DEPARTMENT OF HEALTH AND HUMAN SERVICES
NATIONAL INSTITUTES OF HEALTH
NATIONAL CANCER INSTITUTE
27th CLINICAL TRIALS AND TRANSLATIONAL RESEARCH ADVISORY COMMITTEE (CTAC) MEETING

Summary of Meeting
July 8, 2015

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

CLINICAL TRIALS AND TRANSLATIONAL RESEARCH ADVISORY COMMITTEE
BETHESDA, MD
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The 27th meeting of the Clinical Trials and Translational Research Advisory Committee (CTAC) of the National Cancer Institute (NCI) was held on Wednesday, July 8, 2015, at 9:00 a.m. in Conference Room 10, C Wing, Sixth Floor, Building 31, on the National Institutes of Health main campus in Bethesda, MD. The CTAC chair, Dr. James Abbruzzese, presided.[1] The meeting was adjourned at 1:59 p.m.

Chair
James L. Abbruzzese

CTAC Members
Susan G. Arbuck
David F. Arons
Curt I. Civin
Kevin J. Cullen
Nancy E. Davidson
J. Philip Kuebler
Michael L. LeBlanc
Scott M. Lippman (absent)
David A. Mankoff
Mary S. McCabe
Edith P. Mitchell
Nikhil C. Munshi
Nancy Roach
Peter G. Shields
George W. Sledge, Jr.
Chris H. Takimoto (absent)
Gillian M. Thomas (absent)
Miguel A. Villalona-Calero
George J. Weiner
Louis M. Weiner

Ad Hoc Members
Susan M. Blaney
Walter J. Curran (absent)

***Ex Officio* Members**
James H. Doroshow, NCI
Paulette S. Gray, NCI
Rosemarie Hakim, CMS
Lee J. Helman, NCI (absent)
Michael J. Kelley, VA (absent)
Richard Pazdur, FDA
Alan S. Rabson, NCI (absent)

Executive Secretary
Sheila A. Prindiville, NCI

Presenters
James L. Abbruzzese, MD, Chief, Division of Medical Oncology; Associate Director for Clinical Research, Department of Medicine, Duke Cancer Institute, Duke University Medical Center, Duke University
Jeffrey S. Abrams, MD, Associate Director, Cancer Therapy Evaluation Program, Division of Cancer Treatment and Diagnosis, NCI
James H. Doroshow, MD, Deputy Director for Clinical and Translational Research, NCI
M. K. Holohan, JD, Acting Director, Office of Government and Congressional Relations, NCI
Warren Kibbe, PhD, Director, Center for Biomedical Informatics and Information Technology, NCI
Sheila A. Prindiville, MD, MPH, Director, Coordinating Center for Clinical Trials, Office of the Director, NCI
Nancy Roach, Consumer Advocate, Fight Colorectal Cancer

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

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I. Call to Order and Opening Remarks

James L. Abbruzzese, MD

Dr. Abbruzzese called the 27th meeting of CTAC to order and welcomed participants to the meeting. He introduced Dr. Blaney, a new CTAC member.

Dr. Abbruzzese 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. An announcement was made that National Institutes of Health Events Management was videocasting the meeting and that the videocast would be available for viewing following the meeting at http://videocast.nih.gov.

Motion. A motion to accept the minutes of the 26th CTAC meeting held on March 4, 2015, was approved unanimously.

II. Deputy Director's Report

James H. Doroshow, MD

Dr. Doroshow provided an update on recent clinical and translational research activities at NCI. He briefly mentioned the federal budget request for fiscal year 2016, which contains $70 million for NCI as part of the Precision Medicine Initiative (PMI). This was described in detail later in the day.

New Acting NCI Director's Priorities. Douglas R. Lowy, MD, is NCI's new acting director. Dr. Lowy plans to attend CTAC's November 4, 2015, meeting to share his plans for NCI. Dr. Doroshow provided an overview of Dr. Lowy's priorities for NCI. One longstanding interest is whether NCI should develop an approach to "unsilencing" tumor suppressor genes. This will be the focus of an upcoming workshop.

Another of Dr. Lowy's priorities is to expand NCI's precision prevention activities. Precision prevention requires a better understanding of the target in its clinical context. For example, although invasive cervical cancer incidence has declined in recent years, most of this decline has occurred in squamous cell cancers, which are detected by Pap smears. Little of the decline is due to decreases in rates of adenocarcinoma, a subtype of cervical cancer better detected by human papillomavirus testing, which recently received Food and Drug Administration approval. The PMI in the President's budget would enable the institute to shift the current cancer screening practice based mainly on pattern recognition to one based mainly on a molecular understanding of disease and its application to molecular diagnostics.

Another priority that Dr. Lowy has announced is to improve biological understanding of specific cancers associated with health disparities. For example, a recent study identified a novel signature gene for colorectal cancers in African Americans. NCI would like to better understand this type of signal and identify other genetic alterations in underrepresented minorities.

Outstanding Investigator Award. This award provides long-term support to experienced investigators with outstanding records of cancer research productivity who propose to conduct exceptional research. Each awardee receives $600,000 per year for 7 years. NCI has received and scored the first batch of applications from a remarkable group of investigators.

Pancreatic Ductal Adenocarcinoma. NCI recently issued a funding opportunity announcement for research on the development and testing of new molecular and imaging biomarkers to identify patients at high risk of pancreatic ductal adenocarcinoma (PAR-15-289). There is strong commitment from NCI senior leadership to support excellent applications received in response to this announcement.

NCI Budget. The NCI budget has been flat since 1999 in constant dollars. In 2012, the institute's budget was $5.1 billion, but NCI's payline dropped significantly in 2013 due to the sequester. The "restoration" of the funds lost to the sequester in 2014 did not fully restore the budget to its 2012 level. In 2015, NCI's budget has still not reached its 2012 level in actual or real dollars.

NCI invested all of its restored funding in 2014 into research project grants, and total funding for these projects in 2015 is likely to be similar to 2014 levels. To increase the purchasing power of its grants, NCI recently reduced the cuts to modular grants from 17 percent to 8.5 percent.

The good news is that Democrats and Republicans in both the House of Representatives and the Senate have expressed strong enthusiasm for increasing the National Institutes of Health budget. The proposed House and Senate appropriations bills would provide a significant increase in funding for NCI.

Core Grants for Cancer Centers. NCI has engaged in discussions for 2 years about ways to make the funding formula for P30 core grants for cancer centers more equitable. The sizes of cancer center core grants vary considerably due to the timing of each center's initial and renewal grants. New cancer centers with great promise tend to have very low initial funding levels. If NCI has sufficient funding in fiscal years 2015 and 2016, it will increase funding for the cancer centers with the smallest P30 grants.

Changes in NCI Personnel. The following NCI staff members recently retired: Robert H Wiltrout, PhD, Center for Cancer Research (CCR); Joseph E. Tomaszewski, PhD, Division of Cancer Treatment and Diagnosis; and Susan Erickson, Office of Government and Congressional Relations. New NCI leaders are Toby Hecht, PhD, Deputy Director, Division of Cancer Treatment and Diagnosis; Lee J. Helman, MD, Acting Director, CCR; Glenn Merlino, PhD, Acting Scientific Director (Basic), CCR; M.K. Holohan, JD, Acting Director, Office of Government and Congressional Relations; and Peter Garrett, Director, Office of Communications and Public Liaison.

Cancer.gov. The NCI website has a new look and a new smartphone version.

Questions and Discussion

Ms. Roach asked about the 2016 budgets for the Specialized Programs of Research Excellence and National Clinical Trials Network (NCTN). Dr. Doroshow replied that the budgets for these programs depend on the 2016 appropriation for NCI and whether Congress appropriates funds for the PMI. These funds would benefit the NCTN by, for example, allowing NCI to expand the NCI-Molecular Analysis for Therapy Choice trial and to increase the number of trials conducted through NCTN. In addition, such funds cannot help but benefit centers, Specialized Programs of Research Excellence, P01s, and other programs. Dr. Doroshow added that a related question is whether the National Institutes of Health budget increases substantially in 2016 for the first time since the stimulus funding in 2008 and 2009. This increase is needed to eliminate the disequilibrium in cancer center funding.

III. Legislative Update

M. K. Holohan, JD

Fiscal Year (FY) 2016 Budget. The appropriations committees of both the House of Representatives and the Senate have approved FY 2016 budgets for the U.S. Departments of Labor, Health and Human Services, and Education and related agencies. The House bill includes $31.2 billion for the National Institutes of Health (NIH) (a $1.1 billion increase from FY 2015), including $5.081 billion for NCI (a $131,000 increase from FY 2015). The Senate bill provides $32 billion for NIH (a $2 billion increase from FY 2015), including $5.204 billion for NCI (a $254,000 increase from FY 2015). Both the House and Senate appropriations committee bills provide $215 million to NIH for the Precision Medicine Initiative, including $70 million for NCI.

The House and Senate appropriations committees plan to finish marking up all of the FY 2016 bills by mid-July. Appropriations bills are unlikely to be passed by the beginning of the new FY on October 1, 2016. A continuing resolution is likely to be implemented, followed perhaps by an omnibus spending bill. If a continuing resolution is passed instead of a new budget, federal agencies will operate under their FY 2015 budgets and will not implement new programs. In contrast, an omnibus bill could provide budget increases and funding for new programs.

21st Century Cures Initiative. This bipartisan effort is aimed at accelerating the discovery, development, and delivery of treatments and cures for diseases. The act would establish a mechanism to increase funding for NIH and the Food and Drug Administration, but it would also increase accountability and specify proportions of the annual NIH budget that must be spent on certain types of research. NIH would be required, for example, to develop a strategic plan with measurable outcomes, and the institutes and centers would develop similar plans.

Questions and Discussion

Dr. Cullen asked about a briefing by Ms. Holohan later in the summer on NCI's views regarding specific legislation. Ms. Holohan offered to provide updates in whichever format is most helpful. She added that little activity on the budget is likely to occur in August, but September will be very busy. She invited any other interested members of CTAC to contact her.

IV. CTAC Working Group Updates

National Clinical Trials Assessment Working Group

Jeffrey S. Abrams, MD

The planned periodic strategic assessments of NCI's clinical trial portfolios will provide essential feedback to the steering committees, National Clinical Trials Network (NCTN) groups, and NCI Community Oncology Research Program (NCORP) research bases.

The steering committees have identified priorities for their portfolios. They will review these priorities annually and revise them as needed in response to advances in the field. In late 2015, the committees will start the self-assessment of their clinical trials portfolio. This initial assessment will include only concepts approved since the NCTN Working Group's assessment. The steering committees will also assess the rationales for disapprovals of concepts.

The steering committees will present their self-assessments to the National Clinical Trials Assessment Working Group, which will include representatives of CTAC as well as chairs and statisticians of NCTN groups and NCORP research bases. This working group will analyze the quality and objectivity of the steering committee portfolio self-assessments, focusing on adherence to the strategic priorities, responses to recommendations from the last review, suitability for the federal clinical trials system, clinical and scientific importance, and feasibility. Other responsibilities will be to perform cross-portfolio analyses and report the results of the individual and cross-portfolio analyses to CTAC.

Dr. Abrams anticipated that the CTAC working group would begin conducting its reviews in 2016 and present its initial findings to CTAC in March 2016. It is expected that the working group will complete its assessment of all of the steering committees by late 2017. The working group will need more time to complete the cross-portfolio assessment that will evaluate the overall clinical trials portfolio across the steering committees, the value of the assessment process, and recommendations for future assessments. These findings are projected to be presented to CTAC in 2018.

NCI staff will provide information to assist the steering committees with the self-assessment process, including summaries of trial concepts and steering committee deliberations, information on trial status, and each study's population/public health impact. The workload of the self-assessment process should be manageable, because each steering committee approves one to four approved concepts on average each year.

Questions and Discussion

Ms. Roach raised the concern that the self-assessments by the steering committees might not be objective. She suggested including experts from outside the United States to assist with these assessments, perhaps as members of the National Clinical Trials Assessment Working Group. Dr. Abrams replied that the working group will be formed in fall 2015 and that including international experts would ensure that the group has a broad spectrum of views.

Dr. Davidson asked what would happen if the working group does not approve a steering committee assessment. Dr. Abrams explained that if this happens, the working group will offer recommendations and discuss these issues with CTAC. NCI would consider these recommendations when deciding to make any changes.

Dr. Louis Weiner noted that for steering committee priorities focused on immunotherapy, the diseases in which immunotherapy might be used could be less important than the best ways to use immunotherapy and understanding its mechanisms. He asked whether a group would make recommendations about enriching studies to ensure that they have optimal correlative studies and protocol designs. Dr. Abrams responded that NCI will call on experts in immunotherapy, including members of the NCTN and NCORP, to help determine how to incorporate immunotherapy research in NCI's clinical trials. Every steering committee has translational scientists, and committees will increase their immunotherapy representation as the role of this treatment modality grows.

Dr. George Weiner asked how NCI will encourage interactions among steering committees that oversee clinical trials of immunotherapy and targeted therapies that cross disease sites. The steering committees should assess how well they work with one another in their self-assessments. Dr. Abrams said that NCI needs to determine how best to optimize collaborations among the steering committees and

ensure that the knowledge gained in one disease is translated to another disease. He welcomed suggestions on this issue from CTAC members.

Dr. Sledge said that the NCTN Working Group members at this meeting were pleased with the progress that Dr. Abrams described. He asked how NCI would measure the effectiveness of the process over 3 or 5 years. Dr. Abrams said that the short-term metrics will include whether the trials meet their goals for accrual. Measuring the long-term effects of clinical trials on clinical practice and science will be more difficult, especially because many phase III trials do not produce results for several years. The National Clinical Trials Assessment Working Group will help assess whether the trials are having an impact on cancer care and whether any important gaps need to be addressed.

Dr. Mankoff asked how trials that cut across cancer sites, such as those involving imaging, will be assessed. Dr. Abrams replied that the Imaging Steering Committee will primarily review imaging trials and that disease-specific steering committees will assess imaging studies that are part of disease-specific trials. None of the steering committees focuses on correlative science, but the Correlative Science Committee (which is a review committee, not a steering committee) will provide oversight of the use of tissues that are stored in groups' banks after trials end. These samples will become a national resource that will be available to investigators worldwide. This committee will have representatives from all of the groups that contribute resources and will decide which correlative science studies using that tissue should go forward.

Dr. Munshi asked whether the National Clinical Trials Assessment Working Group would assess the outcomes of the NCTN Working Group's recommendations. Dr. Abrams said that the new working group will assess whether the steering committees implemented the recommendations of the previous working group.

Dr. Abbruzzese asked whether the steering committees reviewed the state of the science in their reports on priorities for their portfolios. These priorities should be justified by such assessments. Dr. Abrams said that some steering committees provided a rationale for their priorities, but others did not. NCI has not yet reviewed the priority documents from the steering committees for consistency, but it will do that. Dr. Abbruzzese emphasized the importance of such a review to give CTAC and NCI a sense of how thoroughly each steering committee reviewed the state of the science to develop its priorities.

Progress in Pancreatic Ductal Adenocarcinoma (PDAC) Research Working Group
Dr. Abbruzzese

The Recalcitrant Cancer Research Act of 2012 (Public Law 112-239, §1083) called on NCI to identify two or more recalcitrant cancers that have a 5-year relative survival rate of less than 20 percent and cause more than 30,000 deaths per year in the United States and to develop scientific frameworks that will assist in making progress against these cancers. PDAC is a recalcitrant cancer according to the definition of recalcitrant cancers, and its 5-year relative survival rate is less than 5 percent, translating into the loss of almost 40,000 lives per year. A report focusing on NCI's scientific framework for PDAC was submitted to Congress in 2014 and posted on NCI's website at http://deainfo.nci.nih.gov/advisory/ctac/workgroup/pc/PDACframework.pdf. Approximately a year later, NCI convened the Progress in PDAC Research Working Group to advise NCI on the research progress of the four initiatives outlined in the scientific framework. Working group members represent the broad clinical and translational research and advocacy communities.

The working group's main objectives are to:

- Assess the research progress of the scientific initiatives to date
- Provide recommendations for the process used for future annual assessments
- Review and provide recommendations for updating the scientific framework no later than 5 years after the initial development
- Advise NCI on the effectiveness of the scientific framework no later than 6 years after the initial development

The working group has been meeting over the past year, and its initial report will be presented to CTAC in November 2015.

Dr. Abbruzzese provided informal updates on progress toward the implementation of the four initiatives of the Scientific Framework:

- Biological relationship between PDAC and diabetes mellitus: NCI and the National Institute of Diabetes and Digestive and Kidney Diseases have issued a request for applications (RFA-DK-14-027) for the Consortium for the Study of Chronic Pancreatitis, Diabetes, and Pancreatic Cancer Clinical Centers. Applications in response to this U01 opportunity are under review, and NIH will make a final funding decision in fall 2015. In addition, the National Institute of Diabetes and Digestive and Kidney Diseases and the National Institute of Biomedical Imaging and Bioengineering cosponsored a meeting on July 22, 2015: Advances in Biomedical Imaging, Bioengineering, and Related Technologies for the Development of Biomarkers of Pancreatic Disease.

- Early detection and biomarkers: NCI issued a funding opportunity announcement (PAR-15-289) on June 30, 2015, for the Pancreatic Cancer Detection Consortium (U01).

- New therapeutic strategies in immunotherapies: The working group needs an additional face-to-face meeting to finalize its assessment of the implementation plan for this initiative.

- RAS therapeutics: Details on the RAS initiative are available on the website of the Frederick National Laboratory for Cancer Research. This initiative is well under way, and the working group plans to hold a teleconference with Frank McCormick, PhD, the RAS Initiative National Advisor, soon to learn more about the initiative's progress.

Questions and Discussion

Mr. Arons asked whether the activities of the Progress in PDAC Research Working Group could lead to new clinical trials. Dr. Abbruzzese replied that clinical trials could arise from the initiatives. The working group is particularly interested in addressing the need for immunotherapy research in PDAC, where little progress has been made and major opportunities exist to understand the relationship between cancer stroma and therapy, including immunotherapy. RAS proteins could serve as immunotherapy targets.

Dr. Kuebler suggested that the working group's report be shared with the Gastrointestinal Steering Committee.

Clinical Trials Informatics Working Group
Sheila A. Prindiville, MD, MPH

Dr. Louis Weiner and Dr. Kibbe will lead this new group, which is seeking additional members from CTAC. The group's purpose is to provide extramural expertise and advice on the implementation of clinical trials informatics initiatives. Its goals are to:

- Minimize the burden of cancer clinical trial data management
- Improve the value of cancer clinical trial data
- Increase the impact of clinical trials by streamlining initiation, conduct, data analysis, and reporting as originally envisioned in the 2005 Clinical Trials Working Group report

The group's initial focus will be NCI's Clinical Trials Reporting Program, a comprehensive registry of interventional cancer clinical trials.

Questions and Discussion

Dr. Shields asked whether NCI will require investigators to report on observational trials in the Clinical Trials Reporting Program. Dr. Prindiville said that submitting reports on observational trials to the database is not currently mandatory. The extramural research community needs to determine whether adding observational trials to the database would be valuable; NCI has not yet made a decision on this issue. The working group will consider this potential requirement.

V. Other Board Updates: NCI Council of Research Advocates

Nancy Roach

The NCI Office of Advocacy Relations defines a "research advocate" as someone who "brings a nonscientific viewpoint to the research process and communicates a collective patient perspective." The roles of research advocates at NCI include the following:

- Advise: help develop recommendations or advise on strategic directions or broad policy issues
- Design: develop new programs or activities or enhance existing ones by, for example, providing the patient perspective as a member of a committee to develop a new program
- Review: evaluate and analyze research proposals and ongoing research activities, including participating in peer or concept review panels
- Disseminate: interpret and communicate

The value of research advocates is that they provide a perspective that can increase accrual feasibility and patient acceptance of research projects. Advocates can also enhance public understanding and support of research by serving as a bridge between the scientific community and the public.

The Office of Advocacy Relations at NCI manages research advocate activities at the institute. The office maintains a database of advocates, identifies opportunities for advocates to serve at NCI, and matches advocates to opportunities. The office also coordinates the NCI Council of Research Advocates, which is the only NCI federal advisory committee composed exclusively of advocate leaders. Mr. Arons is a member of the council, whose meetings are open to the public.

Ms. Roach is co-chair of the Advocate Engagement Working Group of the National Council of Research Advocates. This working group's charge is to explore best practices for engaging advocates to further the research goals of NCI, identify opportunities to enhance and improve advocate engagement efforts, and identify processes and resources available to recruit and support the next generation of cancer research advocates.

Ms. Roach invited CTAC members to send the names of research advocates who might be effective at NCI to the Office of Advocacy Relations.

Questions and Discussion

Dr. Abbruzzese asked whether organizations outside NCI provide training for research advocates. Ms. Roach replied that the American Society of Clinical Oncology and American Association of Cancer Research have advocacy training programs. However, existing programs do not provide enough practical training. Dr. Sledge added that the National Breast Cancer Coalition also provides training for advocates.

VI. Retiring Members Ceremony

Dr. Doroshow thanked the four retiring CTAC members: Drs. Arbuck, Civin, Shields, and Thomas. Each retiring member has served NCI in many ways beyond their roles in CTAC. All have contributed a great deal of time and input that have improved NCI's efforts on behalf of the public. He awarded each retiring member a plaque.

VII. Clinical Trials Working Group (CTWG): A Decade of Progress

Overview
James H. Doroshow, MD

It has been 10 years since the NCI CTWG presented its report to the National Cancer Advisory Board. Dr. Doroshow acknowledged Dr. Abbruzzese as the only remaining CTAC member who participated in the CTWG. The CTWG's summary vision was to integrate NCI's existing clinical trials programs into a cross-disciplinary, scientifically driven, cooperative research network to realize the promise of molecular medicine for advancing oncologic clinical practice in the 21st century.

This session reviewed the progress that NCI has made since 2005 on the initiatives in the CTWG report. These initiatives were grouped into six common themes for the presentation: coordinated clinical trials oversight, coordination, standardization, operational efficiency, prioritization, and scientific quality. The implementation progress on each initiative was assessed and categorized as achieved, partially achieved, or not achieved. Potential future CTAC activities related to each group of initiatives were outlined, and CTAC members were asked whether these were the correct future oversight activities and what other activities might be useful to address in the coming decade.

Coordinated Clinical Trials Oversight
James H. Doroshow, MD

Goal: Provide coordinated management and oversight for the NCI clinical trials enterprise

- Initiative 1. Establish a permanent federal body to provide extramural advice on the implementation of the CTWG initiatives and the ongoing conduct of clinical trials across NCI: Achieved through the creation of CTAC, a permanent federal advisory committee that provides extramural advice and oversight for NCI clinical trials and translational research. CTAC has guided NCI on the implementation of the CTWG initiative and continues to help with midcourse corrections and long-term planning.

- Initiative 2. Establish a standing internal operations committee to provide ongoing integration, coordination, and oversight of clinical trial activity across NCI: Achieved through the formation of the NCI Clinical and Translational Research Operations Committee (CTROC), an internal group that brings together leadership from NCI divisions, offices, and centers to share their clinical trial activities. CTROC monitors the CTWG implementation and other CTAC working group activities, reviews clinical and translational research funding initiatives, advises on clinical trials policies, and guides the Recalcitrant Cancer Research Act of 2012 activities.

Coordination
Sheila A. Prindiville, MD, MPH

Goal: Improve the coordination and cooperation among the functionally diverse components of the NCI-funded clinical trials system

- Initiative 1. Enhance information sharing concerning the status and results of NCI-funded clinical trials: Partially achieved with the creation of the Clinical Trials Reporting Program (CTRP), a comprehensive database of NCI-supported intervention trials. CTRP now contains more than 12,000 trials and is the source of data for clinical trial searches on the NCI website. The CTAC Clinical Trials Informatics Working Group will continue to monitor progress on this initiative and advise NCI on future CTRP enhancements.

- Initiative 2. Facilitate collaboration and cooperation across the NCI-funded clinical trials system: Achieved through the revision of guidelines for Specialized Programs of Research Excellence (SPOREs), cancer centers, and the National Clinical Trials Network (NCTN) to facilitate collaboration across NCI programs as recommended by the CTAC Guidelines Harmonization Working Group in July 2009. Other recent activities to facilitate collaboration include the establishment of the NCTN Group/NCI Leadership Management Committee in 2014, whose proposed activities include creating operating policies and procedures, addressing operational issues, planning new initiatives, and addressing recommendations for changes in NCTN. Another accomplishment is the creation of the Cancer Clinical Investigator Team Leadership Awards, a new form of recognition for outstanding midcareer clinical investigators who promote collaborative team science and clinical trial cooperation at NCI cancer centers.

- Initiative 3. Enhance interactions with the Food and Drug Administration (FDA) and Centers for Medicare & Medicaid Services (CMS) to promote coordination of regulatory and reimbursement policies with the scientific enterprise: Partially accomplished, but NCI needs to reassess some aspects of it. Accomplishments include the creation of a joint NCI-FDA fellowship program to educate investigators about regulatory review; meetings of NCI, FDA, industry, and academia representatives to discuss use of molecular diagnostics for clinical decision making; and joint

coordination to launch major target-based clinical trials. NCI also collaborated with CMS to apply "coverage with evidence development" for non-routine costs in certain NCI-sponsored trials and investigational use of fluorodeoxyglucose positron emission tomography and sodium fluoride positron emission tomography.

Proposed future CTAC coordination activities for discussion included:

- Monitoring the progress of CTRP through the Clinical Trials Informatics Working Group
- Receiving periodic updates from NCI on:
  - The extent, nature, and impact of collaborations among cancer centers, SPOREs, NCTN, and Experimental Therapeutics Clinical Trials Network (ETCTN)
  - The extent, nature, and impact of collaborations among the NCTN groups and activities of the NCTN Leadership Management Committee
  - Interactions with FDA
- Deciding whether and how to assess the impact of the Cancer Clinical Investigator Team Leadership awards on awardees' career status
- Deciding whether to explore approaches to improve interactions with CMS and/or other federal agencies

Questions and Discussion

Dr. Prindiville asked for CTAC's feedback on future coordination activities, including ways to further increase collaboration among cancer centers, SPOREs, and NCTN. Dr. Abbruzzese noted that NCI devoted a great deal of effort to harmonize these diverse funding mechanisms and stimulate collaboration. CTAC should ensure that the changes that NCI has made have had the desired effect. Ms. Roach commented that NCI's review process needs to ensure that applicants and reviewers pay serious attention to collaboration and not simply give lip service to this issue.

Ms. Roach pointed out that many tests are used to direct clinical treatment, even though the evidence on these tests is weak. NCI has an opportunity to work with CMS to quickly gather large amounts of data to determine whether these tests are worthwhile.

Dr. Mitchell stated that a barrier to communications among cancer center researchers and those involved in other NCI-funded clinical trials is that different groups collect and store data in ways that other sites cannot use. Dr. Prindiville explained that the CTRP will facilitate the sharing of information about clinical trials across the NCI system.

Ms. McCabe suggested that NCI work with CMS to assess ways to enroll more participants from underserved populations in NCI trials now that many individuals in these populations have health insurance due to the Patient Protection and Affordable Care Act.

Dr. Mankoff noted the difficulty of obtaining funding for correlative molecular diagnostics and imaging studies that are integrated and not integral to clinical trials. NCI's Biomarker, Imaging, and Quality of Life Studies Funding Program (BIQSFP) gives lower priority to integrated studies, and industry rarely pays for such studies. Dr. Mankoff suggested approaching CMS about applying "coverage with evidence development" to integrated studies in clinical trials.

Standardization
Sheila A. Prindiville, MD, MPH

Goal: Standardize tools and procedures for trial design, data capture, data sharing, and administrative functions

- Initiative 1. Create interoperable, standards-based information technology tools to facilitate the collection, management, and analysis of clinical trial data: Partially achieved, but progress needs to be monitored as NCI works toward making its systems interoperable. Cancer centers can now provide data to CTRP by direct electronic linkage. The Cancer Trials Support Unit provides common patient registration, a menu of trials, regulatory support, and site verification for NCI multicenter trials. The Medidata Rave Clinical Data Management System provides NCTN groups, ETCTN, and the Adult Brain Tumor Consortium with such features as remote data capture and preparation of data for analysis.

- Initiative 2. Develop standard case report forms incorporating common data elements that use standard vocabularies: Partially achieved. Activities include developing common data elements and standard case report form modules. The Network Rave Data Standards Committee is working with NCI to identify common data elements for NCTN and ETCTN trials that use the Rave data management system.

- Initiative 3. Build a standard credentialing system for investigators and sites to avoid duplicative credentialing for every trial: Partially achieved by development of the Online Credentialing Repository software for the FDA 1572, curriculum vitae, and financial disclosure forms. NCI will begin shortly to further develop and implement an electronic credentialing system for the NCTN groups and NCORP research bases.

- Initiative 4: Develop commonly accepted clauses for clinical trial contracts with industry to facilitate clinical trial initiation: NCI has achieved this initiative through development of standard terms of agreement clauses for research trials (START) in collaboration with the CEO Roundtable on Cancer. The clauses cover clinical trial agreements between industry and academic medical centers for company-sponsored and investigator-initiated trials. NCI evaluated the use and impact of the START clauses in 2010 among 45 cancer centers and nine CEO Roundtable Life Science Consortium companies. Users described these clauses as useful for beginning negotiations or as fallback positions during negotiations.

Potential future CTAC standardization activities for discussion included:

- Monitoring progress of the partially initiated standardization initiatives through the CTAC Clinical Trials Informatics Working Group:
    - Establishing direct electronic links between internal NCI clinical trials data systems and CTRP
    - Developing common data elements and standard case report form modules through the Network Rave Data Standards initiative
    - Developing an online central repository of investigator credentials
- Determining whether further NCI action is needed on the START clauses to facilitate timely negotiation of clinical trials agreements between academic centers and industry

Questions and Discussion

Dr. Abbruzzese asked whether the work on the START clauses is ongoing and whether NCI should continue to work on these clauses. Dr. Prindiville said that NCI does not currently plan any additional work on the START clauses. Dr. George Weiner suggested that NCI review and consider modifying these clauses, because new issues have arisen since NCI developed them.

Dr. Prindiville asked whether cancer centers are using the START clauses. Dr. George Weiner replied that cancer center investigators are familiar with the clauses, but some believe that the clauses are obsolete. They were a positive step forward, but they need a modest review at this time. Dr. Prindiville commented that NCI did not develop clauses pertaining to the molecular and biological materials collected in clinical trials. Dr. Abbruzzese agreed that it is time for NCI to review the clauses, given the pressure that investigators face to shorten negotiation timelines. Dr. Arbuck added that industry would be interested in these discussions, because it also faces pressure to reduce timelines.

Dr. Abrams commented that NCI now limits the duration of its negotiations with companies to 6 months. Since NCI imposed that deadline, almost all of its negotiations have concluded within 6 months. Dr. Arbuck noted that 6 months is too long, because industry faces so much competition and patients are demanding rapid development of new drugs. Dr. Abbruzzese added that many sponsors have set a limit of 90 days for the interim between protocol submission and first accrual. CTAC should review these timelines and encourage NCI and other stakeholders to shorten them dramatically.

Dr. Louis Weiner stated that the list of tasks for the new Clinical Trials Informatics Working Group is growing and asked CTAC for a sense of the working group's top priorities. He planned to give a report at the next CTAC meeting on the list of activities that the CTAC Clinical Trials Informatics Working Group is considering and how the group suggests prioritizing these activities. Dr. Prindiville suggested that the new working group's initial priority be to collect feedback on CTRP.

Operational Efficiency
Jeffrey S. Abrams, MD

Goal: Increase the rate of patient accrual and reduce operational barriers to timely trial initiation

- Initiative 1. Restructure NCI's dedicated clinical trials programs to improve patient accrual and cost-effectiveness: Achieved. NCI restructured the NCTN in 2014 by consolidating the program into four adult groups and one pediatric group, increasing per-case funding for high-accruing sites, establishing a tiered accrual reimbursement system, and linking infrastructure costs to accrual levels. Changes to NCORP in 2014 included providing base infrastructure funding for all community and minority/underserved sites and increasing per-credit funding for high-accruing sites. NCI also restructured the ETCTN in 2014 into integrated phase I and II cooperative agreements so that it can adapt to the new era of targeted therapies where separation of phase I and II activities is less distinct than in the past. In 2015, the ETCTN program solicited competitive phase II supplements to current phase I awardees and unaffiliated cancer centers.

- Initiative 2. Identify and address barriers to timely trial initiation: Achieved. The Operational Efficiency Working Group issued a report in March 2010 that established target timelines for opening NCI-sponsored trials and absolute deadlines for canceling unopened Cancer Therapy Evaluation Program (CTEP) trials. Fourteen initiatives for achieving trial activation deadlines

were also recommended and subsequently implemented by NCI. NCTN and ETCTN trials have significantly reduced their median time to open trials since the implementation of actions to achieve the Operational Efficiency Working Group protocol development timelines.

- Initiative 3. Analyze the status of patient accrual to NCI clinical trials, develop strategies to improve accrual rates, and increase patient and public awareness and understanding of clinical trials: Partially achieved; continue to monitor progress. NCI has completed the analysis portion of this initiative and collected information on accrual best practices and research needed to improve accrual. NCI created the Network Accrual Core Team to improve messaging for promoting trials, develop templates for trial education, standardize trial tools and processes, and coordinate accrual enhancement efforts in NCTN.

- Initiative 4. Increase minority patient access to clinical trials to improve the participation of underserved and underrepresented populations: Not achieved; needs reassessment. NCI implemented a pilot administrative supplement program to promote minority accrual to clinical trials in 2006–2010, but this program did not improve minority accrual rates. NCI therefore decided not to continue it in its original form.

- Initiative 5. Promote adoption of the NCI Central Institutional Review Board (CIRB) facilitated review process: Achieved. NCI modified CIRB operating procedures to improve efficiency and compliance; obtained Association for the Accreditation of Human Research Protection Programs accreditation; and established CIRBs for pediatric, cancer control/prevention, and early-phase trials. As of May 2015, more than 1,500 institutions are enrolled in the CIRB.

Potential future CTAC operational efficiency activities for discussion included:

- Receiving periodic updates on:
  - The timeliness of NCTN, NCORP, and ETCTN trial activation and whether target timelines should be further reduced
  - The status of actual versus expected accrual rates for NCTN, NCORP, and ETCTN trials and decide whether additional improvement is needed
- Deciding whether and, if so, how the results of completed NCTN, NCORP, and ETCTN clinical trials contribute to progress in cancer treatment, prevention, and symptom management (including how to assess these results)
- Deciding whether to explore additional opportunities to improve the operational efficiency of NCTN, NCORP, and ETCTN trials
- Identifying additional actions that might enhance access to clinical trials for minority and underserved populations

Questions and Discussion

Dr. Arbuck commented on the need to continue speeding up the initiation of clinical trials described under Initiative 1. She suggested that NCI examine all aspects of every trial in detail (including scientific importance, feasibility, and drug supply issues) to identify the sources of problems and determine next steps. Identifying the areas with the greatest potential for improvement and knowing early on which approaches are not worth pursuing is very helpful.

Ms. Roach suggested that NCI consider funding proactive accrual planning and minority accrual. Investigators often fail to consider how they will accrue their sample when they design their trials, so NCI could fund this type of planning. Dr. Abrams said that the new cross-NCTN accrual working group is addressing this need, and NCORP is supporting some related approaches.

Dr. Villalona-Calero asked about the impact of project team member applications (PTMAs) on time to protocol activation since 2013 and the effects on approval rate of unsolicited letters of intent for PTMAs. Dr. Abrams said that it is too soon to measure the effects of the PTMAs on accrual rates. James Zwiebel, MD, Branch Chief, Investigational Drug Branch, CTEP, added that the approval rate of unsolicited letters of intent is about 30 percent, but he expected this rate to increase. Dr. Abrams said that NCI has not changed its protocol activation timelines for these studies and that sites have met these deadlines, even though they are ambitious. Dr. Zwiebel noted that studies seem to be opening more rapidly.

Dr. Villalona-Calero pointed out that investigators put a great deal of work into their PTMA letters of intent and that NCI starts measuring the time to study activation once the letter of intent is submitted. He asked whether the new PTMA process reduces or increases the time. Dr. Zwiebel replied that NCI now negotiates its cooperative research and development agreements with companies at the same time that it negotiates with project teams, instead of conducting these negotiations sequentially as in the past. This new approach has eliminated about 6–8 months from the timeline. For the PTMAs, NCI simply requests a biographical sketch and some information about the investigator's accrual ability. Only individuals approved for a project team submit a letter of intent. This makes the process much more efficient and reduces much of the time wasted at sites writing fully fleshed-out letters of intent.

Dr. Arbuck asked how long it takes now for companies that approach NCI to negotiate agreements. Dr. Abrams replied that when a company approaches NCI with a request to collaborate, both the company and NCI have 6 months to complete their negotiations. This timeline starts once NCI approves the application, based on internal and external reviews and a senior leadership decision. These reviews typically take about 3 months.

Prioritization
Jeffrey S. Abrams, MD

Goal: Establish an open, collaborative process for examining clinical trial strategic directions, encouraging innovation, reducing duplication and overlap, and prioritizing clinical trials based on the best science

- Initiative 1. Obtain broad extramural scientific and clinical input into strategic directions for CTEP-funded phase I and II trials: Achieved. Accomplished through creation of the Investigational Drug Steering Committee in 2005, which has provided input on drug development plans for 32 new CTEP agents. NCI also established the NCI Experimental Therapeutics Program in 2009 to translate to the clinic promising new anticancer drugs, biologics, imaging agents, and medical devices. Approved projects have access to a broad array of NCI resources.

- Initiative 2. Obtain broad scientific and clinical input from academic disease experts, practicing oncologists, patient advocates, and NCI staff into the development and selection of NCI-funded late-phase trials: Achieved. NCI has now formed scientific steering committees for 12 disease areas, symptom management and quality of life, cancer care delivery, and imaging. These

committees are composed of NCTN group representatives, community oncologists, special clinician experts, biostatisticians, patient advocates, and NCI staff. They evaluate trial concepts, recommend changes to concepts prior to approval, and develop national strategic approaches for each trial portfolio. NCI also established the Patient Advocate Steering Committee to ensure that patient advocates are effectively integrated into the steering committees.

Potential future CTAC prioritization activities for discussion included:

- Receiving periodic updates on Investigational Drug Steering Committee activities and interactions with the newly reorganized ETCTN
- Receiving periodic updates on the success of drugs, biologics, imaging agents, and medical devices supported by the NCI Experimental Therapeutics Program in making progress from early- to late-phase development
- Overseeing the scientific steering committees
- Assessing the active trial portfolios (through the National Clinical Trials Assessment Working Group)
- Reviewing strategic research priorities
- Assessing operating policies and procedures
- Assessing value of clinical trials planning meetings
- Overseeing cross-disease prioritization of approved concepts due to resource constraints

Questions and Discussion

Dr. Abbruzzese pointed out that CTAC has a major ongoing role in these activities, including oversight of the steering committees.

Mr. Arons asked how NCI responds when several companies submit requests to study molecules with the same target, given the limited number of clinical trial opportunities. Dr. Abrams said that in this situation, NCI applies an evaluation process. NCI sometimes agrees to studies on products with the same target from more than one company if, for example, the companies want to use their compounds in different tumor types. However, NCI must often choose from several molecules, and it asks external advisors for assistance with these decisions.

Scientific Quality
James H. Doroshow, MD

Goal: Enhance the scientific quality of NCI-funded clinical trials by improving prioritization, funding, and standardization of associated biomarker and quality of life studies

- Initiative 1. Ensure that adequate funding is available for clinical trials involving biomarkers, imaging, and quality of life: Achieved by establishing the BIQSFP in 2008, which has funded 42 integral and integrated biomarker studies for clinical trials for a total of $50 million as of April 2015.

- Initiative 2. Establish quality control standards for laboratory assays and imaging procedures used in association with NCI-funded clinical trials: Achieved. The Program for the Assessment of Clinical Cancer Tests defined *in vitro* assay and imaging test performance standards for integral and integrated assays conducted in association with clinical trials as well as integral and

integrated assay requirements. NCI has established an internal review committee to examine the correlative sciences proposed in letters of intent utilizing these standards. In addition, NCI created the Clinical Assay Development Program to provide support for assay development.

Potential future CTAC scientific quality activities for discussion included:

- Receiving periodic updates on BIQSFP-funded projects, including outcomes of trials incorporating BIQSFP-funded tests
- Periodically assessing the status of assay and imaging standards and decide whether NCI needs to take additional action
- Advising NCI on whether to reexamine BIQSFP policies and procedures to determine whether the program has an optimal structure

Questions and Discussion

Ms. Roach commented that one of the criteria that steering committees consider when they review a protocol is whether the trial is uniquely suited to the federal clinical trial system, for example, because it includes innovative correlative studies. She asked how steering committees can approve a trial without knowing the details of the correlative science. Dr. Abrams explained that concepts that require BIQSFP funding contain the details of the correlative studies. Such details are not included in concepts that do not require BIQSFP funding to save time for the study team and the reviewers. Instead, such correlative studies are reviewed by CTEP after concept approval.

Dr. Louis Weiner said that NIH is interested in the use of verifiable standards in correlative studies. He asked whether NCI views these as discovery or development tests. Dr. Doroshow replied that an assay must undergo a substantial amount of additional validation before it can be used as an integral marker associated with an eligibility requirement. In contrast, an integrated study could consist of discovery only. NCI tries to use its BIQSFP funds primarily for the integral tests that are used to establish eligibility for a trial. This does not mean that integrated studies are inappropriate but, rather, that they can be done at a later time. The tissues can be stored, and non-integral studies can be considered for discovery research during or after the study.

Dr. Mankoff commented that some aspects of the discovery phase can be supported by R01 and R21 grants. However, real-time validation studies, including studies of imaging, do not lend themselves to the timing of an R01 review. Dr. Mankoff suggested a review of the successes and limitations of the current process and the balance between integrated and integral studies to ensure that NCI's biomarker funding serves the needs of all biomarkers, including imaging.

Dr. Kuebler said that obtaining funding for correlative studies takes time and asked how this affects the timing of study activation. Dr. Doroshow said that requests for BIQSFP funding are considered at the same time that the concept is evaluated, so these requests do not slow down the review process. If the concept is approved and includes an integral marker, NCI must decide whether to fund the integral correlative study.

NCI Clinical Trials: The Next Decade
James H. Doroshow, MD

Dr. Doroshow reviewed the summary vision that the CTWG identified a decade ago in 2005. He asked CTAC to consider the following questions in updating the summary vision for the next decade:

- What are the new scientific opportunities that offer the most clinical promise?
- What are the most important scientific priorities for NCI-supported clinical trials over the next decade?
- What are the major challenges in addressing these opportunities and priorities?
- What operational/structural improvements are needed to achieve a new 2015 summary vision?
- How can CTAC best help NCI continue anticipating scientific change and focusing government-supported clinical trials and translational research to meet new scientific priorities?

Questions and Discussion

Dr. Abbruzzese asked CTAC to consider forming a small group to draft the 2015 summary vision for the next decade. Ms. Roach supported this idea. Over the last 10 years, scientific and structural changes have occurred that need to be considered. Ms. Roach volunteered to join this new group.

Dr. George Weiner suggested asking for input from the general cancer scientific community and to publish a summary of NCI's accomplishments related to clinical trials over the past 10 years in a major cancer journal. Dr. Doroshow said that NCI would like to do this.

Dr. Abbruzzese said that he will work with Drs. Prindiville, Doroshow, and Gray to determine the best mechanism for CTAC to create a new 10-year vision for clinical trials at NCI. Dr. Abbruzzese will report back to CTAC on the outcome of these discussions.

VIII. The Precision Medicine Initiative (PMI)

PMI for Oncology
James H. Doroshow, MD

The fiscal year 2016 budget submitted by President Obama calls for $215 million for the PMI, including $70 million for cancer research and $130 million for a national cohort of more than a million people. In this presentation, Dr. Doroshow discussed how NCI plans to use the PMI funding if this component of the President's budget is implemented.

The definition of PMI that NCI is using was modified by NCI Acting Director Doug Lowy, MD, based on an Institute of Medicine 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.

Historically, cancer treatment has relied on drugs that are only marginally more toxic to malignant cells than to healthy tissues. Developing targeted therapy holds promise for improving efficacy while decreasing toxicity. Furthermore, the field needs molecular markers to predict benefits or understand therapeutic resistance in the clinic. The proposed PMI for oncology would increase genomics-based clinical and preclinical studies of cancer treatment to identify and target molecular vulnerabilities of individual cancers.

Although Dr. Doroshow focused his presentation on genomics, precision medicine can include a wide range of molecular characteristics, such as RNA or proteins, that can be characterized in sufficient detail to enable treatments that are safer and more effective.

With PMI funding, NCI would increase genomics-based clinical and preclinical studies of cancer treatment. These activities would include:

- Expanding genomics-based clinical trials
- Understanding and overcoming resistance to targeted drugs, testing drug combinations, and developing a mechanistic understanding of immunotherapy
- Creating a repository of patient-derived preclinical models to evaluate targeted therapeutics
- Creating a national cancer database to integrate genomic information with clinical response and outcome data

NCI has already launched several precision oncology trials, including Molecular Profiling-Based Assignment of Cancer Therapy for Patients with Advanced Solid Tumors (MPACT), Lung Cancer Master Protocol (LungMAP), and Adjuvant Lung Cancer Enrichment Marker Identification and Sequencing Trials (ALCHEMIST). In July 2015, NCI will launch the NCI Molecular Analysis for Therapy Choice (NCI-MATCH). These initiatives are designed to maximize available molecular information for use in deciding how to treat patients.

NCI-MATCH will assign therapy based on molecular abnormalities, not site of tumor origin, for patients for whom no standard therapy is available. NCI-MATCH will probably be the largest trial to date that will assign treatment regardless of tumor histologic origin. It truly is a national effort. More than 20 companies have agreed to provide more than 40 drugs for this initiative, and more than 150 clinical and preclinical scientists have helped decide which genes and genetic mutations to address and how to prioritize agents. NCTN and NCORP will screen 3,000 patients to find 1,000 who might benefit from an NCI-MATCH drug. The initiative will use an algorithm to select a treatment within 2 weeks that is based on a tissue sample for each patient. NCI-MATCH will include some drugs that are commercially available and which will be used for indications that have not received Food and Drug Administration approval. The initiative also includes some investigational drugs.

If NCI-MATCH results in some exciting observations, NCI would use the PMI funding to broaden the NCI-MATCH umbrella by, for example, expanding or developing new phase II trials to explore novel clinical signals or add new agents to trials and new genes to the panel based on evolving evidence. The institute could also accelerate the launch of NCI-Pediatric MATCH, apply genomics resources to define new predictive markers in novel immunotherapy trials, expand the approach to study mechanisms of response and resistance, and include additional hematologic malignancies in NCI-MATCH.

The Exceptional Responders Initiative has collected specimens from approximately 100 patients and will analyze these samples shortly. The Cancer Genome Atlas (TCGA) has completed deep analysis of seven of these specimens. NCI would use additional resources to expand on the early information from this program.

Until recently, sensitive tools were not available to study some areas of drug resistance in depth. If PMI funding becomes available, NCI could develop new patient-derived murine models for precision oncology to study and overcome drug resistance instead of relying on preclinical cellular models. The principles of combination therapy to overcome resistance have not changed since 1975. Several potential new principles need experimental verification, such as that the agent in a combination must have therapeutic effect on a molecular pathway *in vivo* and that the regimen be scheduled to maximize target inhibition. NCI plans to develop the Patient-Derived Models Repository composed of clinically annotated patient-derived xenografts (PDX), patient-derived tumor cell cultures (including conditionally reprogrammed tumor cell cultures) developed from primary or metastatic tumors and/or PDXs, tumor cell lysates, DNA, RNA, and cancer-associated fibroblast cell lines (autologous when possible) as a resource for academic discovery efforts and public-private partnerships for drug discovery. Dr. Doroshow provided some encouraging preliminary data on the use of PDX models, demonstrating the power of the approach. With PMI funding, NCI could expand this repository to store more than 1,000 PDXs and 1,000 patient-derived tumor cell cultures and to include at least 50 models per disease.

Precision Medicine and Cancer Informatics
Warren Kibbe, PhD, Center for Biomedical Informatics, NCI

Some of the requirements for precision medicine big data are:

- Open science in the form of support for open access, open data, open source, and data liquidity for the cancer community
- Standardization through common data elements and case report forms
- Interoperability by exposing existing knowledge through appropriate integration of ontologies, vocabularies, and taxonomies
- Sustainable models for informatics infrastructure, services, data, metadata, and curation

NCI and the National Human Genome Research Institute launched TCGA, a comprehensive effort to accelerate understanding of the molecular basis of cancer, in 2006. TCGA has now characterized about 35 adult cancers. A sister program, Therapeutically Applicable Research to Generate Effective Treatments (TARGET), has similar activities in pediatric populations. TCGA has now assessed approximately 11,000 tumor and normal samples. TCGA has been a huge success, with more than 1,000 journal articles published to date using TCGA data. The overall conclusion is that molecular characterization of cancer is incredibly informative for treatment. With this success came huge challenges related to data sharing because of the types, technology platforms, and data levels (e.g., raw data and summary data).

NCI's Genomic Data Commons (GDC) will store, analyze, and distribute cancer genomics data generated by NCI and other research organizations. This interactive system is designed to advance the molecular diagnosis of cancer and suggest potential therapeutic targets based on genomic information. NCI plans to consolidate all of its genomic and clinical data from TCGA, TARGET, the Cancer Genome

Characterization Initiative, and other projects in the GDC. The GDC will become accessible to the extramural research community in late spring 2016.

The NCI Cancer Genomics Cloud Pilots explore innovative methods for accessing and computing large genomic data. They aim to bring data and analysis together on a single platform by creating a set of data repositories with collocated computational capacity and an application programming interface that provides secure data access. The first three cloud pilots will begin in 2016.

The NCI GDC and cloud pilots will work together on several activities. For example, they will jointly build common application programming interfaces and work with the Global Alliance for Genomics and Health to define the next generation of secure, flexible, meaningful, interoperable, and lightweight interfaces.

NCI plans to use PMI funds to:

- Expand the GDC to incorporate additional data types
- Include the learning from the cloud pilots into the GDC
- Scale up the GDC from 10 to hundreds of petabytes
- Include imaging by interoperation between the GDC and the Cancer Imaging Archive
- Expand clinical trials tools from NCI-MATCH to NCI-MATCH Plus
- Strengthen the Informatics Technology for Cancer Research Initiative to explicitly include precision medicine-relevant proposals

Questions and Discussion

Dr. Civin asked Dr. Kibbe about access to the information that NCI plans to make available to extramural researchers. For example, he wondered whether researchers could find out how many patients in the NCI dataset have mutations in DNA damage repair genes. Dr. Kibbe replied that the cloud pilots and GDC have worked with many cancer research groups to understand how the average biologist or clinician would use these systems and what interfaces they need. For example, NCI might develop an interface that allows researchers to use GDC and cloud pilot tools to analyze not only TCGA data but also any data that they choose to upload. Dr. Civin commented that the Bill & Melinda Gates Foundation has tools that makes its complex dataset on causes of death available to almost anyone. Dr. Kibbe explained that NCI is creating a user-friendly interface for the GDC based on the International Cancer Genome Consortium's interface.

Dr. Louis Weiner asked Dr. Kibbe whether NCI is working with the U.S. Department of Energy's National Laboratories. Dr. Kibbe said that NCI has talked to the Department of Energy about biological problems that would be relevant to the department's efforts in exascale computation.

Dr. Louis Weiner asked whether pharmaceutical companies might be interested in taking on phase II trials of compounds found to have interesting signals in NCI-MATCH. Dr. Doroshow replied that pharmaceutical companies are likely to take on some compounds that have a "hit" in NCI-MATCH. The academic community will conduct studies of other compounds. NCI will have many more contracts and drugs than it has resources to study. If it receives additional funding, NCI could open many more arms in its trials. NCI has been able to work with more than 20 companies on NCI-MATCH, because the institute does not plan to obtain intellectual property rights for the NCI-MATCH trial results. In addition,

NCI has spoken with the companies that supply agents for NCI-MATCH about making their drugs available to the extramural community for studies beyond NCI-MATCH.

Ms. Roach asked whether NCI-MATCH will focus its research on specific organ sites. Dr. Doroshow explained that a goal of NCI-MATCH is to use its umbrella to expand studies rapidly when a signal is observed. For example, if 3 of 15 patients with colorectal cancer who have a given mutation have "hits," the study should be expanded into a broader phase II disease-oriented study. NCI-MATCH should not conduct phase III trials, but it should better define the signals identified. Many constituencies want their own trials, and whether MATCH can address those needs as they arise will be determined.

Dr. Abrams said that NCI has worked with various steering committees to discuss ways to integrate their activities more seamlessly into NCI-MATCH. Once NCI obtains a hit in NCI-MATCH and expands a study, principal investigators who focus on a specific organ site would take the research to the next step.

Dr. Blaney asked about research on ways to overcome multidrug resistance, especially in central nervous system tumors, where drug delivery is an issue. Dr. Doroshow said that both pharmacology and genetics are important and that NCI-MATCH will not address this issue. Instead, multidrug resistance and drug delivery is better addressed by disease-focused consortia.

IX. Adjournment

James L. Abbruzzese, MD

There being no further business, the 27th meeting of CTAC was adjourned at 1:59 p.m. on Wednesday, July 8, 2015.

Appendix

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

CHAIR

James L. Abbruzzese, MD, FACP **2015**
Chief, Division of Medical Oncology
Associate Director for Clinical Research
Department of Medicine
Duke Cancer Institute
Duke University Medical Center
Durham, NC

MEMBERS

Susan G. Arbuck, MD, MSc, FACP **2015**
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Kevin J. Cullen, MD (NCAB) **2015**
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Nancy E. Davidson, MD **2015**
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J. Philip Kuebler, MD, PhD **2015**
Principal Investigator
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Research Professor
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Mary S. McCabe, RN **2016**
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Jerome Lipper Multiple Myeloma Center
Dana-Farber Cancer Institute
Associate Professor of Medicine
Harvard Medical School
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Nancy Roach **2015**
Consumer Advocate
Fight Colorectal Cancer
Alexandria, VA

Peter G. Shields, MD **2015**
Deputy Director
Comprehensive Cancer Center
Professor
College of Medicine
Ohio State University Medical Center
Columbus, OH

George W. Sledge, Jr., MD **2015**
Chief
Division of Oncology
Stanford University Medical Center
Stanford University
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Chris H. Takimoto, MD, PhD **2016**
Vice President and Head, Translational Medicine Early and Development, Oncology Therapeutic Area
Janssen Research & Development, LLC
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Professor, Department of Internal Medicine
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Holden Comprehensive Cancer Center
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Louis M. Weiner, MD (BSC) **2016**
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