DEPARTMENT OF HEALTH AND HUMAN SERVICES
NATIONAL INSTITUTES OF HEALTH
NATIONAL CANCER INSTITUTE
31st CLINICAL TRIALS AND TRANSLATIONAL RESEARCH ADVISORY COMMITTEE (CTAC) MEETING

Summary of Meeting
November 2, 2016

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

CLINICAL TRIALS AND TRANSLATIONAL RESEARCH ADVISORY COMMITTEE
BETHESDA, MD
Summary of Meeting
November 2, 2016

The 31st meeting of the Clinical Trials and Translational Research Advisory Committee (CTAC) of the National Cancer Institute (NCI) was held on Wednesday, November 2, at 8:04 a.m. in Conference Room 10, C Wing, Sixth Floor, Building 31, on the National Institutes of Health main campus in Bethesda, Maryland. The CTAC chair, Nancy E. Davidson, MD, presided.[1] The meeting was adjourned at 2:55 p.m.

Chair
Nancy E. Davidson

CTAC Members
David F. Arons
Susan M. Blaney (absent)
Walter J. Curran, Jr.
David M. Gershenson
Michael L. LeBlanc
Patrick J. Loehrer, Sr.
David A. Mankoff
Edith P. Mitchell
Nikhil C. Munshi
Augusto C. Ochoa
Gloria M. Petersen (absent)
Louis M. Weiner

***Ad Hoc* Members**
Debra Barton
Timothy Eberlein
Howard Fingert
Gwendolyn A. Fyfe
Paul A. Godley
Anne-Marie Langevin
Lynn M. Matrisian
Roman Perez-Soler
Dan Theodorescu

***Ex Officio* Members**
William Dahut, NCI
James H. Doroshow, NCI
Paulette S. Gray, NCI
Rosemarie Hakim, Centers for Medicare & Medicaid Services
Michael J. Kelley, U.S. Department of Veterans Affairs
Warren A. Kibbe, NCI
Richard Pazdur, U.S. Food and Drug Administration

Executive Secretary
Sheila A. Prindiville, NCI

Presenters
Jeffrey S. Abrams, MD, Associate Director, Cancer Therapy Evaluation Program, Division of Cancer Treatment and Diagnosis, NCI
Nancy E. Davidson, MD, Director, University of Pittsburgh Cancer Institute
James H. Doroshow, MD, Deputy Director for Clinical and Translational Research, NCI
Toby T. Hecht, PhD, Acting Director for Clinical Research, Division of Cancer Treatment and Diagnosis, NCI
Stephanie R. Land, PhD, Program Director and Statistician, Tobacco Control Research Branch, Division of Cancer Control and Population Sciences, NCI

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

Michael L. LeBlanc, PhD, Member, Fred Hutchinson Cancer Research Center; Research Professor, University of Washington
Douglas R. Lowy, MD, Acting Director, NCI
Dinah S. Singer, PhD, Acting Deputy Director, NCI
Deborah A. Zarin, PhD, Director, ClinicalTrials.gov, Information Engineering Branch, National Library of Medicine, National Institutes of Health

TABLE OF CONTENTS
WEDNESDAY, NOVEMBER 2, 2016

I. Call to Order and Opening Remarks

Nancy E. Davidson, MD

Dr. Davidson called the 31st meeting of CTAC to order and welcomed participants to the meeting. She introduced new ad hoc CTAC members: Drs. Barton, Eberlein, Fingert, Godley, Langevin, Perez-Soler, and Theodorescu.

Dr. Davidson reviewed the confidentiality and conflict-of-interest practices required of CTAC members during their deliberations. She 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 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 30th CTAC meeting held on July 13, 2016, was approved unanimously.

II. NCI Acting Director's Update

Douglas R. Lowy, MD
James H. Doroshow, MD

Acting Director's Update

Fiscal Year (FY) 2017 Budget. Dr. Lowy stated that NCI and the National Institutes of Health continue to have strong bipartisan support in Congress. The potential exists for continuing increases in federal cancer research funding, although the amount is not known. The federal government will continue operating under a continuing resolution through December 9, 2016. Private funding efforts and cooperation with other agencies remain important.

Investigator-Initiated Research. NCI will continue to support investigator-initiated basic, prevention, screening/early diagnosis, treatment, and survivorship research. Between FY 2013 and FY 2015, NCI increased its funding for new and competing type 1 and 2 awards by 25 percent (approximately $400 million to $500 million per year). During this period, the NCI budget rose by 3 percent. Although the final data are not available for FY 2016, the total was a few million dollars higher than in FY 2015. NCI will need to increase the total funding for the research program grant pool over the next few years to support types 1, 2, and 5 awards at the current level. In FY 2017, this will require an addition of at least $80 million from the institute's appropriation.

Cancer Health Disparities. NCI is focusing on specific cancers associated with health disparities, such as lung, colorectal, liver, breast, and prostate cancer as well as multiple myeloma. NCI research is identifying biological, lifestyle, and health care access and use risk factors and assessing their relative contributions to the disparities.

Cancers of the colon and rectum are associated with health disparities. Blacks have benefited from the improvements in screening and treatment over the last 15 years. But although incidence and mortality rates have declined in this population, they are still higher than among whites. Furthermore, American Indians and Alaska Natives have not benefited from recent advances in prevention, screening, and treatment in the way all other populations have.

Dr. Lowy planned to attend a meeting with representatives of Native American tribes to discuss NCI support for research with the goal of understanding and addressing cancer disparities in this population. Cancer incidence and mortality rates are substantially higher in Native Americans than in most other groups, except perhaps for African Americans.

To address cancer disparities, NCI plans to follow these principles:

- Develop better genomic, biologic, environmental, and treatment response information about cancer in minority populations
- Make sure that minority populations are represented in clinical trials and preclinical cancer models
- Ensure appropriate minority representation in studies from the beginning

NCI has established two new research initiatives to address cancer health disparities. The early onset malignancy initiative, the first minority-based cancer tissue bank, will collect specimens of early onset tumors and information on treatment, response, and outcome. This resource will offer detailed molecular characterization of fully annotated tumors and will be organized through the NCI Community Oncology Research Program. The second initiative is the development of new cancer models from tumors of minority patients.

Precision Medicine Initiative in Oncology (PMI-O). The PMI-O has three main components: foundational clinical trials, preclinical models to advance predictive oncology, and the Genomic Data Commons. NCI's Board of Scientific Advisors recently approved five concepts for new requests for applications designed to support:

- Preclinical drug development and preclinical clinical trials using patient-derived xenograft models
- Approaches to identify and overcome resistance to cancer therapy
- Canine immunotherapy trials and correlative studies
- Studies on translational implications of the microenvironment in pancreatic ductal adenocarcinoma
- Biomarker development and correlative studies associated with immunotherapy clinical trials

The adult and pediatric NCI Molecular Analysis for Therapy Choice (NCI-MATCH) trials are among the PMI-O foundational clinical trials. These trials select treatments for patients with cancer progression and no standard-of-care treatment based on molecular abnormalities in their tumor rather than the tumor site of origin. The adult NCI-MATCH trial opened in 2015, and the pediatric NCI-MATCH trial will open in 2017.

The initial goal of screening 3,000 patients in the adult NCI-MATCH trial has been expanded to 5,000 patients. The study started with 10 treatment arms. The trial has expanded to 23 arms in the last few months and will increase to 29 arms soon. NCI-MATCH is accruing approximately 500 patients per month (the initial estimate was 50 per month). Approximately 24 percent of screened tumors have molecular abnormalities that make the patient eligible for at least one treatment arm.

Vice President's Cancer Moonshot. The goals of the Cancer Moonshot are to:

- Accelerate progress in cancer, including prevention and screening

    - From cutting-edge basic research to wider uptake of standard of care
- Encourage greater cooperation and collaboration
    - Within and between academia, government, and the private sector
- Enhance data sharing

NCI is developing the Virtual Drug Formulary as part of the Cancer Moonshot. Its goal is to greatly reduce the time needed to start cancer treatment trials involving drugs from more than one pharmaceutical company. The formulary will overcome a major barrier to precision medicine clinical trials not funded by NCI in academic centers (NCI trials already have access to combinations of drugs from multiple companies). Ten companies have now agreed to provide 40 drugs for these studies, which are expected to start in early 2017.

A related activity is the Applied Proteogenomics Organizational Learning and Outcomes (APOLLO) consortium, a collaboration between NCI, the Department of Defense, and the Department of Veterans Affairs (VA). This program will use state-of-the-art research methods for proteomics and genomics analysis.

The need for the Cancer Moonshot has existed for decades. The need was finally matched by the opportunity to benefit from a major infusion of additional resources. Many opportunities exist for bold and feasible initiatives that could have important implications for understanding cancer and helping patients through improved prevention, screening, treatment, and survivorship.

The Cancer Moonshot's Blue Ribbon Panel (BRP) recently issued its recommendations for opportunities to pursue through the Cancer Moonshot. One of these recommendations was to create a national cancer data ecosystem. NCI is already responding by creating the NCI Genomic Data Commons, which will house publicly available data from annotated tumors in NCI-supported and other clinical trials. In its report, the BRP also recommended:

- Development of immunological approaches to prevent cancers not attributable to infectious agents
- Creation of a tumor cell atlas that will enable NCI to go beyond The Cancer Genome Atlas through three-dimensional organization of the microenvironment in addition to the tumor and by including premalignant lesions
- Harnessing of immunotherapy and fusion oncoproteins for application in pediatric cancers

Where We Need to Go. NCI needs to improve cancer prevention, screening, and treatment to continue to lower cancer mortality rates, including in cancers for which progress has been limited. NCI must also redouble its efforts to understand and overcome cancer health disparities. Finally, the institute needs to take full advantage of the opportunity to accelerate progress by working together on a wide range of projects, from the most basic to the most applied.

Questions and Discussion

Dr. Theodorescu asked about plans to integrate the Million Veteran Program into some of NCI's precision medicine trials. Dr. Doroshow explained that Dr. Kelley and his colleagues at the VA plan to open NCI-MATCH at some VA facilities, and NCI hopes to provide resources to VA sites around the country that will be well positioned to enroll patients into various precision medicine trials. Dr. Kelley

added that the Million Veterans Program, which is part of APOLLO, has enrolled approximately half a million veterans to date, but only a minority of these patients have cancer.

Dr. Loehrer commented on the need for expanded implementation of the human papillomavirus (HPV) vaccine. Dr. Lowy replied that the NCI-designated Cancer Centers have embraced HPV vaccination as part of their mission, and they have discussed ways to increase its uptake. The Centers for Disease Control and Prevention is involved in this effort. NCI recently issued a program announcement asking for applications to increase HPV vaccine uptake in regions with lower-than-average uptake rates. NCI will also start a clinical trial in Costa Rica to determine whether a single vaccine dose confers long-term protection for young adolescents. Positive results from this trial along with the availability of biosimilar vaccines and lower costs would make it feasible and cost-effective to vaccinate cohorts of girls around the world every year.

Dr. Weiner requested information on the alignment of NCI intramural research, including activities at the Frederick National Laboratory for Cancer Research (FNLCR), with extramural research to accomplish the goals of the PMI-O and Cancer Moonshot. Dr. Lowy reported that NCI had been planning a recompetition of the FNLCR contract in FY 2017. However, because of the FNLCR's potentially important role in the Cancer Moonshot, NCI has decided to delay the new award until FY 2018, when the current contract ends. The FNLCR advisory committee was to meet in 10 days and would likely discuss the laboratory's involvement in the Cancer Moonshot.

Dr. Mankoff pointed out that the current ability to develop innovative interventions, such as immune checkpoint inhibitors, and genomics depends on investments made 15 or 20 years ago, when the NCI payline was much higher. He asked about the chance of returning to a 15 percent to 20 percent payline. Dr. Lowy replied that NCI's limited funds and low payline do not mean that it should not support high-risk research. For example, NCI continues to support the Outstanding Investigator Award for investigators with outstanding records of productivity in cancer research, and NCI is supporting increasing numbers of R21 awards. In some ways, NCI is the victim of its own success. Whenever the institute increases its investment in the research program pool, the number of applications rises. As a result, success rates for applications to NCI will continue to be low. A 20 percent payline is an appropriate long-term goal, and it would require an institute budget of at least $7.5 billion.

Dr. Munshi requested clarification on funding for the Cancer Moonshot. Dr. Lowy explained that the funding is not clear. He was cautiously optimistic that Congress would provide funding for the Cancer Moonshot and BRP recommendations. However, NCI will start implementing the recommendations regardless of whether it receives funding, although the amount put towards the implementation process will be less without an appropriate budget increase.

In Memoriam: Dan Sargent

Dr. Doroshow shared the sad news of the recent death of a founding member of CTAC, Daniel J. Sargent, PhD (1970–2016), of the Mayo Clinic. Dr. Doroshow characterized Dr. Sargent as not simply a biostatistician but also a supreme investigator who could reach the heart of almost any issue.

III. Blue Ribbon Panel (BRP) Recommendations and Discussion

Dinah S. Singer, PhD
James H. Doroshow, MD

Vice President's Cancer Moonshot Blue Ribbon Panel 2016

Dr. Singer explained that President Obama first announced the Vice President's Cancer Moonshot in his January 2016 State of the Union address. The goals of the Moonshot are to accelerate progress in cancer, encourage greater cooperation and collaboration, and enhance data sharing.

Cancer Moonshot Task Force. Soon after the Moonshot announcement, a task force consisting of the heads of more than 20 federal agencies was formed to address the following policy and regulatory goals:

- Catalyze new scientific breakthroughs
  - Expand mobile device use and create a tracking system for patients
- Unleash the power of data
  - Best practices for consent, seamless data environment, open platforms, and workforce development
- Accelerate delivery of new therapies to patients
  - Modernize eligibility for clinical trials, develop cancer site-agnostic trials, and use real-world evidence
- Strengthen prevention and diagnosis
  - Improve human papillomavirus vaccination and smoking cessation strategies, expand colorectal cancer screening, and screen patients for exposure to environmental chemicals
- Improve patient access and care
  - Conduct education outreach, address cancer survivorship issues, map cancer care across the nation, and develop virtual networks

BRP. The efforts of the federal task force are complementary to, but distinct from, those of the BRP, which provides expert advice on the vision, scientific goals, and implementation of the Cancer Moonshot. The BRP is charged with examining the opportunities and impediments in cancer research and reporting its findings and recommendations to the National Cancer Advisory Board, which will make final recommendations to the NCI director.

The BRP's 28 members include 3 CTAC members: Mr. Arons, Dr. Mitchell, and Dr. Ochoa. Dr. Singer co-chairs the BRP with Dr. Tyler Jacks of the Massachusetts Institute of Technology and Dr. Elizabeth M. Jaffee of Johns Hopkins University. The panel formed seven working groups to address the following topics: cancer immunology, precision prevention and early detection, tumor evolution, clinical trials, implementation sciences, pediatric cancer, and enhanced data sharing. The working groups submitted 14 recommendations to the BRP for its consideration in July 2016. The BRP consolidated 13 of these recommendations into 10 final recommendations in its report (available at https://www.cancer.gov/research/key-initiatives/moonshot-cancer-initiative/blue-ribbon-panel). The 14th recommendation was converted into a demonstration project.

The recommendations are as follows:

A. Network for direct patient engagement: Enlist patients in a federated network that includes patient tumor profiling data and "preregisters" patients for clinical trials
B. Cancer immunotherapy translational science network: Organize networks to discover and evaluate novel immune-based approaches for pediatric and adult cancers; eventually develop vaccines
C. Therapeutic target identification to overcome drug resistance: Launch interdisciplinary studies to delineate mechanisms that lead cancer cells to become resistant to previously effective treatments
D. National cancer data ecosystem: Create an ecosystem to collect, share, and interconnect datasets
E. Fusion oncoproteins in pediatric cancer: Improve understanding of abnormal fusion proteins that result from chromosomal translocations and drive many pediatric cancers
F. Symptom management research: Support research to accelerate development of guidelines for management of patient-reported symptoms to improve quality of life and adherence to treatment regimens
G. Precision prevention and early detection: Implement evidence-based approaches; conduct implementation science research to encourage broader adoption of human papillomavirus vaccination, colorectal cancer screening, and tobacco cessation
H. Retrospective analysis of biospecimens from patients treated with standard of care: Analyze biopsies to learn which features predict outcomes to better plan treatment for future patients
I. Human tumor atlas: Catalog the evolution of genetic lesions and cellular interactions in tumor cells, immune cells, and other cells in tumor microenvironment from the earliest detected lesions to metastasis
J. New enabling technologies: Support development of technologies to accelerate testing of therapies and tumor characterization

The report also calls for three demonstration projects. The first is a national effort to systematically screen all patients with colorectal or endometrial cancer for Lynch syndrome. The second is a national pediatric immunotherapy clinical trials network to facilitate testing of new approaches. Finally, a tumor pharmacotyping project would develop intra- and extratumoral technologies to determine the most effective therapeutic agents for individual patients.

The BRP report identifies unique opportunities that are poised for acceleration through the Cancer Moonshot. The panel forwarded some policy issues that are barriers to the implementation of the recommendations along with the BRP report to the Cancer Moonshot task force for its consideration. Implementation of the recommendations will depend on the extent to which these barriers are addressed.

NCI is now considering approaches to implement the recommendations, with a focus on those that are most feasible in Fiscal Year 2017. NCI will seek advice from its advisory boards and the BRP on the implementation. The institute plans to establish public-private partnerships and partnerships with other agencies to implement the recommendations, recognizing that the extent and rate of implementation will depend on congressional appropriations. Finally, NCI plans to continue investing in investigator-initiated research and research areas beyond the scope of the BRP recommendations.

Questions and Discussion

After noting that recommendations A and B call for the creation of new networks, Dr. Curran asked whether the BRP balanced the creation of new networks with the leveraging of existing NCI-supported networks. Dr. Singer explained that the networks in the recommendations are federated and built on existing networks. Furthermore, the cancer immunotherapy translational science network is designed to support basic and translational research, not clinical trials, to inform immunotherapy. This network would link existing research groups in a collaborative and cooperative fashion.

Dr. Theodorescu wondered about links between recommendation H, retrospective analysis of biospecimens, and established networks focused on precision medicine. Dr. Singer said that all of the recommendations are designed to accelerate ongoing activities, and NCI intends to leverage existing efforts whenever possible, including repositories developed through clinical trials. Dr. Mitchell added that any group, including private commercial entities, that wants to participate in this retrospective analysis would be able to do so. This effort would bring together several entities that have already collected some data and specimens.

Dr. Matrisian asked about data supporting the policy barriers that the BRP identified. Dr. Singer said that the BRP did not address the research on these barriers. Dr. Matrisian commented on the need for a strategic approach to overcome these barriers.

Select BRP Recommendations

Dr. Doroshow asked CTAC to discuss three of the BRP recommendations in depth.

A. Network for Direct Patient Engagement. This recommendation is to develop a federated, large-scale network to offer patients comprehensive tumor profiling and the opportunity to "preregister" for clinical trials. This network could include hundreds of thousands of patients who would voluntarily contribute tumor specimens for molecular characterization to advance the field. Even if the high costs are covered, other barriers would need to be overcome, such as who would collect the tissues, how the tissues would be handled, and how they would be processed.

Dr. Matrisian said that several organizations, such as the Pancreatic Cancer Action Network, have created centralized molecular profiling networks to match patients to clinical trials.

Dr. Fyfe asked whether the BRP discussed the Health Insurance Portability and Accountability Act as a barrier to analyzing the data once they are collected. Mr. Arons replied that the Clinical Trials Working Group agreed that these barriers are not insurmountable. The group also discussed changes to the act that might be needed to make this recommendation feasible.

Dr. Weiner said that ideally, the proposed network will level the playing field to enhance access to clinical trials. But in practice, a concern is how to ensure that sufficient numbers of medically underserved patients enroll in the network. Dr. Mitchell replied that the BRP did discuss this concern, not only for this recommendation but for all recommendations. The patient advocates in all of the BRP working groups were in favor of this recommendation. The challenges to recruitment of underserved populations did not appear to be insurmountable.

Dr. Mankoff stated that researchers have difficulty convincing patients to participate in exploratory biomarker studies when they will not benefit directly from these studies and that they might need an additional tissue biopsy or imaging study. Dr. Singer said that this issue came up primarily in discussions of immunotherapy, where a goal is to identify new biomarkers to predict response. Dr. Mankoff said that retrospective tissues and old clinical, laboratory, and imaging data can be used to discover new biomarkers. However, new biopsies and data are sometimes needed for validation of those markers.

Dr. Barton said that she has experience with two different comprehensive cancer centers that have implemented a version of the proposed network. When new patients come to the Mayo Clinic, for example, they sign a form indicating their interest in being screened for clinical trials. Questions that need to be answered are "What is the best operational mechanism to do this? Should this effort be national or local?"

Dr. Eberlein emphasized the need to make sure that patients benefit in exchange for their participation in the network. He also called for the network to identify how it will use the patient data before collecting the data, noting that whenever researchers collect data without knowing what they will do with it, they collect the wrong data.

Dr. Theodorescu said that the cancer centers are an excellent source of this type of information, and ORIEN (Oncology Research Information Exchange Network) and American Association for Cancer Research Project GENIE (Genomics Evidence Neoplasia Information Exchange) are examples. Several companies have national databases, as do some foundations and patient advocacy groups. Dr. Theodorescu recommended bringing representatives of these various groups and companies together to discuss ways to collaborate.

Dr. Curran suggested that NCI provide incentives to members of the National Clinical Trials Network and NCI Community Oncology Research Program to encourage their patients to participate in the proposed patient engagement network.

F. Symptom Management Research. This is a recommendation to accelerate research to monitor and manage patient-reported symptoms, update national guidelines for symptom control and support, improve quality of life, and ensure patient adherence to treatment to improve outcomes, especially for children.

Dr. Ochoa reported that the BRP working group discussed patients who need prolonged treatment (for 5 years, for example), such as antihormonal treatment for breast or prostate cancer. The data show that up to half of patients stop this treatment after just 2 to2.5 years, because well-established guidelines for managing symptoms are not implemented and patients do not have ready access to a caretaker team for assistance in managing their symptoms. Research should address communications between patients or caretakers and management teams (e.g., through mobile devices) and implementation of existing symptom management guidelines.

Dr. Loehrer commented that different populations metabolize the same drugs differently. For example, African Americans metabolize vincristine more rapidly than Caucasians, so they are less prone to develop neuropathy but are also less likely to achieve therapeutic levels. Symptom management should include pharmacogenomic testing to link symptoms with patient characteristics.

Dr. Barton suggested that NCI leverage evidence-based symptom-management guidelines to implement this recommendation. Implementation science is needed to determine how to integrate these guidelines into practice and make it easy for patients to monitor and report their symptoms. NCI's National Clinical Trial Network and the NCI Community Oncology Research Program are perfectly poised to conduct this type of research.

Dr. Munshi asked whether the BRP discussed how to bring pharmaceutical companies into this effort, partly because these companies could provide funding. Dr. Ochoa replied that this possibility was not discussed, although it could be part of the policy to expand public-private partnerships.

Dr. Mankoff suggested linking this recommendation to basic and translational research on normal tissue toxicity mechanisms of symptom perception and extending this effort to other National Institutes of Health (NIH) institutes and centers, including those studying pain and symptom perception. Dr. Ochoa said that the working group did not discuss integration with basic science. Dr. Mitchell added that patient advocacy groups could participate in this effort because of their strong interest in survivorship and symptom management. The BRP's Clinical Trials Working Group discussed translational research on genomics and other factors that could influence symptom presentation and management.

Lori Minasian, MD, Deputy Director of NCI's Division of Cancer Prevention, reported that NCI has issued a few funding announcements in recent years on symptomatic adverse events, and one provocative question addresses the mechanistic understanding of adverse events. NIH has also released a broader funding opportunity announcement on adverse events. NCI supports research on genetics, epidemiology, and survivorship related to cardiotoxicities, and it collaborates with other NIH institutes and centers to conduct basic and translational research on symptoms and toxicities.

H. Retrospective Analysis of Biospecimens from Patients Treated with Standard of Care. This recommendation is to conduct retrospective analyses of tumor samples from patients treated with standard of care whose outcomes are known to better understand the mechanisms driving individual tumor types. This research will help optimize tumor classification and indicate whether standard of care is likely to be beneficial or potential experimental therapies need to be identified.

NCI's Exceptional Responders Initiative is designed to understand the molecular underpinnings of exceptional responses to treatment, primarily chemotherapy, in patients with cancer. This initiative has analyzed specimens from more than 100 patients. Large clinical trials are collecting tissue samples from patients who have very different responses to the same treatments. Dr. Doroshow asked CTAC about its level of enthusiasm for investing in the molecular characterization of existing materials from clinical trials.

Dr. Matrisian expressed a high level of enthusiasm for this recommendation, because it would leverage existing samples and information, which could be a goldmine for making advances. Dr. Theodorescu agreed and suggested that NCI start with trials that show very different responses. Dr. Perez-Soler also expressed enthusiasm for this recommendation, noting that new tools are available to address resistance to classic agents, such as platinum or paclitaxel, and the reasons why some patients respond to certain agents but others do not have to be understood. Modern tools are now available to look at materials collected previously.

Dr. Fyfe pointed out that if the focus is solely on patients who achieve a complete or a partial response, the initiative might miss long-term survivors. Dr. Gershenson agreed that a focus on long-term

survivors is important, because long-term survival is not necessarily related to response to treatment. Dr. Fingert also agreed, describing examples in which kidney cancer progresses after checkpoint inhibitor treatment at 4 months but the patient survives over the long term when crossed over to another treatment or when treated with the same intervention at a later time. Dr. Barton said that social determinants of health and wellness might be important to long-term survival. She suggested integrating multiple types of data to understand the whole picture.

Dr. Theodorescu proposed leveraging data on the neoadjuvant approaches used in many clinical trials. In some cases, complete response tracks long-term outcomes very closely, allowing the use of endpoints other than survival.

Dr. Ochoa asked about the extent to which the community provides samples and identifies patients for the Exceptional Responders Initiative. Dr. Doroshow replied that the response to this initiative has been strong, and community members have contributed tissues for analysis through this program. This initiative is essentially a pilot test of a program that NCI might implement on a larger scale if additional resources become available.

Dr. Loehrer suggested obtaining data from the SEER (Surveillance, Epidemiology, and End Results) program registries around the country to follow patients over the long term. After a certain number of years, these registries discard their tissue samples, which could then be tested and added to the survival analyses of exceptional responders.

IV. Precision Medicine Clinical Trials: A Learning Process

Jeffrey S. Abrams, MD

Dr. Abrams explained that Dr. Lowy modified the Institute of Medicine definition of "precision medicine" slightly to create the following definition:

> Interventions to prevent, diagnose, or treat a disease (e.g., cancer), based on a molecular and/or mechanistic understanding of the causes, pathogenesis, and/or pathology of the disease. Where the *individual characteristics* of the patient are sufficiently distinct, interventions can be concentrated on those who will benefit, sparing expense and side effects for those who will not.

NCI's precision medicine trials screen large numbers of patients with cancer to find those with the appropriate molecular abnormality. With more precisely defined and limited molecular subgroups in each tumor phenotype, precision medicine trials should enable more rapid discovery of therapeutic signals and hence the ability to move from early-phase trials to definitive trials expeditiously.

NCI Molecular Analysis for Therapy Choice (NCI-MATCH). This phase II precision medicine trial is determining whether certain drugs or drug combinations will be effective for tumors with specific gene abnormalities in adults, regardless of cancer type. NCI-MATCH uses a straightforward schema that involves initial genetic sequencing and immunohistochemistry to identify actionable mutations in tumor specimens. If an actionable mutation is detected, the patient is enrolled in a treatment arm matching the actionable mutation to a study agent. If no actionable mutation is detected (or if a patient withdraws consent for the NCI-MATCH protocol), the patient proceeds to unrestricted non-trial therapy and the disease is followed for 3 years.

The trial opened in August 2015 with 10 treatment arms. The number of patients screened, 100 per week, has greatly exceeded the anticipated rate of 50 per week. The initial goal was for at least 25 percent of enrolled patients to have "rare" or uncommon tumors, but about 65 percent of enrolled patients have uncommon cancers. Since May, the trial has screened more than 2,000 patients, and of the 311 (23 percent) assigned to a treatment arm, 217 (77 percent of those assigned) have enrolled in that arm. NCI is planning a rare variants initiative to add samples from standardized platforms to try to increase the rate of rare mutations identified.

Positive lessons learned from NCI-MATCH include that it is popular, its rate of successful biopsies is as predicted, and a majority of biopsies are successful. In addition, sites are learning how to do these trials, and more patients are willing to have their tumors profiled. Negative lessons learned are that 20 percent of biopsies are not fit for rapid turnaround, adding arms takes several months, NCI needs help finding rare variants, NCI-MATCH's rapid accrual means that results will not be available for a while, and the trial needs to test combinations. Logistical lessons are that NCI-MATCH frequently requires considerable work whenever a change is made and that current processes make it difficult for the trial to be nimble.

Pediatric NCI-MATCH will have a similar design to the adult trial, but it will only have approximately 20 patients per treatment arm. NCI hopes to open the trial with approximately seven or eight arms and plans to screen approximately 300 patients per year. As in the adult trial, NCI hopes that matching therapies to specific genetic targets will improve response rates.

Lung Cancer Master Protocol (Lung-MAP). This biomarker-driven clinical trial uses state-of-the-art genomic profiling to match patients with squamous cell lung cancer to substudies testing investigational treatments that target the genomic alterations driving the growth of their cancer. In the initial plan, patients with the targeted genetic alterations were to be assigned to a phase II randomized trial. If the results were positive, a phase III trial could be started, and progress toward registration would be rapid.

NCI made several revisions to the study after it opened. For example, NCI had to relax some of the eligibility criteria and change the timing of the study assignment, because tissue specimen turnaround was not fast enough. Other changes were allowing second lines of therapy and beyond as well as allowing prescreening when patients were undergoing first-line therapy.

NCI has now screened more than 1,000 patients for this trial, including 703 screened at the time of disease progression and 349 who were prescreened during initial therapy. To date, 385 patients have been assigned to one of the substudies. NCI now plans to add two treatment arms.

Adjuvant Lung Cancer Enrichment Marker Identification and Sequencing Trial (ALCHEMIST). ALCHEMIST consists of four clinical trials (one screening trial and three treatment trials) in patients with completely resected, early-stage, non-small-cell lung cancer. NCI originally planned to screen 6,000 to 8,000 patients to recruit enough patients to each arm. Although many patients are not assigned to a treatment arm, all screened patients complete an epidemiological questionnaire, their tumors and blood specimens are analyzed, their clinical outcomes are followed, and they provide biopsies at progression for research genomics.

ALCHEMIST has 1,059 sites that have registered 1,288 patients to date. However, only 117 patients have been assigned to a treatment arm. About half the patients who are eligible for a treatment

arm at screening do not enroll in the study for various reasons, often because they do not want to undergo more therapy. NCI has considered several changes to increase enrollment, such as removing placebo arms for targeted therapies, changing the endpoint to disease-free survival (which would require fewer patients), and increasing outreach to thoracic surgeons. If screening does not improve dramatically, NCI will need to change the trial design.

Dr. Abrams commented that this was an excellent example of team research. These trials were made possible by the changes in the NCI National Clinical Trials Network (NCTN) that occurred in March 2014, when the 10 cooperative groups were consolidated into a network of four adult groups, one pediatric group, and a Canadian group. Lung-MAP, led by SWOG, was the first trial. ALCHEMIST, led by the Alliance for Clinical Trials in Oncology and the ECOG-ACRIN Cancer Research Group, followed next. NCI-MATCH, led by ECOG-ACRIN, was the last to begin. The NCI-MATCH substudies are led by investigators from all of the NCTN groups. Pediatric MATCH will be led by the Children's Oncology Group.

Questions and Discussion

Dr. LeBlanc, who has been involved in Lung-MAP, explained that all of the precision medicine trials that Dr. Abrams had described use a similar process. They start with a screening step, and they are designed to answer multiple questions at the same time. Although he was initially concerned about the logistics of the studies, he has been pleasantly surprised at how well the NCI and NCTN group data collection systems have worked together. However, when a trial needs a change, many of the questions being addressed must change at the same time, which can be challenging. The trials can generate results quickly, but they require complex organization.

Dr. Fyfe, who has also been involved in Lung-MAP, agreed that the logistics of Lung-MAP have been impressive. A challenge is the intense competition from industry-sponsored clinical trials. For example, there are probably more than 50 company-sponsored trials of non-small-cell lung cancer. These trials make it difficult to recruit patients to Lung-MAP in a timely fashion and to answer questions about patients screened for NCI-MATCH but not assigned to a treatment arm.

Dr. Loehrer asked about the standardization of genomic analysis in NCI-MATCH. Dr. Doroshow reported that NCI spent more than a year trying to achieve high concordance rates among four laboratories and put in place quality control procedures for something as simple as making peripheral blood mononuclear cells. NCI is currently determining how to standardize the procedures used in NCI-MATCH to identify molecular abnormalities in screened patients by four or five large laboratories. Extremely trivial differences can change results. NCI-MATCH requires a core group of laboratories that is committed to doing the procedures in exactly the same way every time.

Recommendations for Future Directions for NCI's Precision Medicine Trials. Dr. Gershenson asked about plans for NCI-MATCH to add expansion cohorts of phase II studies in different tumor types with identical mutations that respond differently to a targeted agent. He also asked what NCI will do when it does not accrue patients with a certain type of tumor associated with a given molecular signature that matches a study drug. Dr. Abrams said that NCI will pursue studies of agents in a specific disease if the initial study has a positive signal. If NCI does not recruit patients with tumor types that have a good preclinical rationale for a given signal, it will accrue more patients to that arm. NCI-MATCH has flexibility to expand in different directions based on positive signals. If a genetic abnormality is common

enough and present in a common enough cancer, NCI could also conduct the study outside NCI-MATCH in an NCTN group.

Dr. Mitchell said that the organization of NCI-MATCH has been challenging, but the trial's leaders have it down to a science now, and the challenge is what to do next. A great deal of infrastructure and other resources have been committed to this trial, and the feasibility of this approach has now been demonstrated. NCI also needs to determine what types of trials, single-agent or multiagent, to conduct; the answer will be apparent once the outcome data have been analyzed. Obtaining adequate specimens has probably been one of the greatest challenges because many samples are inadequate for diagnosis or are associated with incorrect diagnoses.

Dr. Loehrer commented that although patients are enthusiastic about enrolling in NCI-MATCH, only about 10 percent of those who are screened enroll in a treatment trial. A follow-up to NCI-MATCH could be the "MATCHmaker" trial, in which patients who are screened but do not have a matching molecular marker and their physicians receive a report listing other trials from ClinicalTrials.gov that are testing treatments matching the patient's molecular marker. NCI could then collect data on how many patients enter a clinical trial as a result of being screened for NCI-MATCH.

Suggestions for Improving the Conduct of These Trials. Dr. Davidson asked about replacing tissue-based assays with blood-based assays in the precision medicine trials. Dr. Abrams said that tissue biopsies are expensive and difficult for patients. Blood-based assays would also be expensive, at least initially, but they would be less invasive. These types of assays could be done sequentially and answer more questions than tissue-based assays. Several investigators and commercial entities are looking into the possibility of blood-based assays.

Dr. Loehrer suggested that NCI-MATCH form partnerships to use genomic data from biopsies collected before patients are screened for NCI-MATCH to prevent the need for yet another biopsy.

Dr. Theodorescu asked whether NCI has mined the data to determine whether certain variables predict biopsy failure because it could use this information to change its approach to obtaining a biopsy or selecting patients. He suggested that when patients do not respond to an agent after assignment to an NCI-MATCH treatment arm, they undergo more extensive genomic analysis. The assumption would be that over time, researchers would discover new treatment targets that could be part of a follow-up NCI-MATCH trial.

Dr. Abrams said that through the Precision Medicine Initiative, funding is available for whole-exome sequencing on the NCI-MATCH specimens, and these data will be made publicly available. Furthermore, investigators are mining existing biopsy specimens;other attempts are being made to increase biopsy yields. Dr. Theodorescu pointed out that bone biopsies are difficult to do, and this is an example of an area that would benefit from different sampling strategies or technologies.

Leveraging Histology-Agnostic Approaches. Dr. Pazdur asked about the possibility of including children in NCI-MATCH, because children have some of the molecular targets included in the adult NCI-MATCH trial, and this trial is "site agnostic." Dr. Abrams said that patient advocates have also made this suggestion, but adding children to NCI-MATCH would be challenging. The NCTN groups are adding more and more studies in adolescents and young adults, and NCI is open to including children in its adult trials and vice versa. Pediatric MATCH will use some different approaches, including germline testing and biopsy approaches, from adult NCI-MATCH.

Dr. Pazdur said that the treatment arms in pediatric MATCH might not be feasible because of likely recruitment challenges—many pediatric cancers and many mutations in these diseases are very rare. If children enrolled in adult NCI-MATCH studies, it would at least be possible to make inferences from the results in adults to pediatric cancers.

Nita L. Seibel, MD, head, Pediatric Solid Tumor Therapeutics, Cancer Therapy Evaluation Program, reported that the agents in the pediatric and adult NCI-MATCH trials are quite different. The adult NCI-MATCH trial does include young adults age 18 and older, and NCI might further lower the minimum age.

V. New Precision Medicine Initiatives

Jeffrey S. Abrams, MD
Toby T. Hecht, PhD

Dr. Abrams explained that NCI used some of the additional funding for the Precision Medicine Initiative-Oncology to support the clinical trials he had described in the previous session. NCI is also using this additional funding for new administrative supplements announced in April and May 2016. NCI has now made these awards to support the following activities:

- Expand support for the development of immunotherapy trials
    - Biomarker development and correlative studies associated with clinical trials of immunotherapy
    - Studies of how the microenvironment of pancreatic ductal adenocarcinoma (PDAC) affects immunotherapy
    - Improvement and optimization of T-cell therapies and current good manufacturing practice processes for production of autologous T-cell therapy products targeting solid tumors
- Improve preclinical models for evaluating targeted therapeutics and immunotherapy
    - Research in canine immunotherapy through collaboration of NCI-designated cancer centers and veterinary medical colleges
    - Collaborative research efforts to enhance preclinical drug development and preclinical clinical trials utilizing patient-derived xenograft (PDX) models
- Use clinical materials from drug-resistant patients for molecular analysis, leading to rational studies of targeted combinations
    - Studies of mechanisms of cancer sensitivity and resistance to therapy utilizing samples and information from human clinical trials

The Board of Scientific Advisors recently approved five new Request for Application (RFA) concepts that NCI developed based on the experience with these administrative supplements. Dr. Abrams described each of these RFAs.

Cancer Immunotherapy Monitoring Network. The network will support high-quality correlative studies in NCI-sponsored early-phase clinical trials (in approximately 360 patients a year) to improve treatment outcomes. These early-phase studies will serve as a proving ground for clinically informative biomarkers that can be validated in late-phase trials. The network will consist of up to three Cancer Immune Monitoring and Analysis Centers (CIMACs) and the Cancer Immunologic Data Commons (CIDC). Each CIMAC will be paired with one or more clinical trial networks, and these CIMAC/clinical trials network teams will develop and initiate each trial jointly. The CIDC will store the

trial results for secondary analyses by the greater research community. Some resources will also be available for biomarker assays for trials supported through other NCI mechanisms, such as R01s.

PDX Development and Trial Centers Network and PDX Data Commons and Coordinating Center. Goals are to use PDX models to support more efficient and precise development of investigational new drug agents in the NCI Experimental Therapeutics Clinical Trials Network and test original concepts from extramural investigators. This initiative will be coordinated with the NCI Patient-Derived Models Repository at the Frederick National Laboratory for Cancer Research. NCI plans to fund up to four PDX Development and Trial Centers.

Drug Resistance and Sensitivity Network. This network will consist of up to five sites, each focusing on a unique broad area of drug resistance or sensitivity research, and it will provide NCI with expertise in new drug development. The network will focus on new models and diagnostic techniques, and it will use human tumor samples whenever possible. Each site will conduct several linked projects in its area of drug resistance or sensitivity. Studies involving NCI investigational new drug agents will receive preference, but NCI will consider applications involving other agents.

Canine Immunotherapy Trials and Correlative Studies. Dr. Hecht explained that this RFA will establish a collaborative network of up to five teams (to include academic laboratories, veterinary medicine sites, clinical trial sites, and veterinary pharmaceutical companies) to support canine clinical trials using immunotherapy agents and novel combinations of immunotherapy and other modalities in dogs. The initiative will also include correlative studies to characterize the cellular and molecular mechanisms that determine the antitumor response (or nonresponse) in dogs with spontaneous tumors. Studies will focus primarily on spontaneous B-cell lymphoma, melanoma, glioma, bladder cancer, osteosarcoma, and mammary tumors, but other tumors may be studied if accrual is adequate. A U24 award will coordinate the network and will include the NCI Comparative Oncology Program as a facilitator.

Consortium for PDAC Translational Studies on the Tumor Microenvironment. This network will conduct coordinated research on aspects of the PDAC microenvironment, with the option of conducting early-phase clinical trials, particularly with agents developed at grantee institutions or in collaboration with industry. The initiative will fund up to five U01 grants focused on various characteristics of the PDAC tumor microenvironment that will enable the design of immunotherapies and other treatments. Most of the studies will be preclinical with translational potential, although the funded sites could propose a pilot clinical trial in later years. A U24 resource center for the network will also be supported.

In addition, NCI awarded three administrative supplements to optimize T-cell therapy products targeting solid tumors.

Questions and Discussion

Dr. Weiner noted that the Cancer Immunotherapy Monitoring Network could help establish a cancer immune atlas, and he asked how many samples might be needed to represent the immunological landscape in cancer. Dr. Abrams replied that the CIDC is an important part of this RFA for the reason Dr. Weiner gave. Many more samples than the 360 a year projected for the network would probably be needed to represent the entire immunological landscape in cancer. This network represents a step in that direction.

Dr. Perez-Soler commented that some companies offer PDX development for individual patients who are undergoing treatment. He asked whether the PDX initiative would involve these companies through the Cancer Moonshot so that their models would be available to researchers. Dr. Doroshow replied that NCI accepts models from a variety of sources as long as they meet NCI's high standards for these models. Furthermore, NCI supplies these well-characterized models at low cost to investigators. Dr. Fyfe remarked that the characteristics of the tumor that is implanted into a PDX model can change over time. She asked about data showing that these models are more predictive than xenograft models. Dr. Doroshow replied the mutations usually maintain fidelity through at least three or four passages, and NCI will do the research needed to determine how predictive the PDX models are.

Dr. Matrisian asked about the timeline for the RFAs. Dr. Hecht explained that NCI plans to issue the RFAs in early 2017.

VI. Trial Reporting in ClinicalTrials.gov—The Final Rule

Deborah A. Zarin, PhD

Until a few years ago, individual investigators designed and conducted their clinical trials with little oversight over their analytic methods and without necessarily undergoing related training. These investigators decided when, whether, and how to disseminate their trial results. As a result, about a third of trial results were never published. Several policies issued in the last decade or so have disrupted this status quo, including reporting requirements in a notice of proposed rulemaking from the Food and Drug Administration Amendments Act (FDAAA) of 2007, a draft National Institutes of Health (NIH) policy, and recommendations from the International Committee of Medical Journal Editors. In addition, NCI issued its own policy in early 2015 requiring publication of results or reporting results in ClinicalTrials.gov.

In September 2016, the Department of Health and Human Services issued the FDAAA final rule (https://www.federalregister.gov/documents/2016/09/21/2016-22129/clinical-trials-registration-and-results-information-submission). According to this rule, all applicable clinical trials (including non-phase I interventional studies of drugs, biologic agents, and devices as well as single-arm interventional studies) starting on or after January 18, 2017, must be registered and their results must be reported in ClinicalTrials.gov. Required information will include baseline race/ethnicity, outcome measures, and all-cause mortality data. NIH will be required to withhold funding from sponsors (typically grantee institutions) of NIH-funded applicable clinical trials that are noncompliant.

Also in September 2016, NIH finalized its policy on the dissemination of NIH-funded clinical trial information (https://grants.nih.gov/grants/guide/notice-files/NOT-OD-16-149.html). NIH requires all NIH-funded interventional studies (clinical trials, including phase I studies and studies that do not include drugs, biologic agents, or devices) that start on or after January 18, 2017, to be registered in and submit their results to ClinicalTrials.gov. Publication of study results in a journal will not be sufficient to comply with this requirement, and penalties for noncompliance can include loss of NIH funding.

With the FDAAA final rule and the final NIH policy, the results of most clinical trials at academic medical centers will need to be reported in ClinicalTrials.gov. The National Library of Medicine (NLM) has established a quality assurance process to ensure that results reported in ClinicalTrials.gov are complete and meaningful. NLM ensures that the entered data convey the study design, conduct, and analysis; that they make sense (e.g., the measure name matches the units and data, and all required parameters and data are present); and that the results are logical and internally consistent.

Studies have shown that clinical trials results published in ClinicalTrials.gov are more complete than the results published in journal articles.

NLM's goal is to make the data entry process as straightforward as possible for motivated people with the requisite knowledge, which consists of clinical research knowledge and skills along with an understanding of the trial and access to summary data. Twelve NLM staff members are available to provide individual assistance with entering data into ClinicalTrials.gov. The system issues reports to help administrators within the organization keep track of the status of their records, and email and other warning systems alert responsible parties of problems that require attention.

As of November 1, 2016, 1,035 NCI-sponsored trials that were probable applicable clinical trials had been registered in ClinicalTrials.gov. Of these, 652 trials might need to report results, and 601 (92 percent) had reported results. Among 10 academic medical centers that receive the most NIH funding, compliance rates range from 9 percent to 88 percent. The compliance rates of specific institutions are likely to be reported publicly in the future.

Questions and Discussion

Dr. Fingert asked Dr. Kibbe to comment on the use of structured data in trials from the beginning to ensure that the data can be shared, instead of waiting until the end of the study only to find out that others use different standards and the study data must be reformatted. Dr. Kibbe replied that NCI should ask investigators to capture and report data using the established structure. For example, NCI data are often made available through the Cancer Data Standards Registry and Repository or Enterprise Vocabulary Services, and investigators should apply these standards when appropriate. In particular, the use of standardized vocabulary for adverse events is important. However, because ClinicalTrials.gov is not specific to cancer, the applicability of NCI's standards to data reported to this resource is not clear.

Dr. Zarin explained that NLM is constrained by various legal rules in the standards it can establish for ClinicalTrials.gov, which includes studies that are and are not funded by NIH. NLM cannot require all users to use the latest version of the Medical Dictionary for Regulatory Activities, for example, because NLM does not have the authority to require studies to collect data in a certain way. However, NLM does encourage users who have applied a standard to specify that standard.

Dr. Fingert noted that the Joint Task Force on Clinical Trial Competency is working to integrate efforts to identify the core clinical trial competencies required for investigators and support professionals. He asked what CTAC could do to improve clinical trials competency and thus enhance the value of using some of the available standards. Dr. Doroshow replied that NIH has undertaken some activities to retrain the entire intramural staff along these lines, and NCI will consider ways for CTAC to contribute to enhancing these competencies. Professionals need to update their credentials in this area on a regular basis.

Dr. Fingert said that industry has learned that the best approach is managing requirements, like those in the FDAAA final rule and NIH policy, in advance to prevent the need to clean up the data later on or learn that a regulator has rejected the data.

Dr. Prindiville pointed out that Francis S. Collins, MD, PhD, Director of NIH, and other senior NIH leaders recently published a brief commentary in the *Journal of the American Medical Association* describing NIH plans to require Good Clinical Practice training for investigators and NIH staff

responsible for conducting or overseeing clinical trials. In addition, NIH will require all applications for clinical trials to respond to clinical-trial-specific funding opportunity announcements, which will help NIH track trial-related activities.

Dr. Mankoff asked whether ClinicalTrials.gov can accommodate information on trials that do not fit the standard model. For example, registering a trial that is somewhere between a phase I and a phase II trial can be challenging. Dr. Zarin replied that ClinicalTrials.gov has approximately 230,000 registered trials and 23,000 sets of results, only about half of which fall under FDAAA. So about half of the reported results come from studies that do not fit the criteria for the standard types of trials governed by the legislation; these include observational studies and others that do not involve drugs or devices. NLM therefore has a great deal of experience with a very broad array of trials, and Dr. Zarin expressed confidence that the system can accommodate the registration of just about any clinical trial. NLM has worked hard to try to accommodate results reports from many different trials, such as its recently developed reporting instructions for adaptive trials. If someone trying to register a trial or report trial results has a problem, he or she should contact Dr. Zarin or her staff.

Dr. Mankoff commented that the iterative process involved in working with an NLM staff member is educational for both sides. However, he was concerned about the possibility that results from a study with a novel design might be judged to be incorrectly entered. Dr. Zarin said that the one-to-one assistance she had described guarantees that the information submitted will pass NLM's quality control requirements. A concern would be if the study results were entered in a way that the investigator thought was misleading, but this has not happened.

Dr. Weiner pointed out that some departments or disciplines have a less well-developed clinical research enterprise, and difficulties complying with the regulations could result in penalties. Dr. Zarin explained that the NIH Office of Extramural Research and Office of Science Policy are responsible for outreach about the new requirements. Leaders of academic medical centers need to determine when they need assistance to comply with the regulations. For this reason, NIH leaders are writing articles and giving presentations to explain that institutions will be accountable, which is a new idea for many. She asked for help from CTAC in spreading the word about these new policies.

Dr. Weiner asked about the resources required to comply with the policies. Dr. Zarin reported that Duke University hired three high-level staff members to manage the institution's ClinicalTrials.gov reporting, and this group has described its approach and the resources required in a journal article. Dr. Zarin offered to send this article to CTAC. In addition, some Clinical and Translational Science Award representatives started a group that meets by telephone every month to discuss ClinicalTrials.gov reporting, and this group's membership has since broadened beyond recipients of this award. This group has used a survey to determine whether staff at member institutions are sufficient. NLM believes that institutions need one resource person who understands the rules of ClinicalTrials.gov and can help investigators determine how to report their results. This individual should have a PhD or perhaps a master's degree so that he or she has appropriate scientific credentials. The other requirement is motivation from researchers to seek this assistance. Because many institutions do not have this resource, NLM has begun offering its one-on-one support.

Dr. Fyfe asked whether trials that have indirect support from NIH must report their results in ClinicalTrials.gov. Dr. Zarin said that if a clinical trial funded by a pharmaceutical company or foundation is conducted at an NCI-Designated Cancer Center, it does not fall under the NIH reporting

policy. However, the FDAAA final rule applies if a trial funded by a pharmaceutical company is testing a drug or device.

Mr. Arons asked how advocates will know whether the new policies are being enforced after the first year. Dr. Zarin predicted that some enforcement actions will have taken place, and a much higher percentage of trials will have results in ClinicalTrials.gov.

VII. Biomarker, Imaging, and Quality of Life Studies Funding Program (BIQSFP)

James H. Doroshow, MD

NCI created BIQSFP in response to the 2005 Clinical Trials Working Group Scientific Quality Initiatives, which called for adequate funding for clinical trials involving biomarkers, imaging, and quality of life and for the establishment of quality control standards for laboratory assays and imaging procedures used in association with NCI-funded clinical trials. During CTAC's 2015 review of the results of the Clinical Trials Working Group initiatives, it deemed these initiatives to have been achieved and called for periodic updates.

Integral and/or integrated studies associated with phase III treatment trials and cancer prevention trials are eligible for the BIQSFP program, but only randomized phase III clinical trials are eligible for cost-effectiveness analysis funding. Support of studies in phase II clinical trials is limited to large (at least 100 patients), randomized treatment trials with an integral and/or integrated biomarker or imaging study (or studies). BIQSFP uses the definitions of "integral" and "integrated" developed by the Program for the Assessment of Clinical Cancer Tests under CTAC's auspices in 2006.

To date, the program has received 159 applications embedded in 117 clinical trial concepts. Of these 159 applications, NCI approved 71 across 61 clinical trials, but 2 of the 61 concepts were withdrawn before study activation. To date, 50 of the protocols with BIQSFP funding have been activated, and the vast majority (87 percent) of approved studies are of biomarkers. The purpose of most approved integral biomarker studies is to determine trial eligibility, whereas most integrated biomarker studies are designed to evaluate treatment response or toxicities/symptoms related to an intervention. BIQSFP has issued approximately $61 million in the last 8 years.

Although 14 BIQSFP trials have completed accrual, only two of the clinical trials have reached their primary endpoints to date and published their results. Therefore, NCI does not yet have enough data to apply metrics to determine whether the BIQSFP funding has been beneficial. This experience shows how difficult it is to develop an integrated biomarker, which might be one reason why NCI received fewer applications for integrated studies than might have been expected originally. Dr. Doroshow concluded by saying that he believes that providing funding for high-quality integrated analyses associated with large clinical trials has been important.

Questions and Discussion

Dr. Mankoff suggested that one reason why BIQSFP has not received more applications for imaging studies is that very few imaging studies have made sufficient progress to develop true integral biomarkers. Imaging studies are currently "squeezed between mechanisms"—they rarely qualify for BIQSFP biomarker funding, and imaging trials that are embedded in therapy trials are not considered primary trials. Validation of new imaging studies could provide significant biomarkers, including markers that identify therapeutic targets.

Dr. Doroshow pointed out that, periodically, NCI has changed the eligibility criteria for BIQSFP, and it needs to continue modifying the program in response to needs. Dr. Mankoff said that those conducting imaging clinical trials would welcome the opportunity to talk to BIQSFP leaders and staff from NCI's imaging program about needed changes.

Dr. Loehrer asked about the costs of analyzing biomarkers at Clinical Laboratory Improvement Amendments-certified laboratories versus hospitals, and he wondered whether centralized analyses would be more cost-effective. Dr. Doroshow said that the analyses are done centrally. For example, a single certified laboratory for a given NCTN group does all of the testing for the entire trial.

Dr. Curran suggested that NCI encourage the NCI National Clinical Trials Network groups to spread the word about BIQSFP through publications, showing that this investment is worthwhile. The message would be that these trials could not be done without the BIQSFP support. Dr. Doroshow said that this approach would be great and that NCI would be happy to assist with the process. Dr. Prindiville encouraged investigators who have finished integrated studies to publish their results as quickly as possible.

VIII. Development and Implementation of the Cancer Patient Tobacco Use Questionnaire

Stephanie R. Land, PhD
Michael L. LeBlanc, PhD

Development of Cancer Patient Tobacco Use Questionnaire (C-TUQ)

Dr. Land explained the need for assessing tobacco use in cancer clinical trials by pointing out that tobacco use can modify treatment effects and is an important predictive and prognostic variable to consider in trials. Furthermore, many scientific questions about tobacco use by patients with cancer still need to be answered, such as which populations experience diminished treatment efficacy with tobacco use.

Patients with cancer and survivors who smoke cigarettes have poorer health outcomes, including higher all-cause and cancer-specific mortality along with an increased risk of tobacco-related second primary cancer. In addition, smokers may have a higher risk of recurrence, poorer response to treatment, and increased toxicity. Despite its clinical significance, smoking is not widely assessed in cancer clinical trials or practice, the assessment methods used are inconsistent, and follow-up during and after treatment is limited.

NCI and the American Association for Cancer Research jointly created the Cancer Patient Tobacco Use Assessment Task Force to develop recommendations for patient-reported tobacco use measures, assessment timing, and a research agenda. The task force has now developed the C-TUQ (see https://cancercontrol.cancer.gov/brp/tcrb/research_topic-tobacco-use.html for the latest version and user manual), which was tested in a cognitive interview study. The C-TUQ includes four core items on smoking status and history for broad use in trials and practice. An extension set provides a pool of items for comprehensive assessment; its baseline and follow-up items include questions about smoking history and status relative to diagnosis and treatment, use of other tobacco products, secondhand smoke exposure, and smoking cessation. The questionnaire has been downloaded over 1,400 times to date, and the task force recommends broad inclusion of the C-TUQ items in cancer research. At a minimum, tobacco use should be assessed at trial registration and at the end of protocol therapy. Assessments at additional

times—either monthly or before and after surgery, on day 1 of each chemotherapy cycle, at the beginning and end of other therapy, and 6-12 months after the completion of treatment—are also recommended.

NCI has issued three administrative supplements for the collection and analysis of tobacco use data via the C-TUQ for NCI National Clinical Trials Network (NCTN) and NCI Community Oncology Research Program clinical trials. These supplements fund scientific research using the C-TUQ, raise awareness of the questionnaire, fund the initial costs of systems changes that facilitate inclusion of the C-TUQ in future trials, promote shared data, and encourage tobacco use assessment as a routine and essential component of cancer clinical trials. The Lung Cancer Master Protocol (Lung-MAP) study includes the core C-TUQ items, and other NCTN trials in development will include the questionnaire.

Two of the supplements are supporting research by the NCTN ECOG-ACRIN Cancer Research Group and NCI Community Oncology Research Program. Through these supplements, eight different trials are using the core C-TUQ and several extension items to assess the effects of tobacco use on treatment toxicity and symptom burden, treatment duration and dose intensity, and therapeutic benefit.

Implementation of the C-TUQ

Dr. LeBlanc described experiences with the third C-TUQ administrative supplement, which is being used to study the effects of smoking on treatment efficacy and clinical outcomes in a phase III bladder cancer study.

Cigarette smoking is an established risk factor for bladder cancer, yet the impact of current smoking and smoking history on the course of the disease is not well understood. The prospective smoking study using the C-TUQ will be embedded in a 5-year, randomized phase III trial to test the noninferiority of the Tokyo bacillus Calmette–Guérin (BCG) strain and the superiority of the addition of priming in 924 patients with non-muscle-invasive bladder cancer. The supplement aims are to:

- Evaluate the associations of smoking status, cumulative smoking exposure, and time since smoking cessation with patient outcomes
- Evaluate whether the BCG strain's efficacy is modified by measures of smoking exposure
- Estimate adverse event profiles for each treatment arm by smoking status variables
- Test whether changes in urinary cytokine levels after BCG vary by smoking exposure variables

The study will use C-TUQ core items to assess baseline smoking status and cumulative smoking exposure. The study will also use the four core items and two extension items in follow-up questionnaires to capture quit attempts, and it will measure exposure at study entry, 1 year after randomization, and 2 years after randomization. This tobacco use study will provide feasibility results, serve as a non-lung-cancer test case, move toward the addition of limited C-TUQ questions more broadly across NCTN studies, and open opportunities for future smoking-related research questions.

Questions and Discussion

Dr. Davidson asked whether a long-term goal is to embed the C-TUQ into every NCTN trial from now on. Dr. Land confirmed that this is the goal. Use of the questionnaire in NCTN trials is not currently a mandate, but its use in the future is a reasonable goal given tobacco's importance as a host factor.

Dr. Davidson pointed out that several more states might permit use of medical marijuana after the upcoming national election. She asked about plans to measure use of marijuana in clinical trials. Dr. Land said that research on the use of marijuana is increasing, some of which is funded by NCI or the National Institute on Drug Abuse.

Dr. Mitchell asked whether the C-TUQ collects information on use of electronic cigarettes. Dr. Land replied that the questionnaire does capture data on the use of electronic cigarettes and other tobacco products. Many studies of electronic cigarettes are now ongoing, some of which are funded by NCI or the Food and Drug Administration.

Dr. Fingert commented that paper-based questionnaires might lead to more missing data than those administered on an electronic device would, and he asked about the completeness of C-TUQ responses and approaches if data are missing. Dr. Land reported that one of the ECOG-ACRIN supplements is using mobile phones to administer the survey. She added that NCI is interested in using mobile phones and other technologies to administer the C-TUQ, and it should take advantage of any approaches that minimize missing data. Dr. Fingert suggested basing the decision about how to administer the questionnaires on the evidence. Some demographic groups, such as the oldest age groups, provide more complete responses to paper-based questionnaires than those delivered on an electronic device. He suggested that NCI assess compliance rates early on. Dr. Land pointed out that the C-TUQ questions are asked in the context of other measurements in each study. Some issues might be unique to tobacco use assessments, such as stigma and individual willingness to be forthcoming about tobacco use. However, most issues related to missing data will be similar for collection of quality of life and other types of data. NCI will embrace the full set of knowledge available on how to collect data with questionnaires.

Dr. LeBlanc pointed out that the use of mobile devices to administer questionnaires and even deliver interventions raises questions about the possibility of selection bias. Given the ages of most patients with cancer, the use of mobile devices might not always be appropriate in this population. Dr. LeBlanc believes that the opposite of Moore's law (the more data you collect, the poorer the data quality will be) applies to computing science.

Dr. Mitchell commented that electronic cigarettes can be used to inhale several different substances and that it might be important to distinguish between these substances, because they have different physiological effects. Dr. Land agreed, noting that asking about the use of alternative devices to absorb nicotine or other substances is complicated.

Dr. Ochoa stated that the lung cancer immunotherapy trial data suggest that smokers have a better response, because cigarettes increase the number of antigens that the immune system can target.

IX. Ongoing and New Business

Nancy E. Davidson, MD

NCI Council of Research Advocates

Dr. Davidson asked Mr. Arons to give an update on the NCI Council of Research Advocates (NCRA), which he chairs. Mr. Arons explained that the NCRA spent its most recent meeting discussing the national Cancer Moonshot. NCRA members agreed on the importance of funding to implement the Cancer Moonshot recommendations when Congress returns after the upcoming national election. Other

legislation important to the advocacy community includes an appropriations bill to keep the federal government open and to pass the 21st Century Cures Act. This latter bill includes several provisions related to clinical trials, and it has strong bipartisan support. The NCRA is trying to support the activities of CTAC and to help make clinical trials better, stronger, and faster for patients.

CTAC Working Groups Update

Dr. Prindiville reminded CTAC that the committee has the following working groups (http://deainfo.nci.nih.gov/advisory/ctac/workgroup/index.htm): the Clinical Trials Informatics Working Group, the National Clinical Trials Network (NCTN) External Evaluation Working Group, the Progress in Pancreatic Ductal Adenocarcinoma Working Group, and the Progress in Small Cell Lung Cancer Research Working Group. The Coordinating Center for Clinical Trials is forming the Clinical Trials Strategic Assessment Working Group to examine the strategic priorities of the scientific steering committees and the NCTN groups as well as their respective portfolios. The Clinical Trials Informatics Working Group, chaired by Dr. Weiner and Dr. Kibbe, is planning to hold its first in-person meeting in November 2016. The NCTN External Evaluation Working Group will report on its progress at the March 2017 CTAC meeting.

Dr. Curran asked whether the timeline for the NCTN External Evaluation Working Group aligns with the timeline for submitting applications. Dr. Prindiville said that the plan is to align the timelines for these activities. The working group's report, which will be ready for CTAC's review in March, will become part of the concept package presented to senior NCI leadership and the Board of Scientific Advisors prior to the release of the request for applications.

Future Agenda Items

Dr. Davidson listed the following agenda items for upcoming CTAC meetings:

- Report on the Food and Drug Administration Oncology Center of Excellence
- NCTN External Evaluation Working Group report
- NCI Experimental Therapeutics Program update

Dr. Loehrer suggested as a future agenda item a discussion of how to enhance retrieval of clinical trials information globally, including how to minimize the burden on staff and faculty and how to increase public participation. Dr. Prindiville pointed out that making it easier to find clinical trials is one of the topics that the Clinical Trials Informatics Working Group will address.

Appendix

National Institutes of Health
National Cancer Institute
Clinical Trials and Translational Research Advisory Committee

CHAIR

Nancy E. Davidson, MD **2018**
Director
University of Pittsburgh Cancer Institute
Pittsburgh, PA

MEMBERS

David F. Arons, JD (NCRA) **2016**
Director of Public Policy
National Brain Tumor Society
Watertown, MA

Susan M. Blaney, MD **2019**
Vice President for Clinical and Translational Research
Vice Chair for Research
Department of Pediatrics
Baylor College of Medicine
Texas Children's Hospital
Houston, TX

Walter J. Curran, Jr., MD, PhD **2019**
Professor and Chairman
Department of Radiation Oncology
Emory University School of Medicine
Atlanta, GA

David M. Gershenson, MD **2020**
Professor of Gynecology
Department of Gynecologic Oncology and Reproductive Medicine
Division of Surgery
University of Texas MD Anderson Cancer Center
Houston, TX

Michael L. LeBlanc, PhD **2019**
Member
Fred Hutchinson Cancer Research Center
Research Professor
Department of Biostatistics
University of Washington
Seattle, WA

Patrick J. Loehrer, Sr., MD **2020**
Director
Melvin and Bren Simon Cancer Center
Associate Dean for Cancer Research
Indiana University School of Medicine
Indianapolis, IN

David A. Mankoff, MD, PhD **2019**
Gerd Muehllehner Professor of Radiology
Division Chief, Nuclear Medicine and Clinical Molecular Imaging
Perelman School of Medicine
University of Pennsylvania
Philadelphia, PA

Edith P. Mitchell, MD **2016**
Clinical Professor of Medicine and Medical Oncology
Program Leader, Gastrointestinal Oncology
Sidney Kimmel Comprehensive Cancer Center
Thomas Jefferson University
Philadelphia, PA

Nikhil C. Munshi, MD **2016**
Associate Director
Jerome Lipper Multiple Myeloma Center
Dana-Farber Cancer Institute
Associate Professor of Medicine
Harvard Medical School
Boston, MA

Augusto C. Ochoa, MD **2018**
Director
Stanley S. Scott Cancer Center
Professor
Department of Pediatrics
Louisiana State University Health Sciences Center
New Orleans, LA

Gloria M. Petersen, PhD **2019**
Professor of Epidemiology
Department of Education Administration
Mayo Clinic College of Medicine
Rochester, MN

Louis M. Weiner, MD (BSC) **2017**
Director
Lombardi Comprehensive Cancer Center
Francis L. and Charlotte G. Gragnani Chair
Department of Oncology
Georgetown University Medical Center
Washington, DC

***Ex Officio* Members**

William Dahut, MD
Acting Scientific Director of Clinical Research
Center for Cancer Research
National Cancer Institute
National Institutes of Health
Bethesda, MD

James H. Doroshow, MD
Deputy Director for Clinical and Translational Research
National Cancer Institute
National Institutes of Health
Bethesda, MD

Paulette S. Gray, PhD
Director
Division of Extramural Activities
National Cancer Institute
National Institutes of Health
Bethesda, MD

Rosemarie Hakim, PhD, MS
Epidemiologist
Centers for Medicare & Medicaid Services
Baltimore, MD

Michael J. Kelley, MD, FACP
National Program Director for Oncology
Veterans Health Administration
U.S. Department of Veterans Affairs
Washington, DC

Warren Kibbe, PhD, FACP
Acting Deputy Director
Director, Center for Biomedical Informatics and Information Technology
National Cancer Institute
National Institutes of Health
Bethesda, MD

Richard Pazdur, MD
Director
Office of Hematology and Oncology Products
U.S. Food and Drug Administration
Rockville, MD

***Ad Hoc* Members**

Debra L. Barton, RN, PhD
Professor
Mary Lou Willard French Professor of Nursing
Department of Systems, Populations and Leadership
University of Michigan School of Nursing
Ann Arbor, MI

Timothy J. Eberlein, MD
Director
Alvin J. Siteman Cancer Center
Washington University School of Medicine
St. Louis, MO

Howard J. Fingert, MD
Senior Medical Director
Millennium: The Takeda Oncology Company
Cambridge, MA

Gwendolyn A. Fyfe, MD **2020**
Independent Contractor
San Francisco, CA

Paul A. Godley MD, PhD, MPP
Executive Associate Dean for Faculty Affairs
Professor of Hematology/Oncology
University of North Carolina
Chapel Hill, NC

Executive Secretary

Sheila A. Prindiville, MD, MPH
Director
Coordinating Center for Clinical Trials
Office of the Director
National Cancer Institute
National Institutes of Health
Bethesda, MD

Anne-Marie R. Langevin, MD
Greehey Distinguished Chair in Pediatric Oncology
University of Texas Health Science Center
San Antonio, TX

Lynn M. Matrisian, PhD, MBA
Chief Research Officer
Pancreatic Cancer Action Network
Washington, DC

Roman Perez-Soler, MD (BSC)
Professor and Chairman
Department of Oncology
Montefiore Medical Center
Deputy Director
Albert Einstein Cancer Center
Director
Division of Medical Oncology
Albert Einstein College of Medicine
Bronx, NY

Dan Theodorescu, MD, PhD
Director
University of Colorado Cancer Center
Aurora, CO