-relevant to pediatric cancer. The NCI will continue to work with the FDA on updates. The Childhood Cancer Survivorship, Treatment, Access and Research (STAR) Act, which specifies further research efforts in pediatric cancer survivorship and biospecimen collection, was signed into law in June 2018. Implementation planning is underway at the NCI.

VII. GENETIC SUSCEPTIBILITY TO PROSTATE CANCER IN MEN OF AFRICAN ANCESTRY—DRS. ROBERT CROYLE AND CHRISTOPHER HAIMAN

Dr. Robert Croyle, Director, Division of Cancer Control and Population Sciences (DCCPS), and Interim Director, Center for Global Health (CGH), remarked on the Cancer MoonshotSM investments and efforts to address cancer disparities, especially disparities related to African American men and prostate cancer mortality compared to white American men. He noted that this presentation is one example of a project by a Cancer MoonshotSM-funded researcher who is investigating prostate cancer disparities.

Dr. Christopher Haiman, Professor of Preventative Medicine, American Family Life Assurance Company (AFLAC) Chair in Cancer Research, University of Southern California (USC) Cancer Center, scientific lead of the African Ancestry Prostate Cancer (AAPC) Consortium, discussed his research on the genetic susceptibility to prostate cancer in men of African ancestry. Dr. Haiman noted that this research is supported by many NIH ICs, including the NCI and the National Human Genome Research Institute (NHGRI), and large consortia, including the AAPC, the NHGRI Gene Environment Association Studies (GENEVA), and the NCI Genetic Associations and Mechanisms in Oncology (GAME-ON). Per the NCI Surveillance, Epidemiology, and End Results (SEER) data, the incidences of prostate cancer are 70 percent higher in African American men compared to other populations, and African American men are twice as likely to die from prostate cancer compared to those in other populations. Factors likely contributing to these prostate cancer disparities include sociodemographics, risk factors (e.g., age or family history), access to care, and variations in screening, detection, and treatment. However, few established risk factors can be attributed to these increased incidences of prostate cancer, and whether genetics are a factor remains unknown.

To address this question, Dr. Haiman and colleagues investigated the genetic ancestry of prostate cancer. The 2006 admixture mapping studies led by Drs. David Reich and Matthew L. Friedman at Harvard Medical School identified risk alleles that correlate with local genetic ancestry in an admixed population. Further investigation of an admixture scan of 1,600 African American men from the Multiethnic Cohort (MEC) study revealed that the 8q24 locus associates with increased susceptibility to prostate cancer. Dense genotyping studies identified multiple risk alleles at the 8q24 locus that contribute to the prostate cancer risk, and in the broader MEC, seven independent risk alleles in three regions also were identified. These findings provided the first evidence of germline variation contributing to prostate cancer risk. In-depth studies to determine the importance of the 8q24 region of the human genome across multiple racial and ethnic populations showed a striking disparity in frequency and incidences in populations of African ancestry. These observations led to the development of a polygenic risk model for prostate cancer that considers the frequency and size of the effect. Data from the International Genome Sample Resource (IGSR) 1000 Genomes Project showed a twofold difference in the population attributable risk distributions in African Americans compared to white populations. The next logical step would be to determine whether other variants in the genome contributed to racial and ethnic differences in

prostate cancer risk, and these data provided the justification to support such a larger initiative and additional studies.

In 2007, the USC-led AAPC was established to broadly address genetic variants in prostate cancer. It primarily includes U.S. studies, but Africa, Canada, the Caribbean, France, and the United Kingdom (UK) also are participating. To date, there are 10,000 prostate cancer cases and 10,000 control cases in the AAPC. Results of a genome-wide association study (GWAS) of the AAPC confirmed the prior data on the frequency of prostate cancer risk alleles in the 8q24 region and also revealed a noncoding variant within this region that has a 6 percent frequency distinct to the African ancestry populations. In assessing the risk estimates and allele frequency for carriers, data showed that 11 percent of men harbored one variant (i.e., heterozygous), which is associated with a twofold increase in prostate cancer risk (e.g., relative risk [RR]) and close to 3 percent RR in men with a family history of prostate cancer. Men harboring two variants (i.e., homozygous), which is rare, had a fivefold RR that approaches eightfold in men with a family history of the disease.

To put things in perspective, Dr. Haiman pointed out that the most well-established, high penetrance variant in prostate cancer—homeobox protein (HOX) B13 missense mutation—has a low frequency in white populations in the United States, is associated with a threefold increase in risk among cases unselected for family history, and is estimated to account for 5 percent of hereditary prostate cancers. Although the 8q24 variant has similar RR depending on the genotype, it is 30 percent more common in the population and is likely to be a strong contributor to the RR of prostate cancer compared to HOXB13 variants. Studies investigating the RR in families are planned. Dr. Haiman observed that the top signals identified across the genome in the AAPC GWAS were the population-specific risk alleles in men of African ancestry, specifically on chromosomes 13, 17, and 22. The allele frequencies ranged from 2 to 5 percent and were associated with a RR of 1.6 percent per allele. These data suggest that 10 percent of men of African ancestry are carriers, which increases their risk by 60 percent compared to other men in the U.S. population. These observations on 8q24 and population-specific alleles highlight the importance of conducting genetic studies in ancestry-diverse populations.

The majority of GWAS studies in cancer have been conducted in primarily European ancestry populations and have identified more than 700 cancer loci. Of the 700 loci identified, 85 percent were first discovered in white populations, 19 percent in East Asian populations, and 4 percent in multiethnic populations, including African and Latin American populations. The genetic susceptibility of prostate cancer determined from GWAS of efforts of the UK's Institute of Cancer Research Prostate Cancer Association Group to Investigate Cancer-Associated Alterations in the Genome (PRACTICAL), Elucidating Loci Involved in Prostate Cancer Susceptibility (ELLIPSE), and GAME-ON consortia, consisting of a combined 130 studies globally, also were conducted primarily in European ancestry populations. The recent GAME-ON study investigating the association analyses of 140,000 men identified 63 new prostate cancer susceptibility loci. To date, 181 common prostate cancer risk variants have been discovered, 80 percent from GWAS in European ancestry populations, accounting for a 37 percent estimation of familial risk of prostate cancer. The polygenic risk score (PRS) for the 181 risk variants calculated using the polygenic risk model for prostate cancer identified the top 25 percent of men who have a twofold or higher increase in RR and the top 10 percent who have a fourfold or higher RR.

An important public health question of interest to the cancer epidemiology and genetics community is whether a PRS generated from one population is predictive of elevated prostate cancer risk in other populations. Dr. Haiman summarized prostate cancer PRS data stratified by population using the 181 risk variants. The top 10 percent of men of Asian, African, and Latino ancestry who have a threefold or higher increased risk of prostate cancer were identified using the weighted PRS, but the transferability across these populations was incomplete compared to the European population. These data speak to the need for large-scale comprehensive studies investigating germline mutations in minority populations. To

address the initial question on whether genetic factors, in general, contribute to the population differences in prostate cancer risk, Dr. Haiman explained that although the earlier studies of the 14 8q24 variants suggest population-based genetic differences between African and European ancestries, the 181 variants identified in recent GWAS and fine mapping studies in men of European ancestry did not show a similar difference. An equivalent and optimal set of variants for men of African ancestry is yet to be identified.

Dr. Haiman described the ongoing efforts to improve the prediction of PRS across populations. Multiethnic studies combining GWAS data across populations to identify stronger signals in known regions and novel variants that leverage existing prostate cancer consortia (e.g., PRACTCAL/ELLIPSE and AAPC) are in progress. Preliminary results revealed 60 new risk variants from 240,000 prostate cases. Approximately 90 percent of the 181 known variants have been replaced and PRS calculations across populations will be updated. Because the common risk variants and PRS are unable to discriminate between risk for aggressive versus non-aggressive disease, the clinical utility of GWAS-PRS will need to be evaluated. Prostate cancer screening studies that incorporate PRS are ongoing in the UK and Sweden and are specifically designed to detect aggressive disease in high genetic risk groups.

Dr. Haiman emphasized the need for genetic markers of aggressive disease, which would improve the utility of the PRS. Reports of the rare pathogenic mutations in DNA repair genes suggest an association to aggressive prostate cancer. Using a similar 16-gene panel, AAPC investigators evaluated the rare coding variants and prostate cancer risk in men of African ancestry. An African American subset of the MEC study and an ongoing AAPC Ugandan case control study were evaluated, and results showed mutations in 4 percent of prostate cancer cases. Four genes—*BRCA2*, *ATM*, *PALB2*, and *NBN*—accounted for a RR of threefold and higher and the effects were more pronounced in aggressive phenotypes. Data on metastatic disease were limited in these cohorts, but 32 percent of the Uganda cases were annotated with prostate-specific antigen (PSA) data. Metastatic disease was found in 5 percent of the Ugandan cases based on PSA values greater than 100 ng/mL, which associated with a fifteenfold RR in *BRCA2* and *ATM*. These data are consistent with prior reports, and efforts have been expanded to investigate rare variants in aggressive prostate cancer in 20,000 cases of European ancestry using whole exome sequencing. The number of metastatic prostate cancer cases of African ancestry is too limited to support this type of study.

Dr. Haiman provided an overview of the Research on Prostate Cancer in Men of African Ancestry—Defining the Roles of Genetics, Tumor Markers, and Social Stress study (commonly called RESPOND). The goal is to recruit 10,000 African American men with prostate cancer over a 5-year period, collect baseline survey data and tumor samples, and address key scientific questions on genetic susceptibility using GWAS and exome sequencing (Project 1), social factors that contribute to lifetime stress (Project 2), and tumor-related features (Project 3). A multidisciplinary team of investigators, including epidemiologists and oncologists, with proven track records in population-based and clinical prostate cancer and health disparities research comprise the RESPOND team. The study will recruit patients through SEER and the National Program of Cancer Registries across seven states representing approximately 40 percent of African American men in the United States. Focus groups consisting of seven to 10 African American prostate cancer patients at each recruitment site reviewed study materials and address questions on building trust for recruiting patients. Patient responses currently are being incorporated into the study recruitment materials and enrollment is expected to begin early 2019.

Questions and Answers

Dr. Deborah Watkins Bruner, Robert W. Woodruff Chair of Nursing, Nell Hodgson Woodruff School of Nursing, Associate, Director for Outcomes Research, Winship Cancer Institute, Emory University, noted that data from a recent meta-analysis reported by Dr. Daniel Spratt, University of Michigan, at the 2018 ASCO Annual Meeting showed that African American men with advanced prostate

cancer respond better to radiation therapy and asked about the treatment response in these studies. Dr. Mack Roach III, Professor of Radiation Oncology and Urology, Director, Particle Therapy Research Program and Outreach, Department of Radiation Oncology, University of California, San Francisco, Helen Diller Family Comprehensive Cancer Center, who is familiar with the study, observed that in patients treated in prospective Phase III randomized controlled clinical trials (RCTs), race and ethnicity predominates as an independent prognostic factor. Dr. Roach remarked that Dr. Haiman's research is addressing the important question of why the incidence of prostate cancer presents earlier in African American men compared to other races, which is separate from the RCTs that are addressing treatment-related questions. Dr. Roach also emphasized that differences in the polymorphisms in African American men compared to white men do not necessarily correlate to treatment outcomes, which the Roach laboratory has shown in studies of the antigen receptor marker cytochrome P450 3A4. Better understanding of disease incidence is key to addressing the question of prostate cancer disparity in African American men.

In response to a query by Dr. Willman on the type of patient samples collected in the RESPOND study given that patients are enrolled through the SEER registries, Dr. Haiman replied that saliva and formalin-fixed paraffin-embedded tissue samples are being collected. Preliminary experiments were performed to confirm that mutation profiling could be done successfully in biopsy samples. Dr. Willman commended the use of epidemiologic behavioral survey data in this research, which is becoming a common practice, and noted the importance of standardizing these types of data across studies and in other cancers.

Dr. Margaret Spitz, Professor, Department of Medicine, Dan L. Duncan Cancer Center, Baylor College of Medicine, asked about efforts to stratify patients using Gleason Scores in the range of 7 or less and stages 3–4, which remain treatment challenges. Dr. Haiman explained that the genetic susceptibility studies are focused on aggressive disease with high Gleason Scores of 8 to 10 and stages 3–4. Any biomarkers identified for this disease state will be checked against those of the lower Gleason Scores.

Dr. Flaherty commended the success of Dr. Haiman and his cancer disparity research and wondered what the broader cancer research community could do to replicate this success and accelerate new advances and similar genetic associations for the Cancer MoonshotSM. Dr. Haiman commented that the collaborative network has been effective in integrating data from studies led by individual investigators to address multiple research questions.

Dr. Sylvia Katina Plevritis, Professor, Department of Radiology and Biomedical Data Science, Co-Chief, Integrative Biomedical Engineering Informatics at Stanford, Stanford University School of Medicine, asked about efforts to discriminate between aggressive and non-aggressive forms of the disease and to characterize the functionality of the genetic variants relative to Gleason Scores. Dr. Haiman explained that genetic variants associated with aggressive disease have been identified and that only the truncated protein mutations are pathogenic. Many of the variants identified have unknown significance. Research to better understand the biological mechanisms associated with risk is robust and ongoing. Use of newer gene editing methodology, such as clustered regularly interspaced short palindromic repeats (CRISPR), to study the functionality of prostate genetic variants is becoming common practice.

Dr. Roach commented on the challenge ahead to determine the treatment and follow-up for any aggressive phenotypes identified because the SEER registries are the data source. The genetic variants will need to be validated using data from patients who have been systematically diagnosed and successfully treated. Leveraging the National Surgical Adjuvant Breast and Bowel Project, the Radiation Therapy Oncology Group, and the Gynecologic Oncology Group database (commonly known as NRG Oncology database) would be one place to start. Dr. Haiman agreed and noted that such validations are being planned for the next phase of the RESPOND study.

Dr. Rathmell remarked on the need for increased hereditary risk testing in patients' families for germline mutations associated with metastatic prostate cancer, especially for primary family members. Dr. Rathmell also suggested including environmental risk factors in the RESPOND studies and leveraging the existing resources, including the NIH *All of Us* Research Program.

VIII. FDA CENTER FOR TOBACCO PRODUCTS—UPDATE ON COMPREHENSIVE PLAN FOR TOBACCO AND NICOTINE REGULATION—DR. ROBERT CROYLE AND MR. MITCHELL ZELLER

Mr. Mitchell Zeller, Director, Center for Tobacco Products, FDA, provided an update on FDA's comprehensive plan for tobacco and nicotine regulation. The FDA gained regulatory authority over tobacco products with the passing of the Tobacco Control Act on June 22, 2009. This act also permitted the FDA to classify products as meeting the statutory definition of a tobacco product by issuing a regulation. On August 8, 2016, FDA issued a final regulation that deems all products meeting the statutory definition of a tobacco product, including components or parts, subject to FDA's jurisdiction, including electronic nicotine delivery systems (ENDS), all cigars, pipe tobacco, nicotine gels, waterpipes, dissolvables not currently under FDA's jurisdiction, and future tobacco products.

Mr. Zeller outlined the various regulatory authorities that the FDA uses to regulate tobacco products under the Tobacco Control Act. He noted that FDA's standard on tobacco product regulation is different from the safe and effective standard used to regulate medical drugs and devices. A public health tobacco standard considers the effects on users and non-users of tobacco products and assesses the net population-level health effects of these products. The FDA must assess net public health impacts at a population-level when it regulates tobacco products. The authorities that are granted to the FDA for the regulation of tobacco are similar to regulatory authorities given to the FDA to review drugs and devices. However, the authorities are used to reduce harm to the general population in the case of tobacco products.

The FDA uses its authorities to regulate tobacco products; understand the regulated products through pre-market review and post-market surveillance; review proposed modified risk products that imply reduced exposure risk before they can be marketed; restrict marketing and distribution to protect public health; ensure industry compliance with FDA regulations through education, inspections, and enforcement actions; and expand the science base for regulatory action and evaluation. The FDA has an extensive collaboration with the NCI to expand the science base for regulatory purposes.

Mr. Zeller summarized the ways in which the FDA is expanding the scientific knowledge necessary to support the FDA tobacco product regulation. The FDA funds research that then is administered by the NIH Tobacco Regulatory Science Program, including investigator-initiated awards, supplements to existing grants or cooperative agreements, Tobacco Centers of Regulatory Science, and the Population Assessment of Tobacco and Health (PATH) study. Other efforts include support for national surveys (e.g., National Youth Tobacco Survey [NYTS]) and laboratory analyses.

The FDA has developed a comprehensive regulatory plan aimed to advance the FDA vision of cigarettes that no longer create or sustain addiction and alternative and less harmful nicotine sources for adults who seek it. The plan has several thrusts of action that will address the problem by regulatory policies on addiction, appeal, and cessation; a Youth Tobacco Prevention Plan; and a science-based review of potential modified-risk tobacco products. To support the comprehensive plan's regulatory initiatives, the FDA recently issued three advance notices of proposed rulemaking for public comment: (1) the Tobacco Standard for Nicotine Level of Combusted Cigarettes on March 15, 2018; (2) the

Regulation of Flavors in Tobacco Products on 20 March 2018; and (3) the Regulation of Premium Cigars on 23 March 2018.

One of the main concerns of the Youth Tobacco Prevention Plan is the popularity of tobacco products that resemble a USB flash drive, have high levels of nicotine, and have emissions that are hard to detect. Some of these products are sold by JUUL Labs, Inc., but other similar products also are emerging. The above characteristics of these products may make them attractive for use by youth. Enforcement actions have been taken to support the youth access provisions of the Youth Tobacco Prevention Plan for this high-nicotine product. These actions included warning letters to retailers selling these products to minors, working with e-bay to remove existing listings and prevent new listings for JUUL products, and sending letters to JUUL and similar companies requiring documents on manufacturing, toxicology, behavioral, and physiological aspects of these products. Warning letters also were sent to manufacturers, distributors, and retailers for selling e-liquids (used in e-cigarettes) that resemble such “kid-friendly” food items as juice boxes, candy, or cookies.

Mr. Zeller outlined the most recent FDA policy framework regarding the sale of flavored tobacco products. Flavored ENDS products—with the exception of tobacco, mint, and menthol flavors—and non-flavored products must be sold at an age-restricted in-person location or sold online with heightened age verification processes. The FDA also intends to ban menthol-flavored combustible products, including cigars and cigarettes. The new policy framework was formed in response to the dramatic increases in e-cigarette usage by high school and middle school students reported in the 2018 NYTS and the ongoing popularity of all flavored tobacco products with young people.

As part of the Youth Tobacco Prevention Plan, the FDA has expanded its Real Cost Youth Prevention Campaign to include youth 12–17 years of age who are e-cigarette users or likely open to trying them. The advertisements combine a loss of control message with a healthy consequences message. The advertisements will run online and will be in posters placed in location-targeted areas in 10,000 high schools.

Questions and Answers

Dr. Peter C. Adamson, Chair, Children’s Oncology Group, Alan R. Cohen Endowed Chair in Pediatrics, The Children’s Hospital of Philadelphia, University of Pennsylvania, asked about efforts to educate Congress on the magnitude of the problem of regulation of tobacco products. Mr. Zeller stated that several lawsuits have been filed by tobacco companies in response to the FDA’s final deeming rule of 2016. FDA policy-making must be supported and informed by the science done on the topic(s) for regulation.

In response to a query by Dr. Gostin on FDA’s timetable for nicotine reduction in cigarettes and the rationale for the FDA’s proposed rule on mint- and menthol-flavored tobacco products, Mr. Zeller replied that the public comment period for the proposed nicotine reduction policy closed in July 2018. All comments must be reviewed individually. Although a timetable for the promulgation of this rule has not yet been finalized, it is a high priority for the FDA. Because mint and menthol in tobacco products are popular with adults, the FDA believed that banning mint and menthol flavored ENDS products could encourage purchase of flavored combustible tobacco products.

Dr. David A. Tuveson, Roy J. Zuckerberg Professor, Director of the Cancer Center, Cold Spring Harbor Laboratory, asked about the FDA’s position on regulating marijuana as a recreational-used substance. Mr. Zeller pointed out that because the use of recreational marijuana is illegal nationally, the FDA has no jurisdiction in its regulation. Conversely, medical marijuana is considered to be a drug, and

FDA has regulatory authority over marijuana used for this purpose. The FDA shares a larger societal concern that e-cigarette equipment can be used for smoking marijuana.

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, asked about the tobacco industry supporting investigators to conduct research about the safety of ENDS products. Mr. Zeller explained that tobacco companies are engaging investigators to conduct research needed to support pre-market applications for new tobacco products. A controversy exists among researchers regarding their acceptance of tobacco industry research funds; there are researchers on both sides of this issue.

IX. ONGOING AND NEW BUSINESS—DRS. ELIZABETH M. JAFFEE AND DAFNA BAR-SAGI

NCAB *ad hoc* Subcommittee on Global Cancer Research. Dr. Francis Ali-Osman, Margaret Harris and David Silverman Distinguished Professor of Neuro-Oncology Research, Professor of Surgery, Professor of Pathology, Department of Surgery and Pathology, Duke University Medical Center and Chair of the NCAB *ad hoc* Global Cancer Research Subcommittee, presented the report of the December 3, 2018 Subcommittee meeting. Dr. Ali-Osman informed the Subcommittee that the *ad hoc* Working Group on Global Health (Working Group) presented its final report and key recommendations to the NCAB at the August 14, 2018 NCAB virtual meeting, the recording of which can be accessed from the NCI website. He also reminded attendees that establishment of the Working Group, which is charged with advising on the vision, accomplishments, and operations of the CGH, is an early initiative of NCI Director Dr. Sharpless and conveys his and NCI's commitment to a strong global oncology program.

The Subcommittee was updated by Dr. Croyle, Interim Director, and CGH staff on activities and ongoing efforts. Dr. Croyle detailed the CGH/NCI's efforts to address the Working Group recommendations and noted the overall goals. The Subcommittee discussed the recent survey results of the Cancer Centers' global health activities, CGH-supported training mechanisms, and the Affordable Cancer Technologies Program. The Subcommittee also discussed CGH's approach to having separate administrative, research, and health diplomacy activities, which the NCI leadership has endorsed. This division in services will allow the CGH to focus some of its core efforts on the challenges related to conducting international research, such as data collection, sharing, and accessibility, as well as the European Union's new General Data Protection Regulation. The Subcommittee emphasized to the NCI the importance of having the appropriate legal and policy expertise and infrastructure to guide global oncology research initiatives. Dr. Sharpless updated the Subcommittee on the search for a new CGH Director, which the NCI anticipates completing mid-2019.

Motion. A motion to accept the report of the December 3, 2018 NCAB *ad hoc* Global Cancer Research Subcommittee meeting was approved unanimously.

Other Business. Dr. Jaffee called attention to the current Annual BSA Concept Report and archived report that can be accessed via the Advisory Board members-only website. The BSA and NCAB members were asked to forward any suggestions for potential future agenda items to Drs. Gray, Jaffee, or Bar-Sagi.

X. PHYSICAL SCIENCES—ONCOLOGY NETWORK (PS-ON)—DRS. NASTARAN ZAHIR, CLAUDIA FISCHBACH-TESCHL, FRANZISKA MICHOR, AND JANN N. SARKARIA

Dr. Nastaran Zahir, Program Director, Structural Biology and Molecular Applications Branch, Division of Cancer Biology (DCB), provided an overview of the PS-ON program. In 2008, the NCI held a series of community-driven think tank meetings to explore the integration of transdisciplinary research approaches from physical science, mathematics, and engineering into cancer research. In 2009, with assistance from the extramural community, the NCI began an initiative to integrate nontraditional physical science approaches, including computational methodology, into cancer biology. The goal is to foster transdisciplinary research and environments that integrate physical science perspectives and methodology into cancer research. The current scientific themes are physical dynamics, spatial-temporal organization, and evolutionary dynamics.

The PS-ON program's initial phase started in 2009 and lasted until the second phase began in 2015. In this second phase (PS-ON II), 10 U54 centers and 10 U01 projects are funded. Dr. Zahir introduced three PS-ON U54 investigators who presented their research highlights: Dr. Claudia Fischbach-Teschl, Professor, Nancy E. and Peter C. Meinig School of Biomedical Engineering, Director, Cornell Center on the Physics of Cancer Metabolism, Cornell University; Dr. Franziska Michor, Professor of Computational Biology, Department of Biostatistics and Computational Biology, Dana-Farber Cancer Institute; and Dr. Jann N. Sarkaria, Radiation Oncologist, Translational Neuro-Oncology Laboratory, Mayo Clinic.

Cornell Center on the Physics of Cancer Metabolism (PSOC). Dr. Fischbach-Teschl described cancer cell metabolism as the major research focus of the PSOC, which employs engineering approaches and tissue engineering techniques to develop three-dimensional (3D) tumor models that mimic tissue properties. The 3D models are made by combining synthetic and natural biomaterials with microfabrication and microfluidic approaches to devise biomimetic tumor microenvironments for *in vitro* study. The PSOC has three major projects focusing on the effect of the tumor microenvironment on cancer cell metabolism, how tumor microenvironment-induced changes modulate microvesicle and exosome biogenesis, and how the microenvironmental changes affect tumor cell migration and invasion.

The first project has examined the effect of obesity on the microenvironment in which a tumor grows. It was shown that obesity itself, without tumor cells present, induced microenvironmental changes similar to tumor growth. Obesity promotes fibrotic remodeling and mechanical differences in the microenvironmental breast tissue. Tumor cells respond to the obesity-induced changes, increasing their growth and pathways leading to increased mechano-transduction. This has been shown in engineered tumor models and confirmed in patient tissue samples. In addition to increased obesity-induced markers, there was increase in Nanog⁺ cells. Cancer stem cells (CSCs), which are associated with poorer outcomes, express the Nanog marker. It was hypothesized that obesity-induced microenvironmental changes could enhance the numbers of CSCs in a tumor. Obese matrix models increased the incidence of CSCs. Obese adipose stromal cells and tumor cells injected into mice increased the fibrotic remodeling and stemness of the tumors in these mice. Nanog expression and tumor invasiveness also increased.

The project studying cancer cell migration has shown that cancer cells migrating through narrow pores in the engineered 3D models have chromosomal instability and formation of micronuclei in the cells. Rupture of the micronuclei in the cytosol activates the pathway for cyclic GMP-AMP Synthase (cGas)-Stimulator of Interferon Genes (STING) and this promotes tumor invasiveness. Dr. Fischbach-Teschl indicated that future plans for 3D tumor models include integration into a precision medicine program at Cornell's Sandra and Edward Meyer Cancer Center.

Optimal Drug/Radiation Administration Schedules to Delay Resistance. Dr. Michor described the areas of research in the Dana-Farber Physical Sciences Oncology Center as focusing on breast cancer, brain cancer, and leukemia. Dr. Michor outlined research that combined computational evolutionary biology modeling with a mouse model of glioblastoma multiforme (GBM) to optimize the response to radiation. The microenvironmental localization of different GBM cell populations and their response to radiation schedules using differing dosing and timing were studied. Mathematical modeling of the GBM cell response to the radiation treatments was conducted. Both CSCs and differentiated GBM populations were mathematically modeled. A total of 10 Gray (Gy) of radiation fractions (i.e., one fraction is 1 Gy) delivered over 1 week was found to optimize the survival of mice. The slower proliferating, radioresistant CSC population in the mouse model was enriched with this treatment. This result aligns with the result of human clinical trials in which treatment of GBM patients with 60 Gy and adjuvant temozolomide increased CSC enrichment and patient survival times. A pilot clinical trial using patients with refractory GBM testing 35 Gy in 10 fractions against a standard schedule of 28 Gy in seven fractions is in progress.

Dr. Michor discussed another area being examined that involves determining the dose of radiation that is most efficacious when used in conjunction with temozolomide. A mathematical, stochastic model incorporating the parameters of irradiated areas of the GBM tumor, diffusion characteristics of temozolomide within a GBM tumor, and different types of GBM cells is being used to predict the most efficacious radiation dose and schedule. A prediction of 10 Gy given over 1 week already has been validated in a mouse model. Future directions for this modeling approach include clinical trials examining the use of nonstandard radiation schedules alone and in combination with chemotherapy regimens and modeling for other types of therapy (e.g., radiation sensitizers and/or immunotherapy) and other cancer types.

Multi-modal Analysis of Distribution and Efficacy of Epidermal Growth Factor Receptor (EGFR)-Targeted Therapies in GBM. Dr. Sarkaria stated the goal of the Massachusetts Institute of Technology/Mayo Physical Sciences Center for Drug Distribution and Efficacy in Brain Tumors is to conduct multi-modal analysis of drug distribution impacts on GBM from the level of the whole patient or animal model to the subcellular level. Given the enabling capability to image a tumor using magnetic resonance imaging (MRI) and knowing the physicochemical properties of the drug, a prediction could be made whether a small molecule or an antibody-drug conjugate (ADC) would provide the most benefit. Dr. Sarkaria explained that GBM is essentially incurable, and his group hypothesizes that a major reason for its refractoriness against therapy is drug delivery. Most drugs are not very penetrable to the brain, and superimposing brain images of tumor distribution and drug distribution shows that drug concentration would be lower in the normal brain with diffuse tumor cells while the only appreciable drug concentrations would be in the contrast-enhancing region with the greatest density of tumor cells and vascular disruption. A high brain penetrant drug would show higher drug levels in normal brains with richer vasculature and lower but still significant drug concentration levels in the contrast-enhanced region with increased vasculature disruption.

The EGFR inhibitor erlotinib was used as a model system for measuring drug distribution in a GBM mouse model. Matrix-assisted laser desorption ionization-mass spectrometry imaging/MRI was used to image drug distribution in flank and intracranial GBM tumors. MRI imaging shows a normal brain area with the lowest erlotinib level, a T2 penumbra region with an intermediate level of erlotinib, and the contrast-enhanced core region with the highest erlotinib levels. Erlotinib has very heterogeneous distribution in intracranial tumors. Heterogeneous delivery of erlotinib can drive the biology of GBM tumors, as shown by EGFR signaling in the ultra-low dose of drug in flank tumors and intracranial tumors. Erlotinib, although useful as a model system, has limited value as a treatment for GBM. The delivery characteristics of other drug candidates also are being studied. The efficacy of ADCs can be enhanced with increasing disruption of the blood-brain barrier in mouse models. Dr. Sarkaria remarked

that radiomics predictors of genomics and drug distribution/tumor imaging studies hold promise in the possible treatment of GBM in humans.

Questions and Answers

Dr. Bruner asked about the neurotoxicity and cognitive effects of using this radiation dose schedule. Dr. Michor explained that the radiation dose administered was the biologically equivalent dose (BED) of the standard dose delivered. Establishing a radiation schedule not predicted to be worse than the BED was included in the optimization process, which has been validated in this mouse model.

In response to a comment by Dr. Wicha on the CSC enrichment approach using cells thought to be responsible for treatment failure and drug or radioresistance, Dr. Michor pointed out that the goal of this treatment is to prolong survival because no cure for GBM currently exists. She emphasized that the mathematical model for predicting radiation dose and timing for other tumor cell types would have to use parameters for the specific type of tumor cell being studied.

Dr. Roach asked about efforts to validate the model for predicting responses using clinical material. Dr. Michor explained that access to patient samples still is being addressed in this research project and that partial validation of the model has been completed using a retrospective review of clinical trial data.

XI. RFA/COOP. AGR. CONCEPTS—NEW—NCI STAFF

Division of Cancer Biology (DCB)

Cellular Cancer Biology Imaging Research (CCBIR) Resource Program (New RFA)— Dr. Michael Espey

Dr. Michael Espey, Associate Director, Cancer Cell Biology Branch, DCB, presented a concept to establish the CCBIR resource program. In April 2018, the NCI and the American Society for Cell Biology co-sponsored the Strategic Workshop on Imaging Subcellular to Cellular Cancer Biology to examine the state of the science and strategically network the cancer and cell biology communities. Feedback from the workshop indicated that cancer biology lags behind other fields in leveraging advanced cellular imaging tools. Two underlying reasons are that imaging cancer biology often requires specialized modifications to systems designed to study normal biology and technology development and that discovery-based cellular imaging does not do well in cancer peer review.

Dr. Espey explained that existing NCI programs that might be scalable (e.g., molecular, cellular, or tumor) and have advanced imaging components, including the Innovative Molecular Analysis Technologies Program (IMAT) and Small Business Innovation Research (SBIR) programs, are not imaging-specific and do not focus on a specific scale. The CCBIR resource program would fill this gap and unify across the spectrum of scale of basic cancer biology processes and derive the best elements of advanced imaging, cancer biology, and technology development. The goals are twofold. One is to establish resource centers that facilitate development and use of advanced imaging technologies at the subcellular to cellular scale to address basic science research questions. The second is to foster a sustainable collaborative community between cellular imaging technology developers and basic cancer biology researchers across the NCI portfolio. The RFA will support establishing CCBIR centers consisting of three components: cellular-scaled imaging technology development, community engagement that includes pilot projects and training, and a research test bed that includes wet laboratory analyses.

Subcommittee Review. Dr. Christopher M. Counter, Professor, Department of Pharmacology and Cancer Biology, Duke University School of Medicine, expressed the Subcommittee's strong enthusiasm in support of the concept, which is relevant to understanding the fundamental principles of cancer cell communication. Dr. Counter remarked on NCI's use of the UM1 funding mechanism for this concept to address the cancer continuum through imaging that spans from the subcellular to the patient level. The Subcommittee suggested that the central theme of the RFA should primarily focus on cancer rather than imaging. The NCI should consider using a score-based review of applications, providing applicants adequate time (e.g., 6 months) between the initial request and proposal submission, establishing two dates of receipt, and developing clear measures for the CCBIR centers that match the enabling capabilities of that center.

The first-year cost is estimated at \$12 M for four UM1 awards, with a total cost of \$60 M for 5 years.

Questions and Answers

Dr. Willman suggested investigating whether it would be feasible to establish regional high-capacity state-of-the-art cancer imaging centers that would engage the NCI investigators and the broader cancer research community.

Dr. James V. Lacey, Jr., Director and Professor, Division of Cancer Etiology, Department of Population Sciences, Beckman Research Institute, City of Hope, suggested identifying, in the long term, ways that the CCBIR centers could be integrated with the NCI Imaging Data Commons.

Motion. A motion to concur on the DCB's one-time issuance RFA entitled "Cellular Cancer Biology Imaging Research (CCBIR) Resource Program" was approved with 15 ayes, 1 nay, and no abstentions, with the stipulation that the central theme of the RFA be cancer biology-focused.

Division of Cancer Treatment and Diagnosis (DCTD)

Molecular and Biological Effects of High Linear Energy Transfer (High LET) Radiation Exposure (New RFA)—Dr. Jeffrey Buchsbaum

Dr. Jeffrey Buchsbaum, Medical Officer, Clinical Radiation Oncology Branch, DCTD, presented a concept on the molecular and biological effects of high LET radiation exposure, a joint DCB-DCTD proposal. There are many aspects of high LET radiation that are relevant to oncology, including the high relative biological effectiveness, therapeutic advantage in some cases, increased DNA damaging effects to cancer cells, and precise targeting of tumors. Currently in the United States, only systemic radionuclide therapy is available.

Recent interest in high LET radiation in therapy (targeted and systemic) is growing rapidly. However, the infrastructure for clinical particle therapy centers is costly, and the justification for developing these centers has to be based on firm scientific evidence of their utility. There are two barriers to using high LET radiation therapy in the United States: 1) of the 11 active clinical sites (i.e., specialized external beam facilities) - four are in Europe and seven are in Asia; and, 2) none are located in the United States. Additionally, there is a lack of understanding of how human cancer cells respond to therapeutic high LET.

This RFA will support projects that investigate the molecular and biological effects of high LET radiation in cancer, including the chemistry of high LET damage to DNA and the DNA damage repair response and the impact of high LET radiation on tumor versus normal tissues. Proposals must show

relevance to cancer therapy and include study of particles between helium and carbon on the periodic table of elements.

Subcommittee Review. Dr. Plevritis expressed the Subcommittee's support of the concept. The Subcommittee suggested leveraging existing resources for conducting definitive phases of the mechanistic studies, including use of tumor biopsy samples from patients who currently are enrolled in clinical trials at the 11 clinical sites.

The first-year cost is estimated at \$3.84 M for five R01 awards and two R21 awards, with a total cost of \$31.65 M for 5 years.

Questions and Answers

Dr. Willman wondered about the commitment from the active clinical sites and interest from international collaborators in supporting this research. Dr. Roach commented that international investigators who are experts in particle beam radiation at the clinical sites are enthusiastic about collaborating with their U.S. counterparts. Joint U.S.-international meetings on this topic already are occurring.

Motion. A motion to concur on the DCTD's one-time issuance RFA entitled "Molecular and Biological Effects of High Linear Energy Transfer (High LET) Radiation Exposure" was approved unanimously.

Office of the Director (OD)

Informatics Technology for Cancer Research (ITCR) (New RFA/Coop. Agr.)—Dr. Juli Klemm

Dr. Juli Klemm, Acting Branch Chief, Cancer Informatics Branch, CBIIT, presented a concept on new funding mechanisms for the ITCR, a program that began in 2012 to fill an important gap in connecting related NCI initiatives. The ITCR, a trans-NCI program, supports investigator-initiated informatics technology development responsive to critical needs in cancer research. The software and tools developed are user-friendly and open-source and have been broadly disseminated. Since its inception and renewal, the program has had several accomplishments. These include the support of broad development of informatics technology resources that span the cancer research continuum, training for NCI intramural scientists, and outreach. Dr. Klemm emphasized that the ITCR resources comprise some of the most widely used software tools in cancer research, and she highlighted three of those tools: Clinical Interpretations of Variants in Cancer (CIVIC), Tools to Analyze Morphology and Spatially-Mapped Molecular Data, and Trinity Cancer Transcriptome Analysis Toolkit (commonly called Trinity-CTAT). The ITCR promotes collaboration and outreach among its investigators, and these collaborations are supported by set-aside funds and administrative supplements. Further details on ITCR tools can be accessed from the NCI website.

A 2018 evaluation of the ITCR by the Institute for Defense Analyses (IDA) Science and Technology Policy Institute concluded that informatics technology remains a pressing need in the cancer research community and that the program, although successful, will need enhancements to further its impact and influence. The IDA evaluators (i.e., external expert panel reviewers) recommended additional outreach for ITCR-developed tools and establishment of new funding mechanisms to foster collaborations between ITCR tool developers and cancer researchers. Proposed recommendations from the evaluation have informed the latest modifications to the program.

The RFA will support a set-aside budget to promote continuity of the ITCR program, incentivize applications in cancer research not currently supported by the program, support competitive revisions, and establish an ITCR Training and Outreach Coordination Center.

Subcommittee Review. Dr. Michael John Becich, Chairman and Distinguished University Professor, Department of Biomedical Informatics, Professor of Pathology, Information Sciences, Telecommunications and Clinical/Translational Sciences, Associate Vice Chancellor for Informatics in the Health Sciences, Director, Center for Commercial Application of Healthcare Data, Associate Director for Cancer Institute, Associate Director, Clinical and Translational Science Institute, University of Pittsburgh School of Medicine, expressed the Subcommittee's support of the concept. Dr. Becich remarked that the ITCR promotes the use of informatics tools and has made a significant impact in the cancer research community. Dr. Becich and the Subcommittee suggested that doubling NCI investments to support future enhancements to the ITCR program should be considered.

The first-year cost is estimated at \$11 M for six R21 awards, five U01 awards, and seven U24 awards, with a total cost of \$55 M for 5 years.

Motion. A motion to concur on the OD's one-time issuance RFA/Coop. Agr. entitled "Informatics Technology for Cancer Research (ITCR)" was approved unanimously.

Division of Cancer Control and Population Sciences (DCCPS)

Optimizing Management and Outcomes for Cancer Survivors Transitioning to Follow-Up Care (New RFA)—Dr. Michelle Mollica

Dr. Michelle Mollica, Program Director, Outcomes Research Branch, DCCPS, presented a concept on optimizing management and outcomes for cancer survivors transitioning to follow-up care. In its 2005 report entitled "Cancer Patient to Cancer Survivor: Lost in Transition," the Institute of Medicine (IOM) (now the National Academy of Medicine [NAM]) pointed to the transition period immediately following active treatment as critical for cancer survivors. Research in cancer survivors and survivorship demonstrate that this transition period is a challenging time for patients, which also is observed clinically. The IOM/NAM report called for comprehensive post-treatment survivorship care after active treatment consisting of three components: prevention/surveillance of recurrence and new cancers, surveillance/management of cancer effects and treatment, and health promotion/preventative care.

Dr. Mollica pointed out that an existing, widely used model of post-treatment survivorship care involving oncology team leads follows patients for prolonged periods of time, but is not appropriate for all survivors, is not sustainable to support survivorship growth, and does not provide relief to the overburdened oncology workforce. Stakeholders, including ASCO and the Oncology Nursing Society, recommend a model of team-based continuing care that promotes cross-specialty provider collaboration. Two examples include a multidisciplinary survivorship clinic model and a shared care model. The multidisciplinary model is most beneficial to high-risk survivors and is likely to exist in high-resource settings. The shared care model, a partnership between the cancer survivor, oncology team, and primary care specialists, is considered optimal and is beneficial to low-risk survivors (e.g., early stage diagnosis). The shared care model also has been endorsed by many stakeholders, but is challenging to implement in terms of clear responsibilities, communication, and ongoing updates on treatment.

This RFA will support the development and testing of new and innovative models of survivorship care delivery and interventional research to enhance communication, engagement, and coordination between oncology specialists and providers.

Subcommittee Review. Dr. Carol E. Ferrans, Professor and Associate Dean for Research, Director, University of Illinois Chicago (UIC) Center of Excellence in Eliminating Health Disparities, Department of Biobehavioral Health Sciences, College of Nursing, UIC, expressed the Subcommittee’s enthusiasm and strong support of the concept, which addresses a critically important gap—improving cancer survivorship care. Dr. Ferrans commended the NCI for supporting investigator-initiated research to improve cancer survivorship care. The Subcommittee emphasized addressing diversity regarding populations and access to care in the RFA.

The first-year cost is estimated at \$5 M for six R01 awards, with a total cost of \$25 M for 5 years.

Questions and Answers

Dr. Adamson questioned the decision to exclude adolescents from the RFA and constrain applications to adult interventions. Dr. Mollica explained that the NCI discussed including adolescents and young adults (AYAs) in the RFA. Because the transition for AYAs differs from that of adults and has its own set of challenges, the NCI decided to focus these current efforts on adult survivorship. The NCI could consider new funding opportunities in the future that specifically address AYA cancer survivors transitioning to follow-up care. Dr. Mollica called attention to the proposed RFA addressing the Survivorship Treatment, Access, and Research (STAR) Act implementation that will be presented later in the meeting and focuses on some of these aspects.

Dr. Lacey sought clarity on whether the evaluation would be based on implementation and/or results. Dr. Mollica clarified that funded projects will be evaluated based on how they address the process rather than implementation, which would be too preliminary to assess in this RFA.

Dr. Willman suggested revisiting the RFA’s proposed budget to ensure that the scope of work can be supported adequately.

Motion. A motion to concur on the DCCPS one-time issuance RFA entitled “Optimizing Management and Outcomes for Cancer Survivors Transitioning to Follow-Up Care” was approved unanimously.

Research on Pediatric, Adolescent, and Young Adult Cancer Survivorship Through the Childhood Cancer Survivorship, Treatment, Access and Research (STAR) Act (New RFA)—Dr. Danielle Dae

Dr. Danielle Dae, Program Director, Genomic Epidemiology Branch, DCCPS, presented a concept for research in pediatric and AYA survivorship in response to the childhood cancer STAR Act. She noted that the RFA title has been changed to “Improving Outcomes for Pediatric, Adolescent, and Young Adult Cancer Survivors.” In the 2018 STAR Act, Congress strongly encouraged efforts to advance pediatric and AYA research and authorized improvements in four domains - one of which is the focus of this RFA, i.e., research to improve the care of and quality of life for survivors. Efforts to support the other domains are being addressed in parallel across the NCI.

Dr. Dae highlighted two key observations that suggest the need for additional resources in this area. First, there has been great success in cancer treatment in recent years, the population of survivors is growing, and more than 85 percent of childhood cancer survivors are expected to survive beyond 5 years. Similar results have been observed in AYAs. However, disparities remain. Per SEER data on the 5-year relative survival of the age 0–19 category, the percent survival is consistently lower in African American populations compared to white populations. There are an estimated 630,000 cancer survivors ages 0–39 in the United States. Second, survivors have significantly more chronic health conditions per person than

community controls, according to data from the Childhood Cancer Survivorship and St. Jude Lifetime cohorts. In addition, observational research studies reveal that AYA cancer survivors are confronted with a variety of issues in their survivorship involving health care delivery and behavioral, physical, and psychosocial adverse effects. This research will leverage prior NCI investments in observational studies in pediatric and AYA cancer survivor projects.

The RFA, which aligns with the six key research areas of the STAR Act, will support the development, testing, and/or scaling of innovative, feasible, and effective interventions to address adverse physical and psychosocial effects in survivors of pediatric and/or AYA cancers. Dr. Dae explained that the proposals should include proximal endpoints and that a clinical trial is required.

Subcommittee Review. Dr. Robison expressed the Subcommittee’s strong support of the concept. Dr. Robison stated that the Subcommittee appreciates NCI staff responses to their requests on biospecimens, budget, and follow-up.

The first-year cost for the NCI is estimated at \$4.8 M for six to eight U01 awards, with a total cost of \$24 M for 5 years.

Questions and Answers

The BSA and NCAB members lauded NCI’s efforts to quickly implement the STAR Act.

Motion. A motion to concur on the DCCPS’ one-time issuance RFA entitled “Research on Pediatric, Adolescent, and Young Adult Cancer Survivorship Through the Childhood Cancer Survivorship, Treatment, Access and Research (STAR) Act” was approved unanimously.

XII. RFA/COOP. AGR. CANCER MOONSHOTSM CONCEPTS—NEW—NCI STAFF

Office of the Director (OD)

Advancing Cancer Immunotherapy by Mitigating Immune-Related Adverse Events (irAEs) (New RFA)—Dr. Susan McCarthy

Dr. Susan McCarthy, Program Director, Cancer Immunology, Hematology and Etiology Branch, DCB, presented a concept on advancing cancer immunotherapy by mitigating irAEs, a trans-NIH effort supported by the NCI and four other ICs: National Institute of Allergy and Infectious Diseases (NIAID), the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS), the National Institute of Dental and Craniofacial Research (NIDCR), and the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK). Dr. McCarthy explained that immunotherapy is unsuccessful for many reasons and can be attributed to the various tumor escape mechanisms resulting in three distinct tumor immune microenvironments: immune-desert tumor (e.g., cold tumor), immune-filtrated tumor (e.g., hot tumor), and immune-excluded tumor. Approaches to overcome immunosuppression include the use of vaccines, adoptive cell therapy, checkpoint blockade, and non-specific immune activation. Each approach is likely associated with its own set of irAEs. The goal of this concept is to support research that improves cancer immunotherapies by eliminating or reducing the incidence or severity of adverse event responses while maintaining tumor efficacy. This research will leverage existing Cancer MoonshotSM immunotherapy initiatives and support new Cancer MoonshotSM immunotherapy networks when they begin. The RFA will support developing experimental models, technologies, and computational analyses capable of advancing research on mitigating irAEs.

Subcommittee Review. Dr. Jaffee expressed the Subcommittee’s support of the concept. The Subcommittee recommended including language in the RFA to specifically indicate that applications should be focused on mitigating immune-related adverse events and not on developing new cancer immunotherapies.

The first-year cost for the NCI is estimated at \$3 M for eight U01 awards, with a total cost of \$15 M for 5 years.

Motion. A motion to concur on the OD’s one-time issuance RFA entitled “Advancing Cancer Immunotherapy by Mitigating Immune-Related Adverse Events (irAEs)” was approved unanimously.

Patient Engagement for Priority Cancer Sequencing (PE4PC-Seq) (New RFA/Coop. Agr.)—Dr. Leah Mechanic

Dr. Leah Mechanic, Program Director, Genomic Epidemiology Branch, DCCPS, presented a concept on patient engagement for priority cancer sequencing. Direct patient engagement in the context of this concept involves research teams interacting directly with patients (via the internet, social media, and online patient communities) not through health care providers or the clinical care setting. Patient input will be incorporated during the research process through surveys, interviews, and regular communication (e.g., consent forms and return on research results). The goals of the RFA are to generate a comprehensive genomic landscape of cancers that currently are poorly characterized, address research gaps in pediatric and adult cancers using an innovative direct volunteer approach, and optimize direct patient engagement approaches to inform NCI activities.

Dr. Mechanic emphasized that although large-scale genomic characterization efforts such as The Cancer Genome Atlas (TCGA) have been successful, research gaps remain. For example, only 14 percent of tumors in TCGA reflect minority populations and only 3 percent are representative of the Hispanic or Latino population. Existing direct patient engagement models such as internet-based protocols to collect clinical information would complement the approach of this concept and have been successful. The RFA will support cooperative agreement to address the research gap in molecular profiles in cancer using direct patient engagement strategies. Each project grant will focus on a single cancer subset and must support three integrated pilot projects and cores.

Subcommittee Review. Dr. Lacey expressed the Subcommittee’s enthusiasm and strong support of the concept. Dr. Lacey stated that the Subcommittee appreciates the NCI staff responses to their requests on refining the RFA scope and structure.

The first-year cost for the NCI is estimated at \$10 M for four U19 awards and \$2.5 M for one U24 award, with a total cost of \$52.5 M for 5 years.

Questions and Answers

Dr. Willman suggested exploring recent advances in sequencing methodologies, such as enhanced whole exome sequencing, for use in molecular characterizations.

Dr. Paskett commented that the RFA language should be clear to convey that the effectiveness of patient engagement is not the central focus.

Motion. A motion to concur on the DCCPS’ one-time issuance RFA/Coop. Agr. entitled “Patient Engagement for Priority Cancer Sequencing (PE4PC-Seq)” was approved unanimously.

**Technologies Development for Use in Next Generation Cancer Models (New RFA/Coop. Agr.)—
Dr. Daniela Gerhard**

Dr. Daniela Gerhard, Director, Office of Cancer Genomics, presented a concept on technologies development for use in experiments in next generation cancer models (NGCMs) to accelerate understanding of cancer and facilitate the transition to individualized therapy strategies (i.e., precision medicine). Dr. Gerhard noted that the concept, which leverages the NCI Human Cancer Models Initiative (HCMI), now includes a precision medicine component that is reflected in the modified title. The RFA goal is to address the urgent need for robust methods and reagents for high-throughput genetic and chemical screens. The outcome will accelerate the knowledge of cancer initiation, progression, metastasis, and resistance and educate the cancer research community on use of the models and resources to accurately predict treatment success in patients.

Prior NCI investments in projects, including TCGA, Therapeutically Applicable Research to Generate Effective Treatments (TARGET), Institute for Cancer Genomics and Informatics (ICGI), and Cancer Genome Characterization Initiative (CGCI) have focused on whole genome sequencing and molecular characterizations of tumor types and have informed the development of relevant cancer models. Additional resources will be necessary to accelerate functional genomics (e.g., RNAi, CRISPR, small molecules, and mutant open reading frames) to better understand essential cancer pathways. The RFA will support establishing technology centers to develop new tools, reagents, and analyses that will be used for experiments in NGCM.

Subcommittee Review. Dr. Tuveson expressed the Subcommittee's support of the concept, which aims to resolve some of the limitations in generating NGCMs that accurately recapitulate the human disease. Dr. Tuveson remarked on the time and cost to generate faithful models and commented that the Subcommittee's recommendation to expand the scope of the RFA to include a precision component is a strength. The Subcommittee expressed concern that the intent is unclear—whether the goal is to develop a methodology or standardize model development processes—and recommended clarifying the specific focus of work in the RFA.

The first-year cost for the NCI is estimated at \$3.3 M for three U01 awards and \$0.7 M for the development contract, with a total cost of \$12 M for 3 years.

Questions and Answers

Dr. Wicha commented on the need to identify methods that will be used for clinical validations of the NGCMs, which this RFA may not be able to support based on the current scope.

Dr. Victoria L. Seewaldt, Ruth Zeigler Professor, Chair, Department of Population Sciences, Beckman Research Institute, City of Hope, asked about the percentage of NGCMs that reflect minority populations. Dr. Gerhard pointed out that the goal is to have 20 to 30 percent representation from pediatric and underrepresented minority populations in the NGCMs.

Dr. Timothy J. Ley, Professor of Medicine and Genetics, Division of Oncology, Department of Medicine, Washington University School of Medicine in St. Louis, wondered about accurately determining the genetic composition of tumors and noted that aligning with the NCI Patient-Derived Models Repository (PDMR) would be essential. Dr. Ley also suggested focusing the RFA on a single purpose. Dr. Tuveson explained that the objective is to leverage the resources of the HCMI, which contains well-vetted and sequenced primary tumors and conditionally reprogrammed organoids that have cleared quality assurance and control procedures.

Dr. Flaherty emphasized that precision medicine applications usually are accompanied by the development of a Clinical Laboratory Improvement Amendments-approved assay and involve retrospective analyses and wondered whether these would be a focus of this RFA. He also suggested that the RFA language is specific regarding the precision medicine aspect of the applications. Dr. Gerhard explained that the RFA is a technology proposal that is focused on using NGCMs to better interpret high-throughput genetic and chemical screens and to better understand disease progression to metastasis.

Dr. Willman commented on the value of the resources this concept will enable, which will be essential to the cancer research community. She recommended refining the RFA scope to be less broad and diffuse.

Dr. Gray clarified that the motion is to approve the concept. If the concept is not approved, then the floor would be open to the Subcommittee chair to make a second motion.

Motion. A motion to concur on the OD’s RFA/Coop. Agr./Request for Proposal entitled “Technologies Development for Use in Next Generation Cancer Models” was not approved with 2 ayes, 14 nays, and no abstentions.

Motion. A motion to defer on the OD’s RFA/Coop. Agr./Request for Proposal entitled “Technologies Development for Use in Next Generation Cancer Models” was approved with 15 ayes, 1 nay, and no abstentions.

XIII. ADJOURNMENT—DRS. ELIZABETH M. JAFFEE AND DAFNA BAR-SAGI

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

There being no further business, the 12th joint meeting of the BSA/NCAB was adjourned at 5:42 p.m. on Tuesday, December 4, 2018.

_____	_____
Date	Elizabeth M. Jaffee, M.D., Chair, NCAB
_____	_____
Date	Dafna Bar-Sagi, Ph.D., Chair, BSA
_____	_____
Date	Paulette S. Gray, Ph.D., Executive Secretary