DEPARTMENT OF HEALTH AND HUMAN SERVICES
NATIONAL INSTITUTES OF HEALTH
NATIONAL CANCER INSTITUTE
37th CLINICAL TRIALS AND TRANSLATIONAL RESEARCH ADVISORY COMMITTEE (CTAC) MEETING

Summary of Meeting
November 7, 2018

Building 31 C, Conference Room 10
National Institutes of Health
Bethesda, MD

CLINICAL TRIALS AND TRANSLATIONAL RESEARCH ADVISORY COMMITTEE
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The 37th meeting of the Clinical Trials and Translational Research Advisory Committee (CTAC) of the National Cancer Institute (NCI) was held Wednesday, November 7, 2018, at 9:02 a.m. The CTAC acting chair, Dr. Patrick J. Loehrer, Sr., presided.[1] The meeting was adjourned at 2:31 p.m.

Chair
Patrick J. Loehrer, Sr.

CTAC Members
David F. Arons
Debra L. Barton
Walter J. Curran, Jr.
Janet Ellen Dancey
Nancy E. Davidson (absent)
Timothy J. Eberlein
Howard J. Fingert
David M. Gershenson (absent)
Paul A. Godley
Anne-Marie R. Langevin
Michael L. LeBlanc
David A. Mankoff
Lynn M. Matrisian
Neal J. Meropol (absent)
Roman Perez-Soler
Gloria M. Petersen
Augusto C. Ochoa
Steven T. Rosen
Dan Theodorescu

***Ex Officio* Members**
William L. Dahut, NCI
James H. Doroshow, NCI
Paulette S. Gray, NCI
Michael J. Kelley, U.S. Department of Veterans Affairs (absent)
Anthony Kerlavage, NCI
Richard Pazdur, U.S. Food and Drug Administration (absent)
Katherine Szarama, Centers for Medicare & Medicaid Services

Executive Secretary
Sheila A. Prindiville, NCI

Presenters
James Abbruzzese, MD, FACP, FASCO, Duke Cancer Institute Distinguished Professor of Medical Oncology; Chief, Division of Medical Oncology, Department of Medicine; Associate Director for Clinical Research, Duke Cancer Institute, Duke University Medical Center
James Doroshow, MD, Deputy Director, Clinical and Translational Research; Director, Division of Cancer Treatment and Diagnosis (DCTD), NCI
Janet Eary, MD, Deputy Associate Director; Acting Branch Chief, Imaging Technology Development Branch, Cancer Imaging Program, DCTD, NCI
Holly Gibbons, Deputy Director, Office of Government and Congressional Relations, Office of the Director, NCI
Ernest Hawk, MD, MPH, Vice President and Division Head, Division of Cancer Prevention and Population Sciences; Boone Pickens Distinguished Chair for Early Prevention of Cancer, University of Texas MD Anderson Cancer Center
Barry Kramer, MD, MPH, Director, Division of Cancer Prevention (DCP), NCI
Patrick Loehrer, Sr., MD, Director, Indiana University Melvin and Bren Simon Cancer Center; Associate Dean for Cancer Research, Indiana University School of Medicine

[1]A roster of CTAC members and their affiliations is included as an appendix.

Worta McCaskill-Stevens, MD, MS, Chief, Community Oncology and Prevention Trials Research Group; Director, NCI Community Oncology Research Program, DCP, NCI
Gisele Sarosy, MD, Medical Officer, Coordinating Center for Clinical Trials, Office of the Director, NCI
Norman Sharpless, MD, Director, NCI
Eva Szabo, MD, Chief, Lung and Upper Aerodigestive Cancer Research Group, DCP, NCI
Ian Thompson, Jr., MD, President, CHRISTUS Santa Rosa Hospital – Medical Center, University of Texas Health Science Center at San Antonio
Joseph Unger, PhD, Member, Fred Hutchinson Cancer Research Center, University of Washington

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I. Call to Order and Opening Remarks

Patrick J. Loehrer, Sr., MD

Dr. Loehrer called the 37th meeting of CTAC to order and welcomed participants.

Dr. Loehrer reviewed the confidentiality and conflict-of-interest practices required of CTAC members during their deliberations. He invited members of the public to send written comments on issues discussed during the meeting to Dr. Prindiville within 10 days of the meeting. National Institutes of Health (NIH) Events Management was videocasting the meeting, and the videocast would be available for viewing following the meeting at http://videocast.nih.gov.

Motion. A motion to accept the minutes of the 36th CTAC meeting held on July 11, 2018, was approved.

II. NCI Director's Update

Norman Sharpless, MD

Dr. Sharpless thanked Dr. Davidson for serving as the chair of CTAC for several years and Dr. Loehrer for serving as acting chair for the current meeting.

NCI Appropriation. NCI has had a steady increase of funding over the past several years. NCI's total fiscal year (FY) 2019 appropriation is more than $1 billion larger than its FY 2015 appropriation. FY 2019 funding includes $400 million for the Cancer Moonshot, which is separate from the NCI appropriation. NCI's FY 2019 budget increase is a testament to the strong bipartisan interest in cancer research and Congress's determination that cancer research investments are a good use of public funds. Much of legislators' faith in cancer research comes from learning from constituents and news reports about new cancer therapies and successful clinical trials.

NCI Budget. According to the most recent *Annual Report to the Nation on the Status of Cancer* issued by NCI and the American Cancer Society, the incidence and mortality rates of most cancers continue to decline in both men and women in the United States. However, progress is uneven. There are still a few cancers, including liver cancer, whose mortality and incidence rates are flat or even rising. NCI, therefore, has more work to do.

NCI has issued its annual plan and budget proposal for FY 2020. NCI provides this document to Congress every year to describe what NCI would do in various areas with additional funding. This year, the document focuses on the meaning of investments in NCI programs for patients. The document reports that in FY 2018, funding for NCI's research program grant pool received the largest increase since 2003.

In FY 2018, NCI also exceeded its goal of funding 25 percent more early-stage investigators (ESIs) in response to Congress's request in the 21st Century Cures Act. This funding is important because ESIs often have difficulty obtaining their first grant, and support for ESIs is an important mechanism for cultivating the early cancer research workforce.

In FY 2019, for the first time in 22 years, NCI obtained its funding at the beginning of the fiscal year, giving the Institute more time to plan its spending. Compared with FY 2018, NCI's FY 2019 total budget increased by almost $180 million; $100 million of that increase is for the Cancer Moonshot. Most of the $80 million increase in NCI's general allocation is needed to cover the out-year costs for the research program grant pool, especially because the grants that are ending tend to be smaller than the average cost for new grants. NCI has experienced a steady increase in new R01 applications over the past few years that affects paylines. Therefore, NCI will probably not be able to raise its paylines in FY 2019.

Cancer Immunotherapy Research. FY 2018 was a big year for cancer immunotherapy research. Several high-profile publications described the use of cell immunotherapy to treat advanced solid tumors. In addition, the 2018 Albany Medical Center Prize in Medicine and Biomedical Research and the 2018 Nobel Prize in Medicine were awarded to cancer immunotherapy researchers who all have current NCI funding or have had NCI funding in the past.

NCI Clinical Trial Findings. The Food and Drug Administration recently approved moxetumomab for hairy cell leukemia based on the work of NCI intramural investigators and clinical trials conducted at the NIH Clinical Center.

The importance of NCI's continued support for large clinical trials that no other funder is likely to support was underscored by a recent report from NCI's Trial Assigning Individualized Options for Treatment (TAILORx), demonstrating that most women with early-stage breast cancer do not benefit from chemotherapy. This trial enrolled approximately 10,000 patients and took more than a decade to complete. Industry is unlikely to fund this type of de-escalation trial. Another NCI-funded trial showed that the older combination therapy of radiation plus platinum-based chemotherapy is more effective than the newer combination therapy of radiation plus rituximab for the treatment of human papillomavirus-positive head and neck cancer.

The Aspirin in Reducing Events in the Elderly (ASPREE) trial, funded by NCI and the National Institute on Aging, examined whether the potential benefits of low-dose aspirin (especially for preventing heart disease, stroke, certain cancers, and dementia) outweigh the risks (particularly of bleeding) in people aged 70 years and older. The results showed no strong evidence that use of aspirin was effective for primary prevention in any of the populations studied, and this use was associated with an increase in the cancer-related death rate.

New NCI Projects. Through supplemental funding from NCI, Project HOPE (High-Grade Glioma-Omics in Pediatric and AYA) and Project CARE (Glioblastoma Cellular Analysis of Resistance and Evolution) will conduct single-cell sequencing of pediatric, adolescent/young adult, and adult glioblastomas to better understand the tumor microenvironment. NCI is also launching a Hepatobiliary Cancer Specialized Program of Research Excellence to improve the detection, diagnosis, and treatment of these malignancies. Some new U01 grants focus on liver cancer, whose frequency and mortality rates are increasing in the United States because of alcohol use and obesity.

Centers for Medicare & Medicaid Services (CMS) Coverage for Next-Generation Sequencing. On March 16, 2018, CMS announced its decision to cover the use of next-generation sequencing as a diagnostic laboratory test. NCI played an advisory role in the development of this policy, which states that Medicare beneficiaries who meet certain CMS criteria, such as having an advanced solid tumor that has not responded to standard care, are eligible for sequencing using a Food and Drug Administration–approved assay.

Cancer Moonshot. The Cancer Moonshot Blue Ribbon Panel identified 10 priority areas where investments would support the rapid translation of research to the clinic. NCI has now issued funding announcements for intramural and extramural research in all 10 areas, and it plans to issue more announcements in 2019. After the Cancer Moonshot's annual funding peaks at $400 million in FY 2019, it drops to approximately $200 million each year until it ends in FY 2023. The Moonshot is creating valuable infrastructure and important networks that the Institute will want to maintain after the funding ends, and NCI will need to determine how to make this possible.

New Ad Hoc Working Groups. One recommendation from the Specialized Programs of Research Excellence reevaluation was to obtain advice on important translational opportunities. NCI decided to start these discussions by focusing on glioblastoma and radiation oncology. A CTAC ad hoc Glioblastoma Working Group, co-chaired by Dr. Curran and Chi V. Dang, MD, PhD, has been formed and will begin deliberations soon. The CTAC ad hoc Radiation Oncology Working Group is being assembled.

Leadership Transitions. NCI is seeking new directors for the Center for Global Health, Center for Bioinformatics and Information Technology, Cancer Therapy Evaluation Program, and Division of Cancer Prevention as well as a new associate director for the Frederick National Laboratory for Cancer Research. CTAC applauded Dr. Kramer, who will soon retire from his position as Director of the Division of Cancer Prevention, and Dr. Abrams, who was to retire from his position as Acting Director for Clinical Research and Associate Director of the Cancer Therapy Evaluation Program.

Key Focus Areas in FY 2019. Dr. Sharpless showed the key focus areas for NCI: workforce development, basic science, big data, and clinical trials. He indicated that NCI hopes to increase funding for the National Clinical Trials Network in FY 2019, as it did in FY 2018.

Questions and Discussion

Dr. Curran asked about NCI's global initiatives. Dr. Sharpless explained that cancer is responsible for increasing numbers of deaths worldwide, and NCI's science helps patients around the world. NCI's global oncology portfolio includes studies that could not be conducted in the United States for a variety of reasons, such as studies of diseases that are not common in this country. Representatives of other countries routinely invite NCI to participate in international efforts, and the NCI Center for Global Health (CGH) helps prioritize these activities. CGH is also addressing ways to conduct studies in other countries more efficiently and provides infrastructure to support NCI's large international portfolio. Dr. Sharpless hopes to identify a physician scientist who understands global oncology to become the new CGH director. This individual will play a critical role in setting priorities and making sure that the substantial resources that NCI is investing in global health are optimally spent to answer key questions.

Dr. Loehrer commented on the mortality information from the Annual Report to the Nation and asked why the rate of deaths due to nonmelanoma skin cancer is rising more quickly than that for other cancers. Dr. Sharpless offered to find the answer and share it with CTAC. He added that NCI funds researchers from across the cancer research fields, and focus is given to cancers that are important causes of mortality in the United States, including liver, endometrial, pancreatic, and brain cancer.

Dr. Loehrer asked how CTAC can best serve Dr. Sharpless and NCI. Dr. Sharpless asked CTAC for advice on which types of trials NCI should support versus those that NCI should defer to or conduct with industry. Funding de-escalation trials and complex multimodality trials (e.g., of radiation, surgery, and combinations of drugs from different companies) is appropriate for NCI because of its ability to serve as an honest broker. Dr. Sharpless would also like CTAC's counsel on how to obtain better retrospective data from trials and other studies that NCI has funded, such as how to mine old electronic health records to understand cancer progression and treatment resistance. This type of information is not always captured routinely in electronic health records, and it might not be captured in clinical trials. Clinical trials are very expensive, and NCI would like to ensure that the information and specimens collected are available for additional research purposes beyond assessing the initial primary endpoint. A related question for CTAC to consider is how NCI can collect these data in current trials so that these datasets can be mined efficiently after the trials end.

III. Progress in Pancreatic Ductal Adenocarcinoma (PDAC) Research Working Group Update

James Abbruzzese, MD, FACP, FASCO

Dr. Loehrer explained that CTAC formed the Progress in PDAC Research Working Group to advise NCI on the relevance of the initiatives in the pancreatic cancer scientific framework that NCI developed in response to the requirements of the Recalcitrant Cancer Research Act of 2012. NCI is currently assessing the scientific progress of the scientific initiatives outlined in PDAC scientific framework report submitted to Congress in March 2014. The update on the scientific progress is due to Congress in March 2019.

Epidemiology and Risk Factors. Dr. Abbruzzese explained that pancreatic cancer is one of the most aggressive and least treatable solid tumors. Although it accounts for only 2 percent of all cancer cases, it is responsible for 5 percent of cancer deaths. Advocacy groups project that by 2030, pancreatic cancer will be the second leading cause of cancer-related death. Five-year survival trends have improved slightly, but 40 percent of patients are still diagnosed with metastatic disease, and 20 percent have such extensive vascular involvement that they are not eligible for resection using current surgical techniques.

Risk factors for pancreatic cancer include environmental factors (including cigarette smoking), chronic pancreatitis, obesity, and some hereditary syndromes. The relationship between pancreatic cancer

and diabetes is complex. Pancreatic cancer can cause diabetes, and diabetes is also thought to be a minor risk factor for developing PDAC.

Pancreatic Cancer Research. NCI funding for pancreatic cancer research has increased over the past several years. Recent scientific accomplishments include the development of genomic and transcriptional profiles that could be used to identify prognostic subtypes, as well as genetically engineered mouse models of the disease. Organoids models are being developed and used for drug discovery and precision medicine applications.

The tumor-related stroma plays an important role in pancreatic cancer pathology. Understanding the crosstalk between the stroma and pancreatic cells is critical for the development of immunotherapy methods in this disease. Work in this area is ongoing, as is research funded by NCI and the National Institute of Diabetes and Digestive and Kidney Diseases on the relationships among diabetes, obesity, and pancreatic cancer. Studies are also examining the natural history of mucinous cystic pancreatic neoplasms and trying to identify the highest-risk lesions for progression to invasive pancreatic cancer.

Treatment Options. The Food and Drug Administration has approved paclitaxel and liposomal irinotecan for pancreatic cancer treatment. Chemotherapy after surgery with fluorouracil, irinotecan, and oxaliplatin can significantly prolong the survival of patients who have undergone successful surgery. The combined use of current treatment modalities and neoadjuvant therapies is probably a major driver in the increased survival rate for pancreatic cancer. Methods of managing obstructive complications are also improving.

Update of the PDAC Scientific Framework. The following four initiatives were proposed in the 2014 scientific framework report:

1. Understanding the biological relationship between PDAC and diabetes mellitus
2. Evaluating longitudinal screening protocols for biomarkers for early detection of PDAC and its precursors
3. Studying new therapeutic strategies in immunotherapy
4. Developing new treatment approaches that interfere with *RAS* oncogene-dependent signaling pathways

At its October 2018 meeting, the Progress in PDAC Research Working Group determined that scientific advances have been made in PDAC biology; animal and human tissue models; risk, prevention, screening, and diagnosis; and therapy. The Working Group felt that NCI has addressed the research directions in the 2014 scientific framework. However, working group members recommended that the 2014 initiatives be updated to reflect progress since their development. The group also recommended that NCI continue to prioritize and target other scientific opportunities in pancreatic cancer. The working group will present its scientific progress report to CTAC in advance of the NCI's submission to Congress in March 2019.

Comments from Other Working Group Members. Dr. Matrisian, a member of the Progress in PDAC Research Working Group, said that CTAC commends NCI for taking its responsibility to update the PDAC scientific framework very seriously. The working group still needs to prioritize the scientific opportunities it identified and consider how best to guide future PDAC research at NCI.

Dr. Petersen, another working group member, said that NCI's investment in PDAC research since issuing the framework has been productive. NCI has formed the Pancreatic Cancer Detection Consortium to develop and test new molecular and imaging biomarkers for detecting early-stage PDAC and its precursor lesions. Furthermore, tremendous advances have been made in understanding the genetics of pancreatic cancer, resulting in new practice guidelines. Direct-to-consumer tests can now detect genetic alterations associated with increased cancer risk; screening algorithms and treatment options are needed for people found to have a high risk. Efforts to discover biomarkers have had only limited success. Dr. Petersen recommended more focused biomarker research directed by tumor biology, which requires a better understanding of pancreatic cancer biology. Large philanthropic organizations are working with NCI to co-fund initiatives, and she applauded NCI for being open to this type of opportunity.

Dr. Mankoff, the third CTAC member on the working group, added that investments in basic imaging technology that did not necessarily focus on pancreatic cancer have paid off, and this technology should be integrated into other components of the research framework. In addition, identifying biomarkers that can provide guidance for imaging could change the early detection and diagnosis landscape.

Questions and Discussion

Dr. Curran asked about the future of the Recalcitrant Cancer Research Act. Dr. Sharpless explained that the law established certain requirements for NCI to address PDAC and small-cell lung cancer, for which NCI is currently developing a report. Mr. Arons noted that the Deadliest Cancers Coalition—which is made up of patient advocacy groups focused on recalcitrant cancers—meets quarterly and would welcome discussions with NCI.

Dr. Perez-Soler asked whether research is exploring the isolation of premalignant stem cells from patients with pancreatic cancer. Dr. Matrisian said that the working group discussed this approach, noting that some groups are working in this area, but the group did not consider this research a high priority.

Dr. Sharpless said that he was pleasantly surprised by the recent randomized phase III clinical trial results showing that adjuvant FOLFIRNOX (oxaliplatin, leucovorin, irinotecan, and fluorouracil) was associated with better outcomes than gemcitabine in patients with resected pancreatic cancer. He asked what, if anything, NCI should do differently based on these results. Dr. Abbruzzese replied that a focus on the areas that the working group identified, especially efforts to diagnose patients earlier and identify better targets and more precise management strategies, will make a substantial impact on this disease.

Dr. Fingert asked about plans to optimize the immuno-oncology research in pancreatic cancer, as is currently being done by many industry sponsors. Dr. Abbruzzese said that the report points out that many trials are not optimally designed to gain information on the reasons a particular intervention was or was not effective in patients with pancreatic cancer. This is particularly true for immunotherapy and pancreatic cancer where a deeper understanding of the tumor microenvironment will be needed to activate the immune system in this disease. He agreed that a more coordinated effort would be useful.

IV. Cancer Prevention: Successes, Opportunities, and Challenges

Vision for Cancer Prevention and Implementation

Barry Kramer, MD, MPH

The vision of the NCI Division of Cancer Prevention (DCP) is to reduce the incidence of, and ultimately eliminate, invasive cancers that are potentially life threatening. DCP's activities in support of this vision include preventive agent development, early detection and biomarker research, community-based studies to test hypotheses and develop new ones through the Community Oncology Research Program (which would be the focus of a subsequent presentation in this meeting), and training for the next generation of prevention scientists.

DCP's preventive agent development activities include immunoprevention strategies, such as the development of a frameshift peptide vaccine for Lynch syndrome in the PREVENT Cancer Preclinical Drug Development Program (PREVENT) to prevent cancers associated with Lynch syndrome and a study of the duration of sustained protective antibody levels after a single dose of a human papillomavirus vaccine. DCP also evaluates whether agents, such as aspirin in the Aspirin in Reducing Events in the Elderly trial, can be repurposed for chemoprevention.

In therapeutic oncology, substantial toxicity can be tolerated in exchange for benefits in symptomatic cancer. However, for preventive oncology, very little toxicity is acceptable. For this reason, DCP assesses novel delivery methods to reduce toxicities (e.g., topical tamoxifen for breast cancer, aerosolized bexarotene for lung cancer) in early clinical trials.

DCP supports research for early detection and mitigation of overdiagnosis at molecular, clinical, and population levels. For example, the Consortium for Molecular and Cellular Characterization of Screen-Detected Lesions conducts comprehensive molecular and cellular characterizations of tumor tissue, cells, and microenvironment components to distinguish indolent from progressive screen-detected early lesions and from interval or symptom-detected cancers. Other DCP activities in this area are the Pre-Cancer Atlas (part of the Human Tumor Atlas Network), the Tomosynthesis Mammographic Imaging Screening Trial for breast cancer, and posttherapy surveillance to collect information on screening and early detection. DCP also supports identification of predictive markers in high-risk cohorts, such as the New Onset Diabetes Cohort, Pancreatic Cancer Detection Consortium, and Consortium on Translational Research in Early Detection of Liver Cancer.

For over 30 years, the multidisciplinary postdoctoral Cancer Prevention Fellowship program in DCP has supported the training of the next generation of prevention scientists. This program currently supports 37 fellows.

Long-Term Prostate Cancer Risk in the Prostate Cancer Prevention Trial (PCPT)
Ian Thompson, Jr., MD
Joseph Unger, PhD

Prostate Cancer Background. Prostate cancer is prevalent; approximately 75 percent of men will develop it during their lifetime. Although prostate tumors can often be detected, the risk of overdetection is high, and treatment has many adverse effects and is costly. The presentation of symptoms at diagnosis typically indicates metastatic disease, and most of these patients will die of their cancer. Screening with prostate-specific antigen (PSA) detects disease early but reduces prostate cancer mortality risk only to a modest extent. Delaying prostate cancer onset could have a substantial impact on mortality.

PCPT. In 1992, the Food and Drug Administration approved finasteride, the first 5-alpha reductase inhibitor, to treat symptomatic benign prostatic hyperplasia (BPH) in men with an enlarged prostate. The PCPT, which began in 1993, was designed to determine whether finasteride could prevent prostate cancer more effectively than placebo in almost 19,000 men aged 55 and older. A greater number of prostate cancers were detected in the study population than anticipated, partly due to the end of study biopsies. The study ended early for futility in 2003, when the study endpoint was met. Analysis showed that finasteride reduced prostate cancer risk by 25 percent. The greatest reductions were in numbers of tumors with a Gleason score of 5 to 6, the most common form of the disease. However, the risk of high-grade cancer (Gleason score 8–10) increased slightly with finasteride. When the study results were published in the *New England Journal of Medicine*, an accompanying editorial recommended against using finasteride for prostate cancer because of this increased risk of high-grade prostate cancer.

Subsequent Investigations. Subsequent analyses showed that finasteride increases the sensitivity of PSA screening, digital rectal examinations, and prostate biopsies for detecting prostate cancer. Analyses that corrected for these biases found that finasteride appears to be associated with a 30-percent overall reduction in prostate cancer risk. The reduction is slightly higher for Gleason score 6 and slightly lower for Gleason scores of 7 to 10. Furthermore, finasteride may reduce the risk of Gleason 7 to 10 prostate cancer.

The SWOG Cancer Research Network created the PCPT-Medicare Linked Database, using clinical trial and Medicare claims data to examine late effects, long-term prostate cancer incidence, treatment use, and complications. Data on more than 14,000 participants with Medicare claims were successfully linked, extending follow-up of participants to a median of 16 years. Using the linked database, the investigators showed that 7 years of finasteride treatment reduced prostate cancer risk by 21 percent for 16 years, and prostate cancer risk was stable, neither increasing nor decreasing, after the initial 7 years of finasteride use. Linkage analyses to match PCPT participants with data from the National Death Index with almost 300,000 person-years of follow-up data showed no statistically significant increase in the long-term risk of prostate cancer death in either the placebo or finasteride arms of the study. Therefore, finasteride chemoprevention does not appear to be associated with an excess risk of prostate cancer death after discontinuation.

Finally, finasteride reduces prostate cancer risk in spite of improved prostate cancer detection, and this reduced risk is durable. Most of the tumors prevented have a Gleason score of 3+3. In addition, finasteride significantly reduces urinary symptoms and BPH complications, it is inexpensive, and the reduction in prostate cancer risk could decrease the number of patients undergoing surgery or radiation or experiencing treatment complications. However, finasteride is associated with a slightly higher risk of sexual side effects and gynecomastia.

Dr. Unger and colleagues plan to examine the impact of finasteride chemoprevention on the risk of other outcomes, including prostate cancer treatments and treatment side effects.

Questions and Discussion

Dr. Godley pointed out that the durable effect of finasteride was probably much more robust than expected when the study started. Dr. Thompson said that the magnitude of risk reduction in the PCPT was predicted, but the risk of diagnosis was approximately four times higher than expected. The duration of effect was unexpected, and many biologic questions need to be answered to understand this result.

In response to a question from Dr. Dahut about the overall mortality rate in the PCPT, Dr. Thompson said that determining finasteride's effect on overall mortality would require a study of approximately 100,000 men for 25 years because the death rate from prostate cancer is so low. However, finasteride chemoprevention does reduce the likelihood of prostate cancer diagnosis and its consequences for individual patients.

Dr. Dahut asked whether the results for Gleason 6 prostate cancer came from biopsies or prostatectomy specimens. Dr. Thompson replied that these results came from biopsies. Dr. Dahut asked how imaging might change the study outcomes. Dr. Thompson said that imaging would detect more prostate cancers, which would lead to more biopsies.

Dr. Barton asked whether the other databases used in the analyses could help answer other questions, such as about the factors that predict a greater likelihood of benefiting from finasteride chemoprevention or why the Gleason score 3+3 tumors were more lethal. Dr. Thompson explained that no individual characteristic—including family history, age, race, ethnicity, or original PSA score—was associated with a higher or lower risk reduction rate. Dr. Unger added that plans call for genome-wide association studies and linked claims data to answer these questions.

Dr. Mankoff noted the surprising grade difference in the biopsy results and the unexpected survival difference that was not concordant with prostate cancer grade. A possible explanation, beyond biology, is that the specimens might not have come from the most malignant parts of the tumors. Dr. Thompson said that sampling error can be measured by the number of tumors whose grade was raised at radical prostatectomy. Dr. Mankoff predicted that a great deal of information will come from the use of traditional and more advanced types of magnetic resonance imaging. Dr. Thompson noted that data from the surveillance population could be used with current imaging techniques to answer the question.

Dr. Loehrer asked about outcomes that can adversely affect survival beyond those that are disease specific to measure in prevention trials. Dr. Kramer said that long-term follow-up is important to identify expected and unexpected adverse effects of chemoprevention. He cautioned against making assumptions and public health decisions about intermediate endpoints based on expert opinion alone.

Dr. LeBlanc noted that the information presented was made possible by the linkage of information in different databases and that the ability to genomically characterize participants in large therapeutic and prevention trials would provide an opportunity to test more targeted strategies. Dr. Thompson commented that the findings he had discussed would not have been possible without Social Security numbers for PCPT participants. Dr. Szarama explained that over the next 2 years, Medicare cards will stop including Social Security numbers. Dr. Thompson noted that most clinical trials do not collect Social Security numbers now, so their data cannot be linked to Medicare claims data. Dr. Szarama said that some studies are collecting Medicare identification numbers to assist with linkages, and about 60 to 70 percent of records can be linked using name, date of birth, and address.

Cancer Preventive Agent Development Program: The Early-Phase Pipeline
Eva Szabo, MD

The goal of the Early Phase Clinical Trials Program is to qualify preventive agents for further clinical development in phase 0 microdosing and biomarker modulation trials, phase I pharmacokinetic and safety trials, and phase II preliminary efficacy trials. Additional objectives are to optimize clinical trial designs, develop surrogate and intermediate endpoint biomarkers, test novel imaging technologies, and develop further insights into mechanisms of cancer prevention by agents.

DCP's Early Phase Prevention Trials Consortia perform phase 0, I, and II clinical trials through contracts. Between 2013 and 2018, 43 trials were approved, and many are still ongoing. This program is in the midst of renewal and will be rebranded as the Cancer Prevention Clinical Trials Network and funded using cooperative agreements. Areas of emphasis include immunoprevention; strategies to optimize the risk–benefit ratio of agents; repurposing of old drugs for prevention; and leveraging the Cancer Moonshot and NCI activities, including the Pre-Cancer Atlas and Immuno-Oncology Translation Network, to identify appropriate targets for intervention.

An example of a drug that has come from the PREVENT Program is 9-cis-UAB30. Robust, preclinical data show efficacy in estrogen receptor–positive and –negative breast cancer in mouse models. Early phase I studies were performed in the Early Phase Clinical Trials Program, and a current phase IB presurgical trial is assessing various doses with a short exposure.

Several immunoprevention studies will form the basis for future phase II clinical trials. In addition to an immunobridging HPV vaccine study, the Early Phase Clinical Trials Program is assessing other broadly protective HPV vaccines, such as the RG1 virus-like particle vaccine developed by PREVENT that is almost ready for a first-in-human phase I trial. Dr. Szabo listed other studies of immunoprevention approaches for pathogen-associated cancers and studies targeting tumor-associated antigens.

Dr. Szabo described the rationale for topical approaches to breast cancer prevention, including to minimize toxicity. A phase II trial compared topical 4-hydroxytamoxifen with oral tamoxifen given 6 to 10 weeks before surgery in 27 women with ductal carcinoma in situ. The topical agent resulted in a similar decrease in proliferation in ductal carcinoma in situ lesions and equal tissue concentrations but a much lower systemic effect. Two other studies are assessing this topical agent. Other topical agents being studied for breast cancer prevention are telapristone (an antiprogestin), endoxifen (a tamoxifen metabolite), and bexarotene (a rexinoid).

Studies suggest that metformin can decrease cancer incidence, but these data are subject to multiple confounders and biases. A meta-analysis by DCP and the European Institute of Oncology that corrected for various biases showed that metformin's effects were much less robust than previously reported. The Diabetes Prevention Program's Outcomes Study will provide important information about cancer incidence in a high-risk population with metabolic syndrome. Three phase II trials showed no impact from metformin on tissue biomarkers in Barrett's esophagus, prostate, and colorectal aberrant crypt foci. An additional trial in oral leukoplakia did not show a significant clinical response rate, although histologic responses occurred in two thirds of participants. Additional biomarker analyses are underway for this trial, but no data to date justify a phase III study.

Dr. Szabo concluded her presentation with a list of potential PREVENT and follow-up studies of immunoprevention and chemoprevention agents.

The NCI Cancer Prevention Steering Committee: Opportunities and Challenges
Ernest Hawk, MD, MPH

Studies indicate that up to one-third to one-half of cancer deaths in Western populations are preventable. Domains of activity for individuals to prevent cancer based on the best available evidence are maintaining a healthy weight across the lifespan, eating a healthy diet, being physically active, avoiding tobacco and alcohol use, knowing one's family history, avoiding excessive ultraviolet light

exposure, following an evidence-based cancer screening program, and using preventive medicines and vaccines. Public health initiatives on a population level (e.g., public policy, community-based clinical services) can complement these individual efforts.

The MD Anderson Cancer Center's Cancer Prevention Center, which has 50,000 billable visits a year, uses clinical algorithms to implement the individual-level strategies shown to be effective. The main components of these algorithms are a systematic evaluation, defined triggers for recommendations by the clinician, motivational interviewing and monitoring, and assessments.

Numerous observational studies have demonstrated that the adoption of a healthy lifestyle is associated with a 20–50 percent reduction in cancer mortality rates. Healthy lifestyles are also associated with significant reductions in the risk of cardiovascular and all-cause mortality at the population level. Dr. Hawk listed several evidence-based cancer screening modalities that have demonstrated reductions in cancer mortality rates through randomized controlled trials and/or replicated observational studies over time. He also listed the 14 Food and Drug Administration–approved agents for the treatment of precancerous lesions or cancer risk reduction.

The NCI Cancer Prevention Steering Committee, which has 22 members, has identified the following priorities:

- Better understand the early determinants and drivers of dysplasia.
- Optimally identify individuals at increased risk of cancer.
- Examine repurposed cancer therapeutics for their potential utility in cancer prevention, risk reduction, and treatment of precancers.
- Address challenges in cancer prevention drug development and opportunities to accelerate agent development and validation.
- Increase interactions and coordination across NCORP groups, improve the template for NCORP concept submission, create and disseminate threshold standards for preliminary efficacy data, collaborate more closely with other relevant professionals, and identify germline risk cohorts across NCORP groups.

Dr. Hawk believes that NCI and NCI-designated cancer centers can serve as advocates, stewards, and drivers of the cultural transformation needed to implement and disseminate evidence-based cancer control and prevention strategies more broadly.

Questions and Discussion

Dr. Loehrer asked Dr. McCaskill-Stevens to join the panel for this discussion. Dr. Loehrer suggested that the very large trials that have found extremely limited effects of interventions on prevention have diminished enthusiasm about the potential to prevent cancer.

High Priorities. Dr. Doroshow asked the presenters to identify major priorities for NCI. Dr. Hawk said that one priority is to determine how to use electronic health records (EHRs) to identify individuals with a higher cancer risk in an automated way. Systematic, long-term follow-up will be required to answer questions not only about cancer mortality, but also about the impact of prevention strategies on overall mortality, functioning, morbidity, and other important outcomes. Research should determine how to ensure that clinicians can consistently and efficiently enter such data into EHRs and how these data can be accessed for research on outcomes of importance to patients and providers.

Dr. Szabo said that challenges in identifying prevention agents include the limited understanding of the biology of early cancer development and the heterogeneous ways in which cancer can develop, even within the same organ. Dr. Hawk noted that the Pre-Cancer Genome Atlas is an important first step in this direction, and more basic scientists need to be attracted to the cancer prevention field.

Dr. McCaskill-Stevens said that many of the disciplines that could help identify appropriate participants for cancer prevention are not integrated into the current study infrastructure, and additional funding could support better connections.

Dr. Doroshow explained that this discussion is important because population activities can be very expensive, and the institute's resources are limited. NCI benefits from consulting CTAC from time to time, especially given that the committee has not spent much time addressing prevention in the past.

Surrogate Endpoints. Dr. Barton agreed that more research is needed on early cancer biology and noted that validated surrogate biomarkers will be critical to enable the conduct of smaller trials. Dr. Petersen said that decisions about victories based on surrogate or intermediate endpoints have been unsatisfactory, and firmer rules are needed to conclude that a prevention approach has succeeded.

Dr. Mankoff said that compared with therapeutic trials, intermediate endpoints are less readily available for prevention trials. He suggested using the specimens and images collected during trials to identify not only better detection techniques but also biomarkers of efficacy. For example, relatively inexpensive approaches to data mining can be used with modern mammograms to study detection and identify biomarkers. Dr. Szabo said that the specimens collected in Early Phase Clinical Trials Program trials are available to the research community.

Healthy Behaviors. Dr. Barton pointed out that the potential risk reduction associated with certain healthy behaviors appears to be at least as great as with finasteride. More research is needed on the impact of healthy behavior implementation on cancer prevention. Dr. Hawk said that the effects of changing behavior are shown by the decline in rates of lung and other tobacco-related cancers, as tobacco use rates have dropped from approximately 50 percent to less than 20 percent through concerted public health and clinical efforts. Dr. Barton agreed but emphasized the need to collect more data on the social determinants of health, which might help explain the PCPT findings.

Less-Costly Trials. Dr. LeBlanc argued against small studies. Although resources are tight, large, long-term studies are needed. Dr. Szabo explained that the reason to conduct small studies is to collect robust evidence for use in larger studies that can provide definitive answers.

Dr. Loehrer proposed a working group to discuss ways to conduct trials at a lower cost, such as by using apps instead of data managers to follow study participants. Studies conducted in low- and middle-income countries must be done less expensively than in the United States; these studies might offer lessons on how to conduct trials more cheaply.

Dr. Fingert pointed out that industry has invested a substantial amount of resources into operational efficiency. For example, companies often issue contracts to vendors that conduct research on how to reach older adults who might not comply well with a mobile phone app.

Other Prevention Research Opportunities. Dr. Perez-Soler asked why the list of immunopreventive agents that Dr. Szabo provided did not include checkpoint inhibitors for lung cancer. Dr. Szabo explained that the Consortia for Early Phase Prevention Trials have not studied checkpoint inhibitors to date, but others are doing so.

Dr. Petersen noted that prophylactic surgery (e.g., prophylactic mastectomy, colectomy, or pancreatectomy) can be and is being done but was not listed in the presentations on prevention approaches. Dr. Szabo agreed that prophylactic surgery can be effective but noted that it has its own challenges, including the inability to remove the entire field at risk in some cases. Dr. Petersen suggested a chemoprevention goal of delaying the need for prophylactic surgery (e.g., until after the childbearing years).

Dr. Hawk suggested gathering additional types of data in therapeutic trials. For example, follow-up colonoscopies and surveillance results could be collected in a systematic way to determine whether the incidence of recurrent adenomas changes in Lynch syndrome or sporadic colorectal cancer therapeutic trials. This approach could offer an important way to accelerate prevention research and the exploration of therapeutic agents applied in a preventive context.

According to Dr. Barton, another priority is determining how best to implement effective prevention strategies while considering the fact that the primary care system is overwhelmed.

Dr. Fingert asked whether the prevention trial data are available to external scientists, such as through Project Data Sphere. Dr. Szabo said that the early-phase clinical trials are typically quite small, and their data have not been uploaded into a sharable database. A biorepository is in development that will contain clinical trials data as well. The PCPT collected a great deal more data than the small early-phase trials, which offer much less data to mine. Dr. Fingert explained that Project Data Sphere offers the ability to conduct meta-analyses and use other methods to analyze data from several small trials.

V. Analysis of NCI Community Oncology Research Program (NCORP) Accrual Performance

Worta McCaskill-Stevens, MD, MS

NCORP has a broad portfolio that includes cancer control, prevention, screening, and post-treatment surveillance; quality of life; cancer care delivery; and advanced imaging and treatment trials. The seven NCORP research bases develop concepts and protocols for clinical trials and cancer care delivery research studies in community settings. NCORP's 34 community sites and 12 minority/underserved sites participate in research committees and identify barriers to successful activation and enrollment of participants.

On average, 45 NCORP trials have been available to the network each year since the program began in 2014. Total enrollment in treatment trials has declined slightly since 2014, partly because more small treatment trials and fewer large adjuvant treatment trials are conducted, and because the cancer control and symptom management studies are increasingly mechanistically driven and complex. Enrollment in cancer control studies exceeded enrollment in treatment studies in 2017, reflecting the launch of the Tomosynthesis Mammographic Imaging Screening Trial for breast cancer. Between 2014 and 2018, all NCORP community and minority/underserved sites enrolled more than 24,000 participants.

In 2014, NCORP initiated cancer care delivery research studies to improve clinical outcomes and patient well-being by intervening in patient, clinician, and organizational factors that influence cancer care delivery. To date, these studies have accrued almost 3,000 patients, caregivers, clinicians, and pharmacists. When these participants and those in the quality-of-life studies are included, the total NCORP accrual between 2014 and 2017 was more than 31,000.

NCORP investigators also conduct research at their sites. They have provided almost 200 blood specimens so far, most of which were matched with tissue, for development of a patient-derived mouse xenograft model. The 11 adult minority/underserved community sites are providing tissue specimens for the Early Onset Malignancies Initiative that is investigating the increased risk of developing cancer at an early age in certain racial and ethnic populations. To date, over 80 cases have been enrolled.

NCORP contributed significantly to NCI's Molecular Analysis for Therapy Choice Trial. Approximately 44 percent of patients registered for screening came from NCORP community and minority/underserved sites. NCORP was also responsible for approximately one-third of accruals to the Adjuvant Lung Cancer Enrichment Marker Identification and Sequencing Trial and the Lung Cancer Master Protocol. The quality of the NCORP specimens is equivalent to that of specimens from academic sites.

Approximately 24 percent of study participants enrolled by the NCORP network are from minority populations. Eighteen percent of participants enrolled by community sites are from minority populations, and the minority enrollment rate for minority/underserved sites is 54 percent.

In 2016, a screening tool was developed to better understand participants screened for NCORP trials and barriers to participation. Demographic and clinical data were collected from 8,744 NCORP study participants, including 6,193 who enrolled in a clinical trial. The most common reasons for not enrolling in a trial were not meeting the trial eligibility criteria or being eligible but declining to participate. Interestingly, the participant declined participation in some cases, whereas in others, the health care provider was the one who declined participation. About 17 percent of participants had an income lower than $35,000, and about 28 percent had graduated high school or had less than a high school education. NCORP includes cancer care delivery research that is focused on financial toxicity.

This information is also useful for NCORP in assessing the feasibility of interventions in certain communities.

Starting August 1, 2018, NCORP established the following timeline targets: 120 days from concept receipt to approval, 90 days for protocol authoring, 175 days for protocol review and approval, and 90 days from protocol approval to activation, for a total of 475 days.

Questions and Discussion

Dr. Fingert asked whether Dr. McCaskill-Stevens has compared participants who completed a trial with those who simply enrolled but did not complete a trial. Dr. McCaskill-Stevens explained that several approaches are used to assess trial completers.

Dr. Loehrer asked why NCORP is enrolling patients to provide tissue samples, and he wondered whether this is a responsibility of cancer centers. Dr. McCaskill-Stevens explained that one of the projects she had mentioned was enrolling participants exclusively from minority/underserved sites. Participation of the community sites enhances the generalizability of research results.

Dr. Loehrer asked about enrollment by minority participants in cancer treatment versus cancer control studies. Dr. McCaskill-Stevens noted that minority patients are sometimes ineligible for a trial because they have multiple comorbidities, and she planned to study this issue in greater depth. Dr. Barton suggested that minority/underserved representatives on the steering committee review all eligibility criteria for feasibility.

Dr. Langevin commented that the clinical trial portfolio of the Children's Oncology Group research base is declining, and it is conducting only a few treatment and symptom management trials. Pediatric sites have been unable to participate in several protocols because, for example, the studies only enrolled people who spoke English or were conducted at a single site. The Children's Oncology Group plans to begin reviewing concepts for their ability to be implemented before they are submitted to NCI.

Dr. Loehrer asked Dr. McCaskill-Stevens how CTAC can help her. Dr. McCaskill-Stevens requested CTAC's input on prevention research gaps and how to better collaborate with academic research sites.

Dr. Ochoa commented that community practitioners are responsible for implementing prevention measures and symptom management for some patients who complete treatment at a cancer center. NCORP has discussed how to incorporate community practitioners, including federally qualified health centers, during protocol development. Their involvement might increase the participation of minority and other underserved populations.

VI. Finding Cancer Trials Collaborative

Gisele Sarosy, MD

Patients and providers have a common need to find suitable clinical trials but have different search needs. There are multiple sources of information on cancer clinical trials and determining which ones to use is challenging. Furthermore, searches often retrieve too many trials for which the patient is not eligible or that are not relevant to the patient.

Clinical Trials Reporting Program (CTRP). NCI's CTRP is a database of regularly updated information on NCI-supported interventional trials, including those conducted in at least one NCI-designated cancer center (including industry-sponsored trials at cancer centers) and trials supported by any type of NCI contract, grant, or cooperative agreement. CTRP uses standardized data elements and consistent protocol abstraction to support NCI clinical trials portfolio management and for registration and results reporting to ClinicalTrials.gov. CTRP is the source of data for NCI's clinical trials search tool.

Some of CTRP's unique features are its use of consistent terminology and standardized data elements, standard representation of persons and organizations, and inclusion of structured biomarker

information. Approximately 90 percent of interventional cancer clinical trials open to accrual in the United States that are registered in ClinicalTrials.gov are represented in CTRP.

An application programming interface (computer connection between data and a website) provides CTRP data to NCI's website, Cancer.gov, and its search tool. The application programming interface is open source and provides the data to third parties, such as academic institutions and companies, who can repackage and use the data for their own purposes. Starting in 2017, CTRP became the data source for all cancer clinical trial searches on Cancer.gov. Recent enhancements to the Cancer.gov search function include chat-box help, integration with NCI Thesaurus and Enterprise Vocabulary Services to improve search accuracy, and type-ahead and multiselect options.

Structured Eligibility Criteria. CTAC's Clinical Trials Informatics Working Group identified structuring eligibility criteria (i.e., expressing the information from the protocol in a consistent format) as a priority for improving clinical trials searches. Approaches to structuring the information include standardizing eligibility criteria at the point of protocol authoring, applying a standard ontology or terminology to eligibility criteria by human abstractors, or using natural language processing and artificial intelligence to enhance efficiency.

Finding Cancer Trials Collaborative. This collaborative, composed of NCI staff, is identifying ways to make cancer clinical trials easier to find at the point of need. Input from the community on how best to do so was gathered via a series of teleconferences and meetings with various stakeholders and a request for information that yielded 39 responses.

Stakeholders suggested that NCI—which they viewed as an honest broker—take the lead in structuring the eligibility criteria. They noted that efforts to improve the search process or match patients to trials are limited by the lack of standards and, although natural language processing can be helpful, extensive human curation would likely be involved in structuring clinical trials information. Stakeholders recommended that NCI work with the community to create and adopt data standards for eligibility criteria, identify ways to integrate the presentation of clinical trials into the clinical workflow, make search interfaces user specific, and present eligibility criteria and other clinical trial information in patient-friendly language.

With Presidential Innovation Fellows, NCI participated in two 3-day NIH data science hackathons for computer programmers and scientists to address the issue of unstructured clinical trial eligibility criteria. Furthermore, the Department of Health and Human Services, large companies, and other interested parties are participating in The Opportunity Project "TOP" Health Sprint, that provides an opportunity to work on structuring free text eligibility criteria intensively and collaboratively for three months. Their work will be presented in February.

Next steps following this communication of the findings of the landscape analysis to CTAC and the National Council of Research Advocates (NCRA) are to explore the standardization of protocol authoring for NCI network trials (e.g., NCI Experimental Therapeutics Clinical Trials Network [ETCTN] trials), and to work with various stakeholders to develop an action plan.

Questions and Discussion

In response to a question from Dr. Petersen, Dr. Sarosy explained that NCI can directly manage the content in CTRP and its search algorithms. CTRP has data on trials supported in any way by NCI, including all trials at NCI-designated cancer centers, regardless of whether they are funded by NCI, industry, or other National Institutes of Health Institutes. Most of the trials in ClinicalTrials.gov that are not in CTRP are trials that are not conducted at NCI-designated cancer centers or are conducted outside the United States.

Mr. Arons, who chairs the NCRA, explained that the council agreed that finding the right trial for the patient at the right time is critical for NCI's precision medicine activities as well as for addressing some challenges with using ClinicalTrials.gov. Structured clinical trial information that is interoperable with other systems will benefit patients and clinicians. Integrating the presentation of clinical trials into

the clinical workflow could increase clinical trial participation and address trial participation disparities. The NCRA hoped that this effort will address the need for clinical trial information in different languages and help users find trials based on factors other than histology. The NCRA also hoped that the final product will support better education for providers so that they can help patients choose the right trials. A final recommendation was for NCI to continue to support the Finding Cancer Trials Collaborative.

Dr. Dancey asked why the effort would begin with ETCTN trials. Dr. Sarosy said that ETCTN was chosen because its protocols are currently being written by NCI, offering an opportunity to test the feasibility of using standardized eligibility criteria at this stage. Another option is to structure the eligibility criteria in protocols that have already been written.

Dr. Dancey recommended that the collaborative begin with a specific disease area and use the lessons learned from that experience in other diseases. Dr. Sarosy said that the collaborative has considered this approach and is planning several small pilot tests over the next few months. If the ETCTN protocol authoring effort is successful, the collaborative might try this approach with lung cancer protocols. Dr. Prindiville added that the reason to start with the ETCTN is that NCI can make sure that the ETCTN protocols are written in a standard way if the National Clinical Trials Network groups agree to do this. Dr. Dancey said that the next step would be to simplify the eligibility criteria.

Dr. Dancey commented that the National Library of Medicine, which manages ClinicalTrials.gov, should be involved in this effort. Dr. Sarosy said that NCI staff working on CTRP consult the National Library of Medicine frequently, and it will continue to do so.

Dr. Fingert recommended that the collaborative consult the authors of the new draft revision of the Q8 pharmaceutical development guidelines from the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use. This document addresses the need for standardization of terms used in clinical trial protocols.

VII. Ongoing and New Business

Recognitions
Patrick J. Loehrer, Sr., MD
James H. Doroshow, MD

Dr. Doroshow thanked Mr. Arons, whose CTAC term was ending, for his service on CTAC and other NCI committees. Dr. Loehrer recognized Dr. Jeffrey S. Abrams, who was to retire as Acting Director for Clinical Research in the Division of Cancer Treatment and Diagnosis and Associate Director of the Cancer Therapy Evaluation Program, for his many accomplishments. Dr. Curran also thanked Dr. Abrams on behalf of the National Clinical Trials Network group chairs for all he has done for the groups. Dr. Abrams said that it has been a great pleasure to work at NCI and a privilege to work with CTAC.

Quantitative Imaging Network (QIN) Working Group
Janet Eary, MD

Imaging can offer valuable anatomic, physiologic, metabolic, and molecular information to clinical trials, provide important insights into disease location and stage, and reduce or eliminate the need for biopsies. Quantitative imaging—the extraction of quantifiable (measurable) data from medical images to assess status or change in a disease—provides quantitative tools to support clinical decisions.

The steps in the QIN roadmap are:

1. Evaluate imaging hardware performance
2. Create harmonization methods (software and protocol)
3. Create robust algorithms to extract quantitative information from images
4. Test and validate performance of algorithms
5. Introduce candidate algorithms into clinical workflow

Many of the 67 tools developed by QIN investigators are in stages 3 or 4 of the roadmap, and approximately 12 are ready for clinical trial benchmarking, with the ultimate goal of both research and clinical implementation. QIN is publishing on and promoting its tools, using different approaches to motivate teams to validate their tools as quickly as possible, and increasing participation by industry and the Food and Drug Administration.

To help facilitate testing and implementation of QIN tools in clinical trials, a proposal was made for CTAC to form a QIN Working Group. This group would advise QIN on strategies to enhance the integration of the network's tools into clinical trials. The group would also assess QIN's current status, identify barriers to QIN tool use, and recommend strategic approaches for enhancing integration of QIN tools into clinical trials.

Questions and Discussion

Dr. Mankoff, a QIN investigator, said that a CTAC working group would bring together investigators engaged in NCI's National Clinical Trials Network and Community Oncology Research Program, as well as in cancer centers and industry. He concluded by expressing support for forming the proposed working group.

Dr. Curran noted that the proposed working group would focus on enhancing QIN, which is a much narrower focus than that of most working groups. Furthermore, the proposed group's charge assumes that QIN is the right model. Dr. Doroshow said that the working group's charge could include determining whether the QIN model is the right approach.

Dr. Fingert pointed out that a subcommittee of the Biomarkers Consortium, coordinated by the Foundation for NIH, is addressing quantitative imaging and related issues. Dr. Doroshow suggested that the proposed working group gather input from this subcommittee.

Motion. A motion to form the CTAC QIN Working Group as proposed was approved.

VIII. Legislative Updates

Holly Gibbons

Midterm Election Results. The Democratic Party took control of the House of Representatives in the November 2018 midterm election, and the Republican Party maintained control over the Senate. Several election results were not yet available.

The chairs and members of some committees and subcommittees that interact frequently with or have jurisdiction over the National Institutes of Health (NIH) and NCI will change as a result of the election. Tom Cole (R-OK), chair of the Subcommittee on Labor, Health and Human Services, Education and Related Agencies, was running to succeed Rodney Frelinghuysen (R-NJ) as ranking member of the House Appropriations Committee. The co-chairs of the House Cancer Caucus, Kevin Yoder (R-KS) and Charlie Dent (R-PA), lost their races or retired. The co-chairs of the Congressional Caucus on the Deadliest Cancers, Leonard Lance (R-NJ) and Dave Reichert (R-WA), were also leaving, as were the co-chairs of the Lung Cancer Caucus, Rick Nolan (D-MN) and Frank LoBiondo (R-NJ).

Appropriations. Fiscal year (FY) 2019 was the first year since 1996 that NIH received its funding from the Labor, Health and Human Services, Education, and Related Agencies appropriations bill on time. This year, for the first time, this bill was combined with the Department of Defense appropriations bill and a short-term continuing resolution for several other agencies. This rapid passage of the appropriations bill helps NIH plan and use its resources more efficiently.

The NCI appropriation for FY 2019 was $79 million larger than in FY 2018, and NIH received a $2 billion increase. These increases are part of a strong record of consistent bipartisan support for NIH and NCI. NIH has enjoyed funding increases for the past 4 years, and NIH and NCI appreciate the leadership of the appropriations committee and subcommittees that have made NIH and its Institutes a priority.

Congressional Hearings. Dr. Sharpless joined Dr. Francis Collins, Director of NIH, at hearings of the House and Senate appropriations subcommittees, the Subcommittee on Health of the House of Representatives Energy and Commerce Committee, and the Senate Committee on Health, Education, Labor and Pensions.

Briefings. Several NCI leaders and investigators were invited to speak at events at the Capitol in recent months:

- Dr. Rachel Grana Mayne, a program director in the Tobacco Control and Research Branch, Division of Cancer Control and Population Sciences, gave a presentation at an American Association for Cancer Research briefing on electronic cigarette research.
- Dr. Damali Martin, a program director in the Genomic Epidemiology Branch, Division of Cancer Control and Population Sciences, spoke at the Prostate Health Education Network summit about RESPOND, a study focusing on prostate cancer in African American men and supported through the Cancer Moonshot.
- Dr. Sharpless gave keynote addresses at the Congressional Childhood Cancer Caucus Summit and a One Voice Against Cancer briefing.
- Dr. Meg Mooney, Chief of the Clinical Investigations Branch of the Cancer Therapy Evaluation Program in the Division of Cancer Treatment and Diagnosis, served on an American Cancer Society Cancer Action Network panel on overcoming barriers to clinical trial enrollment.

Congressional Visits. Representative Kevin Yoder (R-KS) visited NCI, where he met with Dr. Sharpless and Dr. Brigitte Widemann, Chief of the Pediatric Oncology Branch. Dr. Sharpless also met with Representative G.K. Butterfield (D-NC), a cochair of the Childhood Cancer Caucus.

Legislation. NCI is working with the Food and Drug Administration to implement the Research to Accelerate Cures and Equity for Children Act, Title V of the Food and Drug Administration Reauthorization Act of 2017. The Childhood Cancer Survivorship, Treatment, Access & Research Act, signed into law in June 2018, has provisions pertaining to childhood, adolescent, and young adult cancer survivorship research, as well as opportunities to enhance biospecimen collection and resources. In addition, this act encourages NCI to continue to include pediatric experts on advisory boards, as NCI has always done. Implementation is ongoing.

NCI Annual Plan and Budget Proposal for FY 2020. NCI has now sent this plan to every member of Congress through email updates to congressional staff (health legislative assistants and key committee staff). In the document, NCI highlights patient and researcher stories that come from the state or district of a member of Congress or that might be of personal interest to a member.

Questions and Discussion

Ms. Gibbons explained that she had described changes in the leadership of cancer-related caucuses, but she had not listed the leaders who would maintain their leadership positions in the new Congress.

Dr. Curran asked about the selection of new leaders now that the Democratic Party will have a majority in the House of Representatives. Ms. Gibbons explained that some leadership races were beginning. For example, Kevin McCarthy (R-CA) and Jim Jordan (R-OH) had announced plans to run for minority leader of the House, and a new House speaker will be elected. The leadership of the subcommittees of greatest interest to NCI was unlikely to change beyond the positions she had mentioned. In addition to Representative Cole, Kay Granger (R-TX) planned to run for ranking member of the Appropriations Committee, and it was not yet clear whether Representative Cole would continue to serve as ranking member of the Subcommittee on Labor, Health and Human Services, Education and Related Agencies. Roy Blunt (R-MO) was likely to continue leading the Senate Subcommittee on the Departments of Labor, Health and Human Services, Education and Related Agencies, and Patty Murray (D-WA) would probably remain the committee's ranking member. The former ranking member of the House Labor, Health and Human Services, and Education Appropriations Subcommittee, Rosa DeLauro

(D-CT), was likely to become the subcommittee's chair. Nita Lowey (D-NY), the ranking member of the House Appropriations Committee, would probably become chair of the committee.

Mr. Arons asked about the proposed amount for the NCI budget in the NCI 2020 annual plan and budget proposal. He also asked whether Ms. Gibbons could share the expected funding level for NCI in the FY 2020 President's Budget Request. Ms. Gibbons explained that the Office of Management and Budget develops the President's Budget Request in consultation with federal agencies, including the Department of Health and Human Services, NIH, and NCI. Proposed FY 2020 funding levels have not yet been finalized, and they will not be available to share with the public until the President's Budget Request is formally released, which traditionally occurs in early February. Ms. Gibbons clarified that the NCI professional judgement budget gives NCI a unique opportunity (as required by the National Cancer Act of 1971) to discuss areas of additional investments needed to advance cancer research.

Dr. Langevin asked whether NCI was likely to receive its FY 2020 appropriation by the beginning of that year, as it did this year. Ms. Gibbons said that it is difficult to know whether this is possible. The midterm election created pressure to pass the appropriations bill this year, but the appropriations leaders—most of whom will retain their positions in the next Congress—are committed to restoring the regular order.

Motion. A motion to form the CTAC QIN Working Group as proposed was approved.

IX. Adjournment

Patrick J. Loehrer, Sr., MD

There being no further business, the 37th meeting of CTAC was adjourned at 2:31 p.m. on Wednesday, November 7, 2018.

Appendix

NATIONAL INSTITUTES OF HEALTH
National Cancer Institute
Clinical Trials and Translational Research Advisory Committee

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Associate Dean for Cancer Research
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Chief Executive Officer
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President & Executive Director
Seattle Cancer Care Alliance Head, Division of
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Vice-Chair for Research
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