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National Cancer Institute

9th Virtual Meeting
Frederick National Laboratory Advisory Committee

Summary of Meeting
February 24, 2022

National Cancer Institute
National Institutes of Health
Bethesda, Maryland

National Cancer Institute
9th Virtual Meeting of the Frederick National Laboratory Advisory Committee

24 February 2022

Summary of Meeting

The Frederick National Laboratory Advisory Committee (FNLAC) convened for its 9th Virtual Meeting on 24 February 2022. The meeting was open to the public on 24 February 2022, from 1:00 p.m. to 3:55 pm EST. The FNLAC Chairperson, Dr. Candace. S. Johnson, President and CEO, M&T Bank Presidential Chair in Leadership, Roswell Park Comprehensive Cancer Center, presided.

FNLAC Members
Dr. Candace. S. Johnson (Chair)
Dr. Andrea H. Bild
Dr. Catherine M. Bollard
Dr. John H. Bushweller
Dr. Timothy A. Chan (absent)
Dr. Lisa M. Coussens
Dr. Scott W. Hiebert
Dr. Allison Hubel
Dr. Dineo Khabele
Dr. Nilsa C. Ramirez Milan
Dr. Denise J. Montell (absent)
Dr. Patrick Nana-Sinkam
Dr. Erle S. Robertson
Dr. Lincoln D. Stein
Dr. Linda F. van Dyk

***Ex Officio* Members**
Dr. Stephen J. Chanock
Dr. James H. Doroshow
Dr. Paulette S. Gray
Dr. Anthony Kerlavage
Dr. Douglas R. Lowy
Dr. Tom Misteli (absent)
Ms. Donna Siegle (absent)
Dr. Dinah S. Singer

Executive Secretary
Dr. Wlodek Lopaczynski

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I. OPENING REMARKS—DR. CANDACE S. JOHNSON

Dr. Candace. S. Johnson, Chair, called to order the 9th Virtual Meeting of the Frederick National Laboratory Advisory Committee (FNLAC) and welcomed the Committee members, National Cancer Institute (NCI) staff, and guests. Dr. Johnson reminded members of the conflict-of-interest guidelines and confidentiality requirements. Members of the public were welcomed and invited to submit to Dr. Wlodek Lopaczynski, Executive Secretary, in writing and within 10 days, any comments regarding items discussed during the meeting.

Motion. A motion to approve the minutes of the 18 October 2021 FNLAC meeting was approved unanimously.

Dr. Johnson called Committee members' attention to the future meeting dates listed on the agenda. She noted that the next FNLAC meeting will be held on 27–28 June 2022 and will be virtual.

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

Dr. Norman E. Sharpless, Director, NCI, also welcomed the FNLAC members and attendees to the meeting. He provided updates on the NCI budget, the Cancer Moonshot℠ 2.0, NCI programs and initiatives, and progress in cancer research. Dr. Sharpless commented on the recent passing of Dr. Paul Farmer, a well-known researcher and leading public health advocate. A great loss to the NIH and NCI, Dr. Farmer was known for his work in global poverty, the establishment of the U.S. President's Emergency Plan for AIDS Relief (PEPFAR), and his interest in the global burden of cancer in recent years. Dr. Sharpless also noted that the Frederick National Laboratory for Cancer Research (FNLCR) offers capabilities for international cancer research.

Dr. Sharpless welcomed a new FNLAC member, Dr. Erle S. Robertson, Harry P. Schenk Endowed Chair Professor, Vice-Chair, Department of Otorhinolaryngology, University of Pennsylvania School of Medicine.

FNLAC members were reminded that 23 December 2021 marked the 50th anniversary of the National Cancer Act (NCA) of 1971 (i.e., NCA-50). The anniversary was recognized widely across the cancer research community, including by NCI-Designated Cancer Centers and national societies, and received substantial media coverage. The anniversary has fostered a national conversation on current progress in cancer research, as well as planning for the future. "Ending cancer as we know it" is a stated top priority for the Biden-Harris Administration.

NCI Budget and Appropriations. Dr. Sharpless stated that the Federal Government is operating under a continuing resolution, which has been extended until 11 March 2022. He noted that the NCI has remained in a trajectory of increased funding between fiscal year (FY) 2015 and FY 2021. The NCI appropriations for FY 2022 includes $194 million (M) for the 21st Century Cures Act, which is set to end in FY 2023, and $50 M for the Childhood Cancer Data Initiative (CCDI). A one-time appropriation was provided in FY 2021 for COVID-19 serology studies. The House and Senate Appropriations Subcommittees on Labor, Health and Human Services, Education, and Related Agencies are beginning to work together on planning the FY 2022 budget.

Dr. Sharpless informed the FNLAC that the NCI has adopted a conservative spending plan until the FY 2022 budget is approved. The NCI has established interim paylines for FY 2022: 9th percentile for R01 grants to established and new investigators, 14th percentile for R01 grants to early-stage investigators, and 9th percentile for R21 exploratory grants. Noncompeting grants will be funded at the 90 percent level.

Dr. Sharpless conveyed that the NCI recognizes the difficulties that these cuts impose on investigators and that he is hopeful that a resolution will be reached soon.

Dr. Sharpless called attention to two opinion columns advocating for increased funding for the NCI. In the 28 December 2021 issue of *Scientific American*, Senators Chris Coons (D-Delaware) and Jerry Moran (R-Kansas) proposed a robust, sustained investment of $1 billion (B) to the NCI to make progress in cancer research, particularly in extramural funding. Additionally, in the 17 February 2022 issue of *The Hill*, Dr. Caryn Lerman, President, Association of American Cancer Institutes (AACI), and Dr. Robert A. Winn, Vice President and President-Elect, AACI, advocated for funding cancer research. They cited data indicating that the cost of cancer in the United States is projected to exceed $245 B by 2030.

Cancer Moonshot℠ Update. Dr. Sharpless reported that on 2 February 2022, President Joseph R. Biden announced his plans to reignite the Cancer Moonshot℠ (i.e., Cancer Moonshot℠ 2.0). In his speech, President Biden stated that fighting cancer was a top priority for his Administration, and he expressed strong support for the initiative. Dr. Sharpless also noted that the success of the initial Cancer Moonshot℠, which was launched in 2016 and has been led by Dr. Dinah S. Singer, Deputy Director, Scientific Strategy and Development, NCI, was a major contributing factor to NCI's progress during the past 5 years.

In his announcement, President Biden detailed his Administration's broader and more ambitious set of goals and priorities that extends beyond any one Agency or Office. He described an all-government approach, which includes convening a Cancer Cabinet. This Cabinet will bring together 19 Agencies, Departments, and Offices, including the NCI; U.S. Departments of Health and Human Services (HHS), Veterans Affairs (VA), Defense (DoD), Energy (DOE), and Agriculture (USDA); U.S. Environmental Protection Agency (EPA); U.S. Food and Drug Administration (FDA); Centers for Medicare & Medicaid Services (CMS); Centers for Disease Control and Prevention (CDC); the White House Office of Science and Technology Policy (OSTP); and others. The NCI will be responsible primarily for the research aspects of this effort (e.g., new treatments, better prevention). Other aspects will include increasing access to care, improving how care is delivered within communities, and promoting health equity.

President Biden also emphasized the importance of cancer screening; he announced a call to action to stimulate progress on missed screenings during the COVID-19 pandemic. Dr. Sharpless noted that the NCI began modeling trends related to cancer screening and care early in the pandemic. First Lady Dr. Jill Biden has been an important partner in advocating on this topic. Dr. Sharpless also informed the FNLAC that on 16 February 2022, President Biden announced temporary leadership to fill the recent vacancy in the OSTP; Dr. Alondra Nelson will perform the duties of the OSTP Director, and Dr. Francis Collins will perform the duties of Science Advisor to the President and Co-Chair of the President's Council of Advisors on Science and Technology.

NCI Programs and Initiatives. Dr. Sharpless provided an update on the Workplace Civility and Anti-Harassment initiative. He emphasized that the NCI is unequivocally committed to ensuring civility, kindness, and mutual respect, which are core values at the NCI and NIH. The NCI does not tolerate bullying or harassment of any kind, as clearly indicated in NIH's Anti-Harassment Policy. Dr. Lawrence A. Tabak, Acting Director, NIH, in his 10 February 2022 statement on the "Commitment to a Safe and Respectful Workplace at NIH," remarked that harassment or inappropriate conduct of any kind will not be tolerated at the NIH; timely and appropriate action will be taken against any individual found to be in violation of these policies. In 2020, the NCI initiated a Workplace Civility and Anti-Harassment initiative that is coordinated by an NCI Workplace Civility Committee comprising representatives from across NCI's Divisions and Centers. The NCI continues to communicate clear policies in this area, provides toolkits and training, and has incorporated anti-harassment training into employee onboarding and

performance evaluations. The NCI offers accessible channels for anyone who experiences harassment to report it safely and discreetly, without fear of retaliation. Dr. Sharpless emphasized that the NCI takes this commitment seriously.

Dr. Sharpless stated that the Cancer Moonshot℠ remains a work in progress. The initiative has three ambitious goals: (1) Accelerate scientific discovery in cancer, (2) foster greater collaboration, and (3) improve the sharing of data. The Cancer Moonshot℠ has led to more than 70 consortia or programs and more than 240 new research projects. Drs. Sharpless and Singer recently published a review on Cancer Moonshot℠ outcomes. Broad goals for ending cancer as we know it have been described: (1) Diagnose cancer sooner; (2) prevent cancer; (3) address inequities; (4) target treatments to the right patients; (5) speed progress against the deadliest and rarest cancers; (6) support patients, caregivers, and survivors; and (7) learn from all patients.

One important approach to changing the experience of cancer for patients is examining the prism of cancer mortality, particularly age-adjusted cancer mortality across the United States. From 2005 to 2019, the age-adjusted cancer mortality declined significantly. Heterogeneity across the states, however, was pronounced and persists today. Geography remains a significant factor in cancer mortality, reflecting such factors as race, poverty, and access to care. The NCI is responsible for understanding the underlying causes of these disparities. Dr. Sharpless acknowledged Zaria Tatalovich, Geospatial Scientist, Division of Cancer Control and Population Sciences (DCCPS), NCI, for her efforts in compiling data on cancer mortality across the United States.

Dr. Sharpless stated that President Biden announced a new White House goal to reduce the death rate from cancer by 50 percent during the next 25 years, a reduction of age-adjusted mortality from 146 to 73 deaths per 100,000. This goal will require a focus on prevention, screening, therapies, tobacco control, and health disparities. Dr. Sharpless reiterated that this goal is ambitious but feasible. Dr. Sharpless commented further on the effects of race and ethnicity on cancer mortality in the United States. Cancer mortality has declined for all populations between 2004 and 2019, but disparities remain. CDC 4-year reports from 2000 to 2019 show that the age-adjusted mortality rates were greater in non-Hispanic Black patients than in other populations. For non-Hispanic American Indian/Alaska Native patients, a large degree of geographic heterogeneity is present, with certain regions displaying greater mortality rates. An understanding of health disparities requires thoughtful use of data and consideration of multiple factors.

A major focus of the Cancer Moonshot℠ 2.0 is on prevention, screening, and early detection, which are important tools to control cancer at the population health level. The President's Cancer Panel recently released a report, *Closing Gaps in Cancer Screening: Connecting People, Communities, and Systems to Improve Equity and Access*. Barriers identified in the report included lack of knowledge of guidelines and provider recommendations, fears or concerns about medical procedures, and difficulty navigating the health system. Community-oriented outreach is needed to address these barriers. Dr. Sharpless reiterated that cancer screenings have declined during the COVID-19 pandemic and have not recovered fully; Americans have missed more than 9 million screenings in the past 2 years. These deficits should be addressed to the greatest extent possible. President Biden emphasized the need to ensure that everyone in the United States benefits equitably from screening capabilities (e.g., at-home screening, mobile screening, community health networks) and called for an all-government approach to address this problem. The NCI continues to pursue efforts in this area (e.g., NCI-Designated Cancer Centers) to ensure that cancer screening is made clear as a national priority. The NCI also will collect qualitative and quantitative data to understand these needs and work in partnership with the CDC, CMS, and Health Resources and Services Administration (HRSA) on this topic.

Emerging technologies have enabled the development of blood-based multi-cancer detection (MCD) tests, which can detect multiple cancers simultaneously in otherwise healthy individuals. This

high-sensitivity and high-specificity test for multiple cancers would require further diagnostic studies in the event of a positive MCD result. More than 20 MCD tests are in development presently. Dr. Sharpless remarked that these developments are exciting and could have a significant impact on cancer detection at the population level if the screening is applied robustly. He cautioned, however, that screening and early detection can incur the potential for overdiagnosis and overtreatment; thus, appropriate clinical trials are needed to understand the benefits of these technologies. The NCI published a request for information (RFI) seeking input from the community on this topic, and responses will be accepted through 1 March 2022.

At the 10 February 2022 National Cancer Advisory Board (NCAB) meeting, Dr. Barry R. O'Keefe, Director, Molecular Targets Program, Center for Cancer Research (CCR), and Chief, Natural Products Branch, Developmental Therapeutics Program, Division of Cancer Treatment and Diagnosis (DCTD), NCI, presented an update on the NCI Program for Natural Product Discovery (NPNPD). Natural products comprise approximately 30 percent of agents in approved drugs but are represented poorly in high-throughput drug screening efforts. The NCI is working to address challenges associated with natural products through a joint program between the DCTD and CCR. This effort involves the use of facilities at the FNLCR, which has unique capabilities for research in this area. More than 1 million semi-pure natural product fractions have been generated; the NCI is hopeful that usage of these products will increase significantly. Hundreds of thousands of fractions have been released to the public, and samples have been shipped to screening centers worldwide. The program is funded by the Cancer Moonshot℠, and the resource also has been used widely across the NIH. An NIH VideoCast recording of the presentation is available.

Progress in Cancer Research. Dr. Sharpless updated the FNLAC members on three research initiatives. He first highlighted work by scientists at the FNLCR, the NCI, Massachusetts General Hospital, Dana-Farber Cancer Institute, EMD Serono, Bristol Myers Squibb, and Pfizer. This team recently identified a genetic variant that can predict whether immune checkpoint inhibitors used to treat cancer might fail in certain patients. These findings were published recently in *The Lancet Oncology*. They reported that the *HLA-A*03* allele could serve as a useful screening marker to determine whether a patient should receive immune checkpoint inhibitors. This allele also might be a causative variant associated with antigen presentation and immune response. These findings provide insight on the immunological response to cancer and highlight the groundbreaking scientific capabilities at the FNLCR.

FNLCR scientists and collaborators recently developed a novel imaging agent that could detect deadly pancreatic cancer at its earliest stages. The group discovered a membrane receptor, CCK-BR, that is overexpressed in cancer cells and precancerous lesions. The group also developed a fluorescent nanoparticle that attaches to CCK-BR on pancreatic intraepithelial neoplasia (PanINs), leading to cellular accumulation of the fluorescent signal and revealing precancerous PanINs. These results recently were published in *Biomolecules*. This goal of this work is to develop a nanoparticle imaging agent for clinical use; such nanoparticles also could be engineered to carry therapeutics.

Recent work through the RAS Initiative has focused on multiscale modeling; this is a crucial component of the NCI/DOE Collaboration. RAS is mutated in more than 30 percent of cancers, and its behavior at the cellular membrane and in cell signaling remains a critical question. Novel RAS therapeutics have been developed and have received FDA approval, and additional opportunities for discovery are present. Modeling is vital for understanding KRAS–lipid interactions, dynamics of RAS, and assembly of local domains and rich signaling components. The results recently were published in the *Proceedings of the National Academy of Sciences*. Dr. Sharpless emphasized that this work is novel in its use of a multiscale machine-learned modeling infrastructure (MuMMI) and is the first example of analysis and machine learning (ML) used for this kind of computational biology at multiple scales (e.g., lipid bilayer, protein complex, atom).

NCI New Personnel Announcement. Dr. Sharpless stated that the NCI has long been committed to unraveling the intricacies of childhood cancer, recognizing that treatment is different for children than adults. The CCDI has demonstrated unique opportunities and challenges in this area. In particular, more efforts related to data aggregation are needed. The NCI recently announced that Dr. Brigitte C. Widemann, Chief, Pediatric Oncology Branch, CCR, NCI, has been appointed as Special Advisor to the Director for Childhood Cancer. Dr. Sharpless remarked that Dr. Widemann has extensive experience in this area, and the NCI looks forward to her support.

Recapping the 2 February 2022 White House event, Dr. Sharpless explained that the First Lady's perception of cancer research was reflected in her speech in which she noted this time being a "golden age of cancer research" and emphasized the need to make progress against cancer. Dr. Sharpless emphasized that this Administration believes that the time is now to make that progress and succeed. The FNLCR has an important role in these efforts.

In the discussion, the following points were made:

- Cancer mortality data appear to indicate several trends that seem counterintuitive. The NCI has not yet explored this issue fully; some of the trends might reflect access to care or another feature of those regions. These questions represent an opportune area for future research. Additionally, many of the highlighted findings are particularly evident in American Indian/Alaska Native populations. Additionally, some of the trends might represent statistical artifacts.

III. UPDATE: NCI/DOE COLLABORATION—DR. DOUGLAS R. LOWY

Dr. Douglas R. Lowy, Deputy Director, NCI, provided an update on the NCI/DOE Collaboration. He provided updates on 2017–2021 activities, outlined recommendations and implementation efforts from the Evaluation Task Force (Task Force), and highlighted current projects. Dr. Lowy expressed appreciation to Dr. Emily Greenspan, Biomedical Informatics Program Director, Center for Biomedical Informatics and Information Technology, NCI, for her role in coordinating this effort.

Three pilot projects were initiated in 2017 and were funded by the Cancer Moonshot℠. Pilot 1 previously was titled "Predictive Modeling for Preclinical Screening," with a goal to improve predictive efficacy of preclinical drug studies through computational modeling. Pilot 2 was titled "RAS Biology on Membranes," with a goal to deepen understanding of RAS biology through integrated development and use of new simulations, predictive models, and next-generation experimental data. Pilot 3 was titled "Population Information, Integration, Analysis, and Modeling," with a goal to modernize NCI's Surveillance, Epidemiology, and End Results (SEER) Program.

On 14 October 2020, Dr. Joe Gray, Professor Emeritus, Oregon Health & Science University, presented the Task Force's Evaluation report to the FNLAC. Dr. Lowy reminded FNLAC members of key points from this presentation: The NCI/DOE Collaboration is uniquely suited to address certain critical challenges in cancer research and should continue, but the current pilots should be evaluated as full-scale projects. Two main recommendations were provided: (1) develop and review future projects using a more structured and rigorous approach and establish project-specific advisory groups and (2) increase engagement with the NCI extramural community. The Task Force recommended that Pilot 1 be concluded and Pilots 2 and 3 be continued. The final reported has been published on the NCI website.

NCI/DOE Collaboration: 2022–2027. Dr. Lowy provided an update on NCI's response to the Task Force's recommendations. On 17 September 2021, the DOE and NCI signed a new 5-year memorandum of understanding for 2022–2027. For the new collaboration, oversight will be performed under the DOE Advanced Scientific Computing Advisory Committee (ASCAC). The group will

incorporate recommendations of the Task Force, increase extramural engagement, increase regular review of projects, host workshops and hackathons, and perform a drastic revision of Pilot 1. Governance and oversight will include an ASCAC Subcommittee, Scientific and Technical Advisory Committees, and an Executive Committee. A Scientific and Technical Advisory Committee has been established for Project 3; committees are being developed for Projects 1 and 2.

Pilot 3 now is titled "Modeling Outcomes using Surveillance data and Scalable Artificial Intelligence (AI) for Cancer (MOSSAIC)." The project leads are Dr. Lynne Penberthy, Associate Director, Surveillance Research Program, DCCPS, NCI, and Dr. Georgia Tourassi, Director, National Center for Computational Sciences, Oak Ridge National Laboratory (ORNL). The project involves 38 NCI/DOE scientists, more than 40 registry staff and leads, 35 technical support staff, and multiple academic partners. Scientific advancements include an application programming interface (API) to auto-extract structured data from unstructured pathology reports, which is 18,000 times faster than manual extraction. Presently, 17 percent of all pathology reports can be auto-coded with greater than 98 percent accuracy. The next case-level API is in development, and preliminary results indicate that 23 percent of pathology reports will be auto-coded with greater than 98 percent accuracy. One activity involves automated extraction of key biomarkers from pathology reports for breast and colon cancers. In the preliminary algorithm, the accuracy range was 92–95 percent for these biomarkers. Next steps involve future integration of the biomarkers task into the SEER workflow, beyond breast and colon cancers.

Pilot 2 now is titled "AI-Driven Multiscale Investigation of RAS-RAF Activation Life cycle (ADMIRRAL)." The project leads are Dr. Dwight Nissley, Director, Cancer Research and Technology Program, FNLCR, and Dr. Fred Streitz, Chief Computational Scientist, Lawrence Livermore National Laboratory (LLNL). Previously, the focus of this project was simulation of KRAS on a membrane and its interaction with RAF, in the context of various lipids by MuMMI. The main goal is to increase focus on protein domain movement and the mechanism by which KRAS activates RAF, as well as bidirectional interaction between simulations and RAS–RAF structure, biochemistry, and biology. Dr. Lowy reminded the FNLAC members that the work of Dr. Deborah K. Morrison, CCR, NCI, is informing this project. Future aims for predictive molecular dynamics simulations are to (1) characterize opening of auto-inhibited RAF protein on 14-3-3 protein disengagement, (2) delineate large-scale domain rearrangement of the RAS-RAF complex, and (3) describe engagement and dimerization of RAF kinase domains.

A new project, called "Innovative Methodologies and New Data for Predictive Oncology Model Evaluation (IMPROVE)," builds on lessons from Pilot 1 and has been designed with a new engagement model with the cancer research community and DOE National Laboratories. The project leads are Mr. Rick L. Stevens, Associate Laboratory Director, Argonne National Laboratory (ANL), and Dr. M. Ryan Weil, Director, Strategic and Data Science Initiatives, FNLCR. Two related goals are aimed at improving deep-learning models for predicting drug responses and tumors: (1) development of semiautomatic protocols for comparing deep-learning models from various investigators and identifying model attributes that contribute to prediction performance, with the goal of improving future models, and (2) development of protocols for specifying drug screening experiments and to generate data aimed explicitly at improving model performance. The anticipated impact of IMPROVE is closing gaps in development and application of deep-learning models for predictive modeling of therapeutic response and potentially generating new treatment approaches.

IMPROVE addresses two key bottlenecks for making progress with broad community engagement. Bottleneck 1 (Aim 1) is comparing a new model to previous N models. The aim will extend beyond simple validation approaches to more biologically relevant assessments, and the group will work with the community to develop more standard approaches for evaluation. The goal is to develop an "automated" framework to make massive cross-comparisons feasible. Bottleneck 2 (Aim 2) is identifying

data that need to be generated to improve models. The vast majority of data were not created for this purpose. By studying model errors and failures and how they relate to training and validation data sets, researchers can determine which data are most useful. An understanding is needed of data quality and model performance, the learning curve scaling behavior, feature types and modality of training data, and impact of data diversity. The goal is to generate new data sets to improve models and make them widely available.

For Aim 1, ANL and FNLCR plan to use an RFI/request for proposals (RFP) process, administered by the FNLCR, to support as many as five extramural groups to participate in designing and building the IMPROVE framework for model comparison and use that framework to produce an annual assessment of drug response models to cancer. DOE National Laboratories also will be involved. For Aim 2, an RFI/RFP process, with a qualification round, will be used to identify commercial firms or other third parties that can be contracted to produce the data specified by the core modeling group. The IMPROVE framework, model analysis results, any improved models, and all data produced will be open-source and available to the community. IMPROVE will hold development hackathons and an annual meeting that will be open to the community. Additionally, IMPROVE will work with agencies, scientific associations, and journals to advocate for open models, data, and sourcing to enable replication of modeling results.

Dr. Lowy noted that other areas are being explored for future collaborations. The Accelerating Precision Radiation Oncology Through Advanced Computing and Artificial Intelligence Workshop Series was held in 2021. He remarked that the NCI anticipates that increased interaction with the extramural research community and regular review by project-specific advisory groups will increase the achievements and impact of the collaboration.

In the discussion, the following points were made:

- Plans for outreach beyond the SEER program are being developed. These efforts could include discussions on standardization of ML processes for extraction of biomarkers from pathology reports.

- Comparison of *in vivo* and *in vitro* studies is important in modeling studies. Patient-derived xenograft (PDX) models will be correlated with patient data as a part of the IMPROVE project.

- The NCI/DOE Collaboration has substantial power in linking processes to improve data usability, and application to other widely used databases might be beneficial.

IV. THE CANCER IMAGING ARCHIVE (TCIA)—DR. JANET F. EARY

Dr. Janet F. Eary, Associate Director, Cancer Imaging Program (CIP), DCTD, NCI, presented an overview of The Cancer Imaging Archive (TCIA). She explained that TCIA provides a platform for investigators to submit and access deidentified, curated image data sets for the research community. Data sets are available for standard types of cancer, unique or rare types of cancer, and specific clinical applications. Initially, TCIA was focused on images generated through standard clinical imaging (e.g., computed tomography [CT], magnetic resonance, positron emission tomography). Over time, the associated metadata for integrated analysis have become increasingly important to TCIA. Recently, the group has become interested in exploring new image data types and developing procedures for data sharing. TCIA was established to address a critical need across the research community. Dr. Eary explained that images are rich data sets; they include spatial and temporal information that can be integrated with other analyses. Additionally, image collection is noninvasive. TCIA is funded and governed through the CIP and managed and implemented though the FNLCR. Mr. John Freymann,

Informatics Manager, FNLCR, is the TCIA lead, and he oversees subcontractors involved in the effort. TCIA collections are sourced primarily from the research community. Proposals are evaluated monthly by the TCIA Advisory Group, which includes expert reviewers from the CIP, CCR, FNLCR, and the Cancer Diagnosis Program. Proposals include requests from NCI and NIH grants, challenge competitions, and publication data-sharing requests. TCIA also supports radiology and histopathology imaging in major NCI research initiatives.

Dr. Eary noted that images are deidentified and curated into well-described data sets. Review criteria for TCIA submissions include importance for research, capacity to address data gaps, novelty and uniqueness, size and scale, and presence of supporting data and documentation. For data sets that include scientific analyses, criteria also include biological hypothesis or proposed discovery, benefits for researchers, and scientific criteria for methodology of analysis. More than 85 institutions worldwide have contributed to TCIA. Different institutions have different data-sharing policies and formats, which poses a broad array of challenges. Working components of TCIA include data collection (e.g., specialized deidentification processes; tools to support collection, curation, and deidentification), specialized teams, and data-hosting and query (e.g., research-focused website graphical user interface, programmatic interfaces). Dr. Eary explained that public sharing of imaging data also presents challenges. Clinical imaging data and animal model research data contain many identifiers. Protected health information (PHI) is of the greatest concern. PHI can appear in pixel data, dates, identifiers, descriptions, and "private tags" with ambiguous proprietary content. The location of PHI varies based on data type and vendor. Increasingly, deidentification tools are becoming automated. All TCIA data are fully deidentified.

TCIA includes 160 collections consisting of about 50,000 subjects and more than 50 million images at various time points. These data include 29 image analysis results databases, standard radiology images, radiation therapy planning images, histopathology images, and associated supporting data. TCIA has been accessed by 768,000 users from 216 countries and regions, and 20,000 users access TCIA each month. Nearly 1.7 petabytes of data are downloaded per year. TCIA is the data publisher and repository of record for a variety of journals and publishers, including *Nature*, *PLOS ONE*, *Medical Physics*, Elsevier, and F1000Research. Data are collected from more than 85 institutions and are represented in more than 1,300 peer-reviewed publications. TCIA also collects Open Researcher and Contributor ID (ORCID) data, assigns digital object identifiers (DOIs), publishes data using Creative Commons licensing, avoids unnecessary account creation or login requirements for open-access data sets, and partners with journal publishers to provide a repository for data-sharing requirements. Recently, TCIA was recognized as an NIH High-Value Data Asset (HVDA). Dr. Early noted that discussions within the HVDA community include defining value and addressing sustainability issues.

TCIA contributes to the Clinical Proteomic Tumor Analysis Consortium (CPTAC), **A**pplied **P**roteogenomics Organizationa**L** **L**earning and **O**utcomes (**APOLLO**) Network, the Cancer Moonshot℠ Biobank, NCI's National Clinical Trials Network (NCTN), Integrated Canine Data Commons (ICDC), and the National Lung Screening Trial. TCIA collects, deidentifies, and hosts standard-of-care imaging from CPTAC patients and links radiology and histopathology imaging to the CPTAC analysis results on the Genomics and Proteomics Data Commons. Dr. Eary emphasized that imaging data are important for proteomic and genomic analyses. Additionally, TCIA is establishing first-of-its-kind clinical imaging deidentification and sharing systems within the DoD and VA through the Cancer Moonshot℠ APOLLO Network. Imaging data from DoD, VA, and civilian sites will be posted on TCIA and mined for clinically relevant information in combination with APOLLO proteogenomic findings. Standard-of-care images are collected from across the research community through the NCI Community Oncology Research Program (NCORP) and the Cancer Moonshot℠ Biobank. Additionally, images from select NCTN trials are being collected, curated, and posted on TCIA with links to clinical data on the NCTN/NCORP Data Archive. TCIA also is partnering with the ICDC to curate and host radiology and pathology imaging data; the two groups have hosted the first data set of its kind to comprehensively describe and report the clinical,

pathologic, imaging, and genomic landscape of naturally occurring canine glioma. Data sets from other species (e.g., murine models) also are available.

Dr. Eary also described TCIA's efforts related to COVID-19 research. She explained that imaging (e.g., chest imaging, CT scans) has been important for the characterization of COVID-19. TCIA pivoted quickly to hosting and sharing COVID-19 data sets, applying its established process to handle large volumes of radiological imaging data. Additionally, TCIA played a critical role in the establishment of the National Institute of Biomedical Imaging and Bioengineering's Medical Imaging Data Resource Center; COVID-19 imaging was the first use case. Dr. Eary noted that TCIA also supports the CCDI. Data sets are available for four children's oncology group clinical trials, and more are under curation presently. Additionally, one community data set has been published. TCIA is engaging with the CCDI Data Catalog to ensure TCIA data sets are discoverable for investigators.

TCIA also is engaged in efforts to prepare data for AI research. These activities include participation in the NCTC Clinical Trial Annotation project, linking American College of Radiology use cases to TCIA collections, connecting to major medical AI imaging platforms, and providing highly curated data to AI-focused challenge competitions. Further, all TCIA data are mirrored on the NCI Imaging Data Commons (IDC) to support users who work in cloud-based environments. TCIA functions as an input mode for deidentification and documentation and handles a broad array of imaging data in low-resource settings and for emerging technologies.

In the discussion, the following points were made:

- The IDC would be more likely than TCIA to support federated ML (i.e., on-premises computing). Federated ML allows investigators to avoid downloading large data sets into their local systems and enables the creation of database networks with common federated software. This approach could reduce the need for data deidentification because the algorithm could be written so that PHI is not retrieved.

- TCIA data are hosted for the imaging community; imaging research is critical to cancer research and an important aspect of data integration and hypothesis generation. Additionally, TCIA data are important for the pathology and pathomic communities. TCIA users are not required to identify themselves to access data, but analysis of scientific publications also indicates that TCIA data are accessed by trainees and postdoctoral associates, as well as computational researchers who are new to cancer research.

- Small grants would be beneficial to enable researchers to begin new projects using TCIA data sets; similar grants are available through other organizations. This effort would expand TCIA's user base.

- The research and translational communities now overlap with the clinical community, and *in situ* correlates of cellular responses to therapy are of particular interest. Availability and hosting of data, as well as mechanisms for data federation and interconnection, are important for these efforts. The Human Tumor Atlas Network, a Cancer Moonshot℠–funded initiative, is developing its own data collection and archive, much of which is image data, and serves as an input for the IDC. TCIA's role is hosting different data common types with which researchers might otherwise be unfamiliar. TCIA will continue to engage with the research community on data types and their importance for integrative research. All relevant image data, regardless of type, can be explored through TCIA.

- Integration with spatial sequencing data represents a challenge for the NCI Cancer Research Data Commons. TCIA's integration nodes enable integration with various data types.

V. UPDATE ON FREDERICK NATIONAL LABORATORY FOR CANCER RESEARCH (FNLCR) AWARENESS CAMPAIGN—MS. NANCY SIEBERT MURPHY AND MR. RICHARD FOLKERS

Mr. Richard Folkers, Senior Editor, Office of Communications and Public Liaison (OCPL), NCI, provided an update on the FNLCR awareness campaign. He reminded FNLAC members that Ms. Nancy Siebert Murphy, Communications Lead Manager, OCPL, NCI, announced this campaign during the 23 February 2021 FNLAC meeting. The goals of the campaign were to increase awareness and use of FNLCR services and resources among extramural scientists and to improve messaging so that all stakeholders appreciate and understand FNLCR's value. The OCPL and NCI Frederick Office of Scientific Operations shared information on the FNLCR to organizations interested in competing for the contract during NCI's Federally Funded Research and Development Center (FFRDC) Virtual Industry Day in April 2021. The event opened with a video of Dr. Sharpless and Dr. Anthony Fauci, Director, National Institute of Allergy and Infectious Diseases (NIAID), discussing the history and contributions of the FNLCR; the video has been promoted through social media and can be accessed through NCI's website.

The OCPL also has worked with FNLCR staff on revamping the FNLCR website to make it more user friendly. The group updated media guidelines for the FNLCR. Additionally, the FNLCR has been highlighted in several feature stories throughout the NCA-50 commemoration. Mr. Folkers acknowledged Ms. Tula Michaelides, Health Communications Specialist, NCI, for her work in the campaign. He stated that the campaign is a work in progress; more data and perspectives on the topic are being collected. Mr. Folkers explained that the FNLCR is complex, and its operations are challenging to describe to the extramural community. The OPCL Analytics and Audience Research Branch conducted an analysis of the FNLCR resource allocation. An upcoming survey will determine the current knowledge of the FNLCR among extramural scientists and how to improve access to services.

The analysis of resource allocation indicated that limited promotion of the FNLCR occurs. Most laboratories do not promote the FNLCR regularly, beyond the NCI or FNLCR websites. Conference presentations and journal publications were preferred tools for communication, and laboratories varied in how they viewed the value of promotion. Short-term recommendations in this area were that the NCI begin a targeted campaign to make members of the extramural community more aware of FNLCR's capabilities that may be accessible to them. Potential initial targets included reagents and services (e.g., antibodies, RAS reagents, cell-based models, PDX models), the National Cryo-Electron Microscopy (Cryo-EM) Facility (NCEF), Nanotechnology Characterization Laboratory, NCI Experimental Therapeutics (NExT) program services, serology services, Genomic Data Commons services, and NPNPD. The group also recommended a cohesive clearinghouse to access resources on a single page of the FNLCR website. A series of plans were proposed. Phase 1 (February–September 2022) includes promotion at conferences, short videos, fact sheets, slide decks with unified messaging, NIH leadership presentations, targeted social media, activities to mark the 10th anniversary of FNLCR's designation as a national laboratory, and internal promotion.

Additionally, Mr. Folkers and Ms. Michaelides conducted interviews with 16 of FNLCR's key leaders. The interviews focused on FNLCR's value. Most interviewees agreed that greater awareness of the FNLCR is needed, and its complexities make promotion challenging. Beyond this point, however, a broad range of responses was recorded. Interviewees differed in their view of the laboratory's name and acronyms (FNL versus FFRDC, inclusion of "Cancer"). Misperceptions regarding the FNLCR were as follows: (1) FNLCR is an extension of the NCI intramural program. (2) FNLCR performs only

task-oriented science. (3) FNLCR funding is detrimental to the extramural program. (4) Excessive bureaucratic process are present. (5) Intellectual property is at risk. (6) FNLCR is funded through a massive allocation that is debited slowly. (7) FNLCR is a part of Fort Detrick. Mr. Folkers stated that the FNLCR is prohibitively difficult to characterize as a single entity. He suggested that promotional efforts consider the FNLCR to comprise multiple intramural, extramural, and hybrid laboratories. The upcoming survey of researchers will help the group better understand how widely the FNLCR is known and how best to reach and inform those scientists. Those results will be included in the final report of this campaign. Long-term goals include greater targeted promotion, which could enhance appreciation by policymakers and advocates. Promotion should embrace FNLCR's complexity, which is necessary to address complex diseases.

The group recommended that NCI use consistent language in naming and describing the FNLCR. Harmonization of NCI's and FNLCR's online presence and reduction of redundancy across websites will require ongoing efforts. NCI personnel also should be educated on FNLCR's structure and activities. FNLAC's assistance in this effort also will be needed. Mr. Folkers concluded by noting comments from respondents about FNLCR's value: The FNLCR (1) offers unique capabilities for cancer research; (2) fills breaches and tackles issues that academic institutions and biomedical companies cannot; (3) is a safe harbor for data and repositories in which all resources are in the public domain; (4) serves the public interest, the country, and the world; (5) provides qualified staff with high-level expertise who make a difference; (6) serves as a neutral place for scientists to meet, perform cutting-edge work, and take risks; and (7) provides resources to help researchers rather than compete with them. Mr. Folkers asked FNLAC members for their input on future directions, opportunities for collaboration, and engagement beyond the NCI.

In the discussion, the following points were made:

- Communication has become challenging in fragmented virtual environments. Many other groups face similar challenges. FNLCR staff could benefit from communications training (e.g., through the Alan Alda Center for Communicating Science). These individuals are the best ambassadors for the FNLCR, and staff members who excel in this area could be identified for future promotional efforts.

- The FNLCR main website is managed by Leidos Biomedical Research Inc. (Leidos), and additional content is available through the NCI website. The OCPL works to ensure that information is kept consistent between the two websites. Recently, updates to the websites were implemented to simplify and clarify relevant programs.

- FNLCR staff would benefit from simple talking points for describing the FNLCR in a consistent manner. The messages from the recent video featuring Drs. Sharpless and Fauci highlights many of the key messages that the OCPL plans to highlight.

VI. FREDERICK NATIONAL LABORATORY (FNL) OPERATIONS AND UPDATE—DR. ETHAN DMITROVSKY

Dr. Ethan Dmitrovsky, Director, FNLCR, and President, Leidos Biomedical Research, presented an update on the FNLCR. In his presentation, he highlighted FNLCR's rapid response to the COVID-19 pandemic and the omicron variant of SARS-CoV-2; demonstrated continuation of operations and quantitative, discovery, translational, and clinical science during the response period; and described NCI and NIAID projects that exemplify federally funded research and development efforts and how the FNLCR shares its expertise with the extramural community. He explained that the FFRDC task order portfolio includes five operational task orders (i.e., one through NCI, three through NIAID, and one lease

task order), in which the benefits of services recur with annual funded appropriations, as well as 103 nonoperational task orders, i.e., 69 in the Clinical Group, 16 in the Scientific Group, and 18 facility or infrastructure refurbishments. Additionally, extensive outreach to the broader research community is performed through subcontracting.

The Task Order mechanism is intended to perform unique work that would not be conducted in industry or academic settings. For example, FNLCR's familiarity with operations in military and politically unstable areas enabled the preservation of equipment and clinical samples at the Charles Henry Rennie Memorial Hospital during a looting event following a fire. As a result of these efforts, the hospital resumed clinical care and research activities about 1 week after the fire. Dr. Dmitrovsky wrote a series of commentaries of the value of public–private partnerships for such publications as *The Baltimore Sun*, *STAT* and elsewhere.

The FNLCR also worked to ensure continuity of essential veterinary, scientific, and clinical services during the COVID-19 pandemic as a part of its contractual obligations. Dr. Dmitrovsky briefly highlighted FNLCR scientific directorates that have been engaged in these efforts. He also acknowledged the work of facilities; custodial; Occupational Health Services Program; and Environmental, Health and Safety Program staff members. He noted that about 225 staff members continued working in person during the pandemic. The omicron variant of SARS-CoV-2 required specific actions to ensure continuation of services. These actions included weekly executive team leadership meetings; split shifts; suspension of routine, non-vital services; maximization of telework; prioritization of health services; automation of case management; and adherence to all CDC guidelines for mission-essential staff.

Dr. Dmitrovsky emphasized that the COVID-19-related measures did not impede FNLCR's efforts related to cancer. He stated that FNLCR's structure was designed to achieve minimal administrative burden and is improving continuously. For example, during the COVID-19 pandemic, the FNLCR automated its system for staff updates in the NIH Enterprise Directory, providing cost-savings that can be applied to scientific research. Dr. Dmitrovsky showed that such benefits are accruing over time. Since 2016, the contract's cost has increased by 19 percent, but the administrative staff has decreased by 6.5 percent. Administrative costs are controlled by not backfilling positions, promoting staff to leadership positions, implementing rigorous refinement of processes, shifting or removing roles for efficiency, and leveraging information technology resources. The FNLCR also invested in the well-being of its staff through several health management programs in partnership with Johns Hopkins Medicine; these programs include Work Stride: Managing Cancer at Work, Decision-making Education for Choices In Diabetes Everyday (DECIDE), act2 (a diabetes prevention program), and Balance (a behavioral health program). These services enhance recruitment and retention and reduce health care costs.

Dr. Dmitrovsky reported that the NCI Serological Sciences Network for COVID-19 (SeroNet) Program is being consolidated under the Vaccine, Immunity and Cancer Directorate into one space at the FNLCR, relocating the Program groups from multiple locations. The refurbishment is being performed in stages to minimize effects on scientific operations of other groups. He highlighted that SeroNet investigators have developed the U.S. Human SARS-CoV-2 Serology Standard, a tool to harmonize assays and increase comparability of results from different studies.

The FNLCR also has continued to provide support for the NCI CAR-T cell trials with the DCTD, with a focus on rare and pediatric cancers. Ongoing efforts include CD33 therapy (e.g., pediatric acute myeloid leukemia) and GD2 therapy (e.g., pediatric neuroblastoma and osteosarcoma). Planned efforts include HYP218 CART (e.g., mesothelioma, ovarian cancer, pancreatic lung adenocarcinoma), GPC2 CART (e.g., neuroblastoma), and STEAP1 CART, e.g., prostate cancer. The current technology involves lentiviral vectors, and a CRISPR-Cas9 system is in development.

The NCEF has collaborated with 119 extramural investigators from more than 50 institutions, at no cost to the investigators. During the past 5 years, 784 imaging sessions were completed. These efforts resulted in 64 publications, including 29 from the past year, many of which are published in such high-tier publications as *Science*, *Nature*, and *Nature Communications*. Dr. Dmitrovsky explained that the NCEF pivoted to COVID-19 research in May 2020. In August 2020, the facility returned to cancer projects at an increased level. A series of repairs was conducted between late 2020 and mid-2021, leading to temporary declines and compensatory increases in imaging activities. Similar patterns occurred in late 2021 and early 2022 as a result of omicron variant exposures.

Dr. Dmitrovsky echoed earlier comments from Drs. Lowy and Sharpless about the MuMMI study. He noted that the work serves as a case study of team science and represents a joint effort by the FNLCR; ANL; LLNL; Los Alamos National Laboratory (LANL); IBM Corporation; San José State University; University of California, San Francisco; the Cancer Research Technology Program; and the RAS Initiative. He noted that opportunities for further team-based development of this model are being pursued. He also echoed Dr. Sharpless' comments on the significance of recent reports on the *HLA-A*03* allele. Dr. Dmitrovsky highlighted recent work with NIAID related to vaccine development and manufacturing. This work includes studies of HIV (neutralizing monoclonal antibody, trimer vaccine), Ebola (bispecific, monoclonal), influenza (nanoparticle influenza vaccine), and malaria (monoclonal antibody).

Dr. Dmitrovsky highlighted training programs associated with the FNLCR. Leidos Biomedical Research is launching educational modules, at no cost to the government, for extramural investigators conducting international clinical trials in resource-constrained and politically unstable countries. Trainees will receive continuing education units (CEU) or continuing medical education (CME) credit and a certificate of completion. The FNLCR also is holding a 5-day cryo-EM training program later in 2022 for novice cryo-EM users. The training objective is to provide theoretical and hands-on training in sample preparation, grid screening, data collection and processing, structure determination, and model building, as well as validation using the single-particle cryo-EM method. Additionally, the FNLCR recognized the International Day of Women and Girls in Science on 11 February 2022 in an event featuring a keynote speaker and scientific panelists from the Howard University Cancer Center, FNLCR, NCI, and U.S. Patent and Trademark Office. He highlighted FNLCR academic partnerships, noting that the FNLCR recently partnered with Howard University to provide mentorship services, conduct disparities research, and provide opportunities for students.

In the discussion, the following points were made:

- Johns Hopkins Medicine's employee wellness programs were selected by Dr. Dmitrovsky and the Leidos Biomedical Research HR team as a new benefit for their workforce. He noted that the programs were founded in honor of a former Cancer Center Director who had passed away from cancer. The initiative is funded through repurposing of the wellness budget at Leidos Biomedical Research and does not incur major costs.

- The FNLCR is committed to addressing the issue of employee behavioral health and has made many investments in this area, beyond those discussed in the presentation. Many former employees choose to return to the FNLCR, and resignation rates within the FNLCR are lower than national averages. A tone of genuine care and engagement is crucial. FNLCR leadership has made an effort to identify women and minorities who can be elevated within the FNLCR based on their talent.

- The Cryo-EM Training Program will focus on 12 trainees in the first year to accommodate spacing requirements. After this time, the group will discuss increasing the number of trainees in the program.

VII. ADJOURNMENT—DR. CANDACE S. JOHNSON

Dr. Johnson thanked the Committee members and other participants for attending. Members were reminded to send potential agenda topics for future FNLAC meetings to Dr. Lopaczynski. There being no further business, the 9th Virtual Meeting of the FNLAC was adjourned at 3:55 p.m. EST on Thursday, 24 February 2022.

Date	Candace S. Johnson, Ph.D., Chair
Date	Wlodek Lopaczynski, M.D., Ph.D., Executive Secretary