U.S. Department of Health and Human Services
Public Health Service
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National Cancer Institute

12th Virtual Meeting
Frederick National Laboratory Advisory Committee

Summary of Meeting
February 27, 2023

National Cancer Institute
National Institutes of Health
Bethesda, Maryland

National Cancer Institute
12th Virtual Meeting of the Frederick National Laboratory Advisory Committee

27 February 2023

Summary of Meeting

The Frederick National Laboratory Advisory Committee (FNLAC) convened for its 12th Virtual Meeting on 27 February 2023. The meeting was open to the public from 1:00 to 3:05 p.m. 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. Carol J. Bult
Dr. John H. Bushweller
Dr. Timothy A. Chan
Dr. Lisa M. Coussens (absent)
Dr. Angela M. Gronenborn
Dr. Mary J.C. Hendrix
Dr. Scott W. Hiebert (absent)
Dr. Rodney J.Y. Ho
Dr. Allison Hubel
Dr. Dineo Khabele
Dr. Anant Madabhushi
Dr. Denise J. Montell (absent)
Dr. Patrick Nana-Sinkam
Dr. Nilsa C. Ramirez Milan
Dr. Erle S. Robertson
Dr. Linda F. van Dyk

NCI Senior Leadership
Dr. Stephen J. Chanock (absent)
Dr. James H. Doroshow
Dr. Paulette S. Gray
Dr. Anthony Kerlavage
Dr. Kristin L. Komschlies
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 12th 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 12 October 2022 FNLAC meeting was approved unanimously.

Dr. Johnson called the Committee members' attention to the confirmed future meeting dates listed on the agenda, noting that the next FNLAC meeting will be held on 10–11 July 2023 and is planned as an in-person meeting.

II. NCI DIRECTOR'S REPORT—DR. MONICA M. BERTAGNOLLI

Dr. Monica M. Bertagnolli, Director, NCI, also welcomed the FNLAC members and attendees to the meeting. Dr. Bertagnolli provided a budget update and reported on the National Cancer Plan, NCI news, and program updates from the Frederick National Laboratory for Cancer Research (FNLCR).

NCI Fiscal Year (FY) 2023 Budget. Dr. Bertagnolli highlighted President Joseph R. Biden's 2023 State of the Union Address, which called for reducing the cancer mortality rate by 50 percent during the next 25 years. In support of this goal, she stated that President Biden signed legislation on 29 December 2022 providing the NCI with a budget increase of $408 million (M) in FY 2023. The budget increase comprises a $386 M increase to the base budget and a $22 M increase for the final year of the first round of Cancer Moonshot℠ funding. Funding specific to Cancer Moonshot℠ programs will total $216 M in FY 2023. Dr. Bertagnolli noted that the base budget funding increase will enable support for the NCI's Research Project Grant (RPG) pool, the National Clinical Trials Network (NCTN), NCI-Designated Cancer Centers (Cancer Centers), workforce training, infrastructure updates, and more. Dr. Bertagnolli announced that NCI R01 grant paylines in FY 2023 have been increased to the 12th percentile (a 13-year high). The payline for early-stage investigator awards also has been raised to the 17th percentile, enabling the funding of more than 100 additional R01 and early-stage investigator awards compared to FY 2022. With these increases, the NCI reaffirms its commitment to supporting researchers whose work has established the foundation for progress in cancer prevention, treatment, and control.

Dr. Bertagnolli noted the challenges associated with the increasing costs of conducting biomedical research and, in particular, the decision to increase RPG paylines. This increase involves a funding commitment for several years after the initial FY 2023 awards to support out-year costs. To this end, even with the significant increases for the FY 2023 appropriations, the rising costs require funding of continuing noncompeting grants (years 2–5) at a level of 90 percent of their total cost, in addition to a 2 percent budget reduction that will be implemented across all NCI Divisions, Offices, and Centers.

National Cancer Plan. Dr. Bertagnolli has been working closely with biomedical leadership within and outside the NCI to answer the question: What must we accomplish to achieve the broad goal of helping people with cancer live full and active lives free from the harmful effects of cancer? Building on NCI's initial charge of leading the National Cancer Program as part of the National Cancer Act of 1971, a new National Cancer Plan is being assembled that outlines the goals that must be achieved to reduce cancer mortality and improve the lives of people affected by cancer. The Plan will incorporate a multifaceted approach that recognizes that the NCI alone cannot achieve the goal of reducing the cancer mortality rate by 50 percent during the next 25 years. The National Cancer Plan will include roles for the

NCI, as well as other federal agencies, private industry, academic institutions, nonprofit organizations, advocacy groups, and even patients and their caregivers. The Plan defines specific areas of focus that will engage both NCI's intramural and extramural research teams and expected contributions by the FNLCR to the National Cancer Plan, which will be discussed in future meetings. After review by the National Cancer Advisory Board (NCAB), the Plan will be communicated to the public through NCI's website and social media platforms, news outlets, and public events.

NCI News. Dr. Bertagnolli explained that she has been in regular contact with Dr. Renee Wegrzyn, Advanced Research Projects Agency for Health (ARPA-H) Director, to discuss partnering with ARPA-H on projects that address cancer research needs. The overarching goal of ARPA-H is to support high-risk, high-impact biomedical research and development that cannot readily be accomplished through traditional funding mechanisms. ARPA-H teams will be deployed at the NCI, NIH, and across multiple health care organizations to develop solutions to these challenges in parallel. Dr. Bertagnolli noted that the FNLCR likely will be utilized for cancer research in collaboration with ARPA-H. She added that more updates would be provided once the first ARPA-H projects have been announced.

Dr. Bertagnolli announced that the NCI—in partnership with the U.S. Food and Drug Administration (FDA) and the extramural clinical cancer research community, has established a Clinical Trials Innovation Unit (CTIU) to accelerate clinical cancer research. The CTIU, which became operational in February 2023, will select high-priority studies deemed amenable to radically new study designs and operational procedures (or that meet previously unattainable study goals) and engage the partners necessary to bring the new trials to fruition. Dr. Bertagnolli emphasized that all aspects of clinical trials are open to innovation and will be explored, including study eligibility, comparator arms, endpoints, diagnostics, study data collection procedures, and participant engagement strategies. She noted that although successful approaches piloted by the Unit can transition to become mainstream, the need for innovation always will be present.

FNLCR Updates. The NCI RAS Initiative is now a decade old and has become an outstanding example of how a Federally Funded Research and Development Center (FFRDC) can crystallize the collaborative efforts necessary to tackle a seemingly intractable problem. *RAS* genes are involved in cell growth, cell maturation, and cell death and are mutated in more than 30 percent of cancers. *KRAS* is one of three human *RAS* genes that previously were considered "undruggable" in their mutant, cancer-causing forms. In 2021, the FDA approved the first *KRAS* inhibitor for tumors with the G12C mutation, which is the most common mutation found in lung cancer. Dr. Bertagnolli outlined several RAS Initiative accomplishments, including using a hub-and-spoke partnership model to collaborate with more than 60 companies, universities, Cancer Centers, and federal agencies; sharing reagents with 623 university and nonprofit organizations in 43 U.S. states and 25 countries; and helping to develop more than 170 therapeutic agents, 150 genetically engineered cancer models, and 150 nanoparticles.

Dr. Bertagnolli reminded the FNLAC of the technical services available through the FNLCR. The FNLCR's Biopharmaceutical Development Program (BDP), which is funded and coordinated by the Biological Resources Branch of NCI's Division of Cancer Treatment and Diagnosis, is expanding its cell therapy manufacturing capabilities. In the coming months, the Program is projecting a sixfold increase in capacity to produce cell therapy products and double the capacity for producing viral vectors. Other technical services areas include HIV/AIDS and simian immunodeficiency virus (SIV) assays, genomics/gene expression, nanotechnology, and preclinical development. The National Cryo-Electron Microscopy Facility (NCEF) is available for protein-structure imaging. Dr. Bertagnolli added that a current goal of the NCI is to make the broader scientific community more aware of FNLCR's resources. She highlighted a short video produced by the NCI to boost the profile of the FNLCR and a *Cancer Currents* blog featuring the perspective of Dr. Douglas R. Lowy, Principal Deputy Director and former Acting Director, NCI, on the importance of the FNLCR. Dr. Bertagnolli noted that the FNLCR website is

being reorganized to be more accessible to extramural researchers and that the new home page will focus on opportunities for collaboration and showcase FNLCR research.

The NCI Serological Sciences Network for COVID-19 (SeroNet) and the FNLCR COVID-19 Serology Laboratory are part of a coordinated effort to expand the nation's capacity for SARS-CoV-2 serologic testing and advance research on the immune response to infection by SARS-CoV-2 or COVID-19 vaccination among diverse and vulnerable populations. The Human SARS-CoV-2 Serology Standard, a pool of plasma from four donors with antibodies to SARS-CoV-2, was developed by the Serology Lab and has enabled global SARS-CoV-2 assay standardization. The standard has been requested 176 times by domestic and international laboratories. The Serology Lab has collaborated with the FDA, Biomedical Advanced Research and Development Authority, Centers for Disease Control and Prevention, National Institute of Allergy and Infectious Diseases (NIAID), and several academic groups to evaluate lateral flow devices and other immunoassays. Of 120 assays and devices, 29 have received FDA Emergency Use Authorization. In total, SeroNet resources have supported the publication of 87 studies and 312 data files. Dr. Bertagnolli remarked that the ability to continue conducting such studies will remain important for the FNLCR as the SARS-CoV-2 virus continues to evolve.

The FNLCR is intended to function in support of the NCI mission by serving as a hub for technology development, sustaining extramural and intramural components of the NCI, and functioning as a nucleus for large-scale projects. Dr. Bertagnolli discussed current efforts to determine the next large-scale initiative to be undertaken by the FNLCR. The NCI held a series of workshops (8 general sessions and 4 focused sessions) attended by approximately 74 cancer researchers who generated more than 100 ideas for new FNLCR projects. Information from these workshops is being compiled with input from the NCI Division, Office, and Center leaders and will be presented to the NCI Scientific Program Leadership and Senior Executive Committee Leadership for consideration.

In the discussion, the following points were made:

- The NCI has several ideas for large programs that will aim to simulate the groundbreaking achievements of the RAS Initiative in a new, challenging field of study. The concepts currently are being evaluated and prioritized by NCI leadership.

- BDP's increased cell therapy manufacturing capacity is intended to serve extramural research organizations seeking access to such capabilities.

- The CTIU will engage and support clinical trials in both adult and pediatric oncology. The Unit will be led by Dr. Sheila A. Prindiville, Director, Coordinating Center for Clinical Trials, NCI, and Dr. Michael J. Morris, Medical Oncologist, Prostate Cancer Section Head, Division of Solid Tumor Oncology, Memorial Sloan Kettering Cancer Center. Unit membership will include Dr. Douglas S. Hawkins, Group Chair, Children's Oncology Group, Professor, Hematology–Oncology, Seattle Children's, in addition to NCTN Chairs and representatives from the FDA.

- To engage the broader scientific community in achieving the goal of getting new technologies to patients, the Clinical Trials Innovation Unit could consider future engagement of earlier (i.e., Phase I) clinical studies.

III. FREDERICK UPDATES—DR. KRISTIN L. KOMSCHLIES

Dr. Kristin L. Komschlies, NCI Acting Associate Director for Frederick, provided updates related to the FNLCR. She reminded the FNLAC that the purpose of NCI's FFRDC is to be at the forefront of developing new technologies and translating basic science discoveries into novel agents, approaches, and devices for the prevention, diagnosis, and treatment of cancer and such other diseases as HIV and SARS-

CoV-2. Dr. Komschlies shared a brief overview of the FNLCR, which comprises NCI facilities located within the Fort Detrick perimeter fence, the Advanced Technology and Research Facility in Frederick, Maryland, other leased facilities and locations, and encompasses a broad, multidisciplinary biomedical research program and state-of-the-art technologies.

FFRDC Recompetition Update. Dr. Komschlies shared updates on the recompetition of the FFRDC contract and NCI's efforts to engage as many interested vendors as possible. Sources Sought Notices were announced on 31 December 2020 and 28 January 2021 to request capability statements from potentially interested businesses. Industry input on potential requirements was solicited via several Requests for Information. In April 2021, an Industry Day was convened for NCI technical staff to explain government requirements for the contract. Draft Requests for Proposals were published in June 2021 and February 2022, and question-and-answer sessions were held for interested parties. In fall 2021, further one-on-one engagement activities were hosted to gain industry input and perspective regarding the solicitation. The Request for Proposal for full and open competition was released in June 2022. Additionally, a Pre-Proposal Conference was organized in November 2022 to review the solicitation terms and conditions and provide a detailed overview of the proposal instructions and review process. Final proposals were due in February 2023, and the solicitation is now closed.

FNLCR-Supported Research. Dr. Komschlies explained that the FNLCR currently performs work on behalf of many NCI Divisions, Offices, and Centers; 17 NIH Institutes and Centers (ICs); and 6 additional federal agencies. She emphasized that, since its inception, the FNLRC has supported every NIH IC. Typically, NCI/cancer research comprises 70 percent of FNLCR's efforts (with the remaining efforts dedicated to other biomedical research support); however, this percentage is subject to fluctuations over time as strategic needs and scientific demands evolve. A total of $920 M was obligated to the FFRDC contract between 1 October 2021 and 30 September 2022. This funding supported research by the NCI (63 percent), NIAID (30 percent), and several other ICs/agencies (7 percent). Dr. Komschlies pointed out that this amount does not align with the federal fiscal year because the contract is supported through multiple sources of funding.

Dr. Komschlies echoed Dr. Bertagnolli's call to promote increased awareness of FNLCR resources and shared detailed information about services that cannot be obtained outside the FNLCR. She presented information collected by the FNLCR Partnership Development Office on these unique technical service agreements. In FY 2022, unique technical service areas included genomics and gene expression (two services offered), nanotechnology (two services offered), HIV/AIDS and SIV (nine services offered), and preclinical development (six services offered). Ten service requests were completed in FY 2022—all within the HIV/AIDS and SIV service area. Dr. Komschlies added that the NCEF documents its engagement with extramural researchers, which comprised 200 data collection events for 54 unique principal investigators in FY 2022. In the same year, NCEF contributions were acknowledged in 28 publications.

In the discussion, the following points were made:

- FNLCR Leadership should explore the possibility of offering a tour of the FNLCR facilities—including the Patient-Derived Models Repository and the vector and cell therapy manufacturing suite—during the July 2023 FNLAC meeting.

IV. FNLAC *AD HOC* WORKING GROUP REPORT: NCI RAS INITIATIVE EVALUATION TEAM (RIET)—DRS. JOHN H. BUSHWELLER AND GIULIO F. DRAETTA

The Co-Chairs of the FNLAC NCI RAS Initiative Evaluation Team (RIET) *Ad Hoc* Working Group (Working Group), Dr. John H. Bushweller, Professor, Department of Molecular Physiology and Biological Physics, Department of Chemistry, School of Medicine, University of Virginia, and Dr. Giulio

F. Draetta, Chief Scientific Officer, Sewell Family Distinguished University Chair, The University of Texas MD Anderson Cancer Center, presented a summary of the Working Group's review of the RAS Initiative. Dr. Bushweller began by thanking the members of the Working Group. He provided an overview of the history of the RAS Initiative, which was launched in 2013 to explore the biology of oncogenic RAS and to discover therapeutic approaches for this previously undruggable target. Mutant *RAS* genes had been deemed undruggable because the small proteins that they encode lack binding pockets for drug interactions. The RAS Initiative began with significant investments in RAS structural biology, biochemistry, biophysics, and chemical screening to address critical knowledge gaps that previously had impeded the exploitation of RAS proteins as drug targets. A 5-year renewal for FY 2018–2022 built on this success with the pursuit of two broad scientific goals: (1) Develop small molecules that bind directly to KRAS and block its function and advance these molecules toward clinical evaluation, and (2) determine how KRAS proteins interact with plasma membranes and how they activate RAF kinases.

To judge the scientific merit, productivity, and innovation of the RAS Initiative before its FY 2023 renewal, the FNLAC convened the Working Group to conduct a review. The review was based on a written proposal and an in-person presentation of the proposal by the RAS Initiative team and focused on the scientific progress of the RAS Initiative during the previous 5-year renewal period. The Working Group's review also considered a recommendation report prepared by the FNLAC RAS *Ad Hoc* Working Group, which has provided the RAS Initiative with technical oversight and scientific guidance since its inception.

In the proposal, the RAS Initiative described progress on nine research projects during the course of the previous cycle. These projects comprised innovative RAS Initiative reagents and analytics; the use of molecular breakers to target the RAS–phosphatidylinositol 3-kinase alpha (PI3Ka) interaction; development of dual KRAS inhibitors that bind to both the GDP- and GTP-bound forms of the protein; construction and screening of a novel disulfide tethering library to explore and identify new chemical matter that can bind KRAS and other related targets; structural biology studies that focus on RAS activation of RAF kinase; RAS in membranes; the structure and function of the SHOC2-MRAS-PP1C (or SMP) protein complex; neurofibromin biochemistry and structural biology; and the study of new KRAS alleles. The RAS Initiative also highlighted interactions with the wider scientific community, including a significant number of collaborations; cooperative research and development agreements (CRADAs) that were developed with various biotechnology and pharmaceutical companies to facilitate the drug discovery efforts of the RAS Initiative; distribution of RAS reagents; development of the RAS interactome to increase interactions with the community; the RAS Synthetic Lethal Network; RAS Initiative symposia; and training efforts. The RAS Initiative identified six future plans: (1) the development of pan-KRAS inhibitors; (2) targeting other small GTPases (e.g., NRAS, RAC1); (3) the biochemistry and structural biology of various signaling complexes involving RAS; (4) RAS activation of RAF; (5) a second-generation disulfide tethering library; and (6) top-down proteomic analysis of RAS proteoforms (i.e., distinct molecular forms of a protein product arising from a single gene) from malignant cell lines.

Dr. Bushweller listed significant accomplishments of the RAS Initiative during the FY 2018–2022 renewal period:

- Development of a RAS G12C inhibitor that binds both the GTP- and the GDP-bound forms of RAS and is expected to enter clinical trials in the coming year. Such first-in-class inhibitors could have unique effects relative to agents currently being evaluated in clinical trials.

- Advancement of a PI3Ka protein–protein interaction inhibitor that is expected to enter clinical trials in the coming year. This novel therapeutic approach is predicted to overcome the hyperglycemia observed during treatment with current PI3K inhibitors.

- Development of outstanding capabilities in protein production, biochemical studies, and structural biology. This effort has resulted in critical structural insights into RAS function and the ability to develop assays for RAS inhibitor discovery and development.

Dr. Bushweller explained that the Working Group was extraordinarily impressed with the RAS Initiative personnel, who demonstrated technical excellence, commitment to the project, deep knowledge of the field, and the ability to successfully execute in a highly multidisciplinary effort. He emphasized that the members of the RAS Initiative are to be commended for their outstanding work. The Working Group offered the following points for consideration as the NCI plans the future of the RAS Initiative:

- The RAS Initiative should be viewed in the context of generous support by the NCI (i.e., direct costs of $10.5 M annually supporting 73 full-time employees); the length of the program (more than 10 years); the productivity of the group with regard to novel discoveries, papers, and clinical compounds; and the likelihood that this work could not be completed using traditional research mechanisms.

- The RAS Initiative has not led the field in developing RAS drugs, which so far have originated with seminal discoveries conducted by research groups in academia and industry.

- The RAS Initiative is not the only entity pursuing the development of additional KRAS inhibitors, several of which target more common KRAS mutants (e.g., G12V, G12D) and are being evaluated in preclinical development and clinical trials.

- RAS Initiative teams appear to have diffuse objectives, and a better delineation of critical goals would be needed for future success. RAS Initiative projects should emphasize the unique capabilities of the FNLCR and have well-defined decision points before being ushered into new phases.

- The RAS Initiative should improve transparency with the wider scientific community regarding how projects are transitioned to commercial entities.

- A process to ensure wider distribution of RAS Initiative compounds and knowledge (especially the recently developed cysteine tethering library) to the external community would be beneficial.

- The RAS Initiative's publication output has been moderate, with just four primary research papers in very high-impact journals (i.e., suggestive of discoveries of wide appeal) and a total of 75 papers attributed to the RAS Initiative since its establishment.

Based on the above points, Dr. Bushweller described two views of the future of the RAS Initiative held by the Working Group members. Some members hold the view that the RAS Initiative's goals largely have been met and that a phased sunsetting of the program will make the extraordinary capabilities of the team available for other efforts. Whereas, other members' position is that the program should remain because important contributions likely will continue being made. However, even the second group considers that the RAS Initiative should operate differently going forward, with the following recommendations being made:

- Focus on research that only the RAS Initiative can tackle effectively. Research projects should meet this uniqueness criterion, include clear decision points, and be guided by an advisory board that is constituted to make objective assessments.

- Make reagents developed by the RAS Initiative available to the research community.

- Provide the scientific community with greater transparency on the process whereby the RAS Initiative engages with pharmaceutical companies via the CRADA mechanism.

- Share the RAS Initiative's outstanding biochemistry and structural biology findings with the extramural community to help guide relevant functional studies of RAS.

In the discussion, the following points were made:

- The number and impact factor of publications associated with the RAS Initiative are only short-term measures of the program's success, which is better measured by how it has accelerated the development of cancer treatments.

- The distribution of RAS Initiative reagents should be accompanied by knowledge of how to use these resources most effectively.

- Although novel RAS therapeutics initially emerged from pharmaceutical development, these private efforts were directly and indirectly propelled by research performed by the RAS Initiative.

- Continued support of the RAS Initiative would not prevent the establishment of new major NCI programs but would divert funding from other opportunities.

- Recommendations related to the process of sunsetting the RAS Initiative or transitioning the team to a new objective were outside the scope of the Working Group's charge.

- The private sector has sufficient expertise and motivation to address next-generation RAS therapeutics and challenges associated with resistance to RAS-targeting drugs.

Motion: A motion to accept the report of the FNLAC RIET *Ad Hoc* Working Group was approved unanimously.

V. MOLECULAR CHARACTERIZATION LABORATORY (MOCHA)—DR. P. MICKEY WILLIAMS

Dr. P. Mickey Williams, Director, Molecular Characterization Laboratory (MoCha), FNLCR, provided an update on the MoChaat the FNLCR. The goal of the MoCha, which was established in April 2010, is to provide cutting-edge genomic technologies and assays that are well characterized, accurate, and reproducible in support of NCI preclinical and clinical research. The MoCha also works with the NCI and commercial partners in the form of CRADAs to gain access to novel technologies before they are commercially available. The MoCha provides technical expertise and functional oversight to laboratory activities subcontracted to Leidos Biomedical Research, Inc. Dr. Williams emphasized that all MoCha data are made publicly available via NCI-approved databases. He provided updates on several groups and initiatives supported by the MoCha.

Cancer Moonshot℠ Biobank. The primary objective of the Cancer Moonshot℠ Biobank is to support current and future investigations into drug resistance and sensitivity and other NCI-sponsored cancer research through the procurement and distribution of multiple longitudinal biospecimens and associated data from a diverse group of cancer patients undergoing standard-of-care treatment at NCI Community Oncology Research Program (NCORP) sites and other NCTNs. The Biobank also develops patient-derived xenografts (PDXs) and cell lines and performs molecular profiling assays on tumor samples in a Clinical Laboratory Improvement Amendments (CLIA), certified laboratory and reports these results for optional use in clinical management. This project has developed a supporting website that supports educational information and provides a secure means of access to patient test results. The

Biobank is coordinated by a central group comprising several NCI personnel and five MoCha staff members. The MoCha runs two clinical assays, an Oncomine cancer panel and a myeloid assay, for the Biobank through its CLIA Genomics groups. The Biobank was launched on 16 September 2020 and, as of 20 February 2023, has enrolled 188 patients. In 2022, a data set comprising clinical information on specimens and associated histological and radiological images was released, and 60 clinical reports have been returned to patients and treating physicians. Future efforts will include expanding the number of study sites, increasing enrollment, continuing to assess specimen and data quality, and preparing for the release of additional data.

Patient-Derived Models Repository (PDMR). NCI's Division of Cancer Treatment and Diagnosis (DCTD) has developed a national repository of PDXs that are available to the extramural research community. PMDR models include PDXs and patient-derived cancer cell lines and organoid models, as well as cancer fibroblasts associated with donated tumors. The MoCha performs molecular analysis of PDMR specimens, and Dr. Williams described the genomic landscape of these specimens. Mutational burden as revealed by whole-exome sequencing (WES), including information on mutational signatures, microsatellite instability (MSI), percent loss of heterozygosity, driver oncogene, single-nucleotide variants (SNVs), insertions/deletions (or indels), copy number variations, and structural changes, is reported for each tumor. Quality control analysis using RNA-sequencing (RNA-seq) data is used to confirm that sample transcriptome profiles are related by histology and PDX model origin and genetic fingerprints are used to confirm identity. To date, WES and RNA-seq have been performed on 822 different models derived from 775 patients. MoCha analysis has confirmed that the models are genetically stable throughout early passages (i.e., the point at which they are provided to researchers).

Blood-Based Comprehensive Genomic Profiling. Dr. Williams described the challenges associated with the genomic profiling of blood samples. A 10-milliliter (mL) blood collection sample contains approximately 5 mL of plasma where circulating tumor DNA (ctDNA) is found. That plasma contains approximately 12,000 haploid genomes, most of which are wild type. In a late-stage cancer patient, cancer genomes often comprise between 0.05 and 1 percent of the total genetic material (or 6 to 120 total molecules), challenging the detection limits of most assays. After assessing several technologies, the MoCha selected the TSO500 ctDNA assay, a precommercial Illumina assay, to develop a liquid biopsy assay. This assay provides the full coding sequence of 523 cancer-relevant genes and information related to such immunooncology biomarkers as tumor mutational burden and MSI. The assay was developed in collaboration with Illumna's assay development and bioinformatics teams under CRADAs with the NCI and Leidos Biomedical Research, Inc. Feasibility testing of the ctDNA assay determined that, when present in 0.25 percent of the assayed genetic material, indels could be detected at a rate of 84 percent, and SNVs could be detected at a rate of 92 percent. In matched tissue and blood samples from late-stage, non–small cell lung cancer patients, the ctDNA assay provided highly concordant results between the two sample types, especially in driver genes. Initially intended as an integrated clinical research assay (i.e., specimens collected during a clinical trial for use in research without returning results to physicians or patients), the MoCha ctDNA assay could serve as a reliable alternative approach to tissue biopsy and could be incorporated as an integral assay (i.e., predictive or prognostic assay biomarker assay to enroll, stratify, or manage patients) for clinical trial support.

Clinical Trial Updates. Dr. Williams provided updates on several clinical trials that were supported by the MoCha. The NCI Molecular Analysis for Therapy Choice (NCI-MATCH) Trial emerged from the NCI Molecular Profiling-Based Assignment of Cancer Therapy (NCI-MPACT), a pilot precision medicine study that assessed the utility of applying tumor DNA sequencing to treatment selection for patients with advanced refractory cancer. NCI-MATCH began with the establishment of a network of four clinical laboratories. Under guidance from the MoCha, each laboratory implemented standard operating procedures for specimen collection and performed a harmonized and validated next-generation sequencing assay. The MATCH laboratory network supported the screening of the first 6,000

NCI-MATCH patients, after which a network of 29 designated NCI-MATCH laboratories was established. A pediatric arm of the study, Pediatric MATCH, utilized the existing laboratory network and the NCI-MATCH clinical assay. The NCI-MATCH and Pediatric MATCH trials officially closed at the end of 2022, and the MoCha will be supporting three new precision medicine trials: (1) ImmunoMATCH (iMATCH), in which patients will be stratified and treated based on the tumor mutational burden and tumor inflammation score status of their tumors; (2) MyeloMATCH, an umbrella trial that will test treatments for acute myeloid leukemia (AML) and myelodysplastic syndromes; and (3) ComboMATCH, which will test combinations of drugs.

The MoCha has developed and validated several assays for these clinical trials. A clinical WES assay was developed for iMATCH and subsequently incorporated as an integrated assay by ComboMATCH and several other clinical trials. The assay covers a target region of approximately 44 megabases and provides high coverage of 671 oncogenic or likely oncogenic genes for increased sensitivity to mutations. The WES assay also reports on MSI, Human Leukocyte Antigen Class 1 typing, and the detection of seven oncogenic viruses, with a turnaround time of less than 2 weeks. The NCI-Myeloid Assay (NMA), which was developed under a CRADA with Thermo Fisher Scientific Inc., requires minimal DNA/RNA sequencing sample input, and the fully automated workflow delivers a clinical report within 72 hours. The second version of this assay (NMAv2) covers all genetic information required for the clinical management of AML and risk stratification according to guidelines established by the National Comprehensive Cancer Network and the European LeukemiaNet.

Other Efforts. The MoCha has collaborated with public and private organizations (e.g., Cancer Immune Monitoring and Analysis Centers, Friends of Cancer Research, Foundation for the NIH, National Institute of Standards and Technology, SeraCare® Life Sciences) to develop reference and quality-control materials. The MoCha also has engaged with the National Clinical Laboratory Network (NCLN) to provide expert evaluation of study proposals and genome assay support. As of January 2023, 70 NCLN studies using MoCha WES assays, 62 NCLN studies using MoCha RNA-seq assays, and 35 NCLN studies using MoCha ctDNA assays have been approved. Dr. Williams expressed appreciation for the NCI and MoCha subcontractors, collaborators, and staff for their continued support.

In the discussion, the following points were made:

- Clinical laboratories were recruited to the designated network through announcements in the Federal Register and word of mouth. Each laboratory performed analytical validation and benchmarking on concordant samples provided by the MoCha. Variations in copy number data were observed, and the MoCha worked with different laboratories to harmonize their analysis methods for the intended trials.

- MoCha data, although publicly available, will require request and approval before being shared.

- Mechanisms are in place whereby external laboratories can be subcontracted as needed to provide expertise and technology not available within the existing infrastructure.

VI. CLOSING REMARKS—DR. CANDACE S. JOHNSON

Dr. Johnson expressed appreciation to the Committee members and other participants for attending. Members were reminded to send potential agenda topics for future FNLAC meetings to Dr. Lopaczynski.

VII. ADJOURNMENT—DR. CANDACE S. JOHNSON

There being no further business, the 12th Virtual Meeting of the FNLAC was adjourned at 3:05 p.m. EDT on Monday, 27 February 2023.

July 11, 2023 /s/

Date Candace S. Johnson, Ph.D., Chair

July 12, 2023 /s/

Date Wlodek Lopaczynski, M.D., Ph.D., Executive Secretary