BIOMARKERS CONSORTIUM

IMPROVING HEALTH THROUGH MEANINGFUL MEASUREMENTS

FNIH Foundation for the National Institutes of Health

CANCER STEERING COMMITTEE (CSC) ANNUAL SCIENTIFIC SYMPOSIUM
VIRTUAL MEETING

Thursday, October 28, 2021, 1:00 PM–4:00 PM
Friday, October 29, 2021, 1:00 PM–4:00 PM
Monday, November 8, 2021, 1:00 PM–4:00 PM
Tuesday, November 9, 2021, 1:00 PM–4:00 PM

EXECUTIVE SUMMARY

Day 1, October 28, 2021

FNIH Welcome
Stacey Adam, Foundation for the NIH (FNIH)

Dr. Adam welcomed the speakers and participants and described FNIH's role in supporting NIH research goals by creating and managing alliances and public-private partnerships. She noted that the FNIH Biomarkers Consortium is charged with forming public-private partnerships (PPPs) to accelerate the development of biomarker-based technologies for drug development and patient care across a broad range of diseases. This annual scientific symposium is sponsored by the Cancer Steering Committee (CSC), one of 4 disease-oriented steering committees working within the Biomarkers Consortium.

Meeting Introduction and Overview
Gary Kelloff, NCI, CSC Co-chair

Dr. Kelloff described the meeting agenda and provided an overview of the first session, covering challenges and opportunities for liquid biopsy-based biomarkers in oncology. He noted liquid biopsy in oncological drug development and patient care includes predictive, response monitoring, and detection of resistance biomarkers including minimal residual disease (MRD), as well as prognostic and early detection biomarkers. Liquid biopsies may be an alternative to tissue pathology for cancer diagnosis and may complement or have advantages over imaging as biomarkers for serial monitoring of patient treatment. CSC projects using liquid biopsies include the completed High-Definition Single Cell Analysis of Circulating Tumor Cells (CTCs) in Metastatic Colorectal Cancer, the circulating tumor DNA (ctDNA) Quality Control Materials (QCM) project now in progress, the International Liquid Biopsy Standardization Alliance, and studies of MRD in acute lymphoblastic leukemia, multiple myeloma, and acute myeloid leukemia (AML).

Keynote: ***Cancer In Vitro Diagnostic Tests Overview: Regulatory Perspective***
Reena Philip, Director, Division of Molecular Genetics and Pathology, Office of In Vitro Diagnostics and Radiological Health, Center for Devices and Radiologic Health, FDA

Dr. Philip described FDA review of in vitro diagnostic (IVD) devices, including FDA-approved cancer diagnostic tests, and commented on the future of liquid biopsy-based assays as IVDs. She emphasized the importance of the device's intended use in determining the type of submission required. She listed the elements of an IVD submission, the components of the intended use, analytical validation studies including contrived sample functional characterization studies, clinical validation study designs to match the intended use, and challenges with tests for early detection.

She discussed companion diagnostics (CDx) and complementary biomarker assays (tests that are not a prerequisite for receiving a drug but that identify a subset of patients that respond well to the assay and aid risk/benefit assessments), providing examples of approved polymerase chain reaction (PCR) and next-generation sequencing (NGS) tests, as well as oncopanel definitions and validation support for claims.

She noted the shifting regulatory paradigm for CDx tests, due partly to emerging complex biomarkers (i.e., covering multiple genes, tests, and drugs), including tumor-agnostic biomarkers, such as tumor mutational burden (TMB), and the questions raised in considering these new tests. She concluded by discussing the use of liquid biopsies in identifying MRD, emerging multiplexed biomarkers, elements involved in cancer screening for early detection, a list of useful links to relevant draft guidances and FDA information websites, and example decision summaries.

Session 1: Liquid Biopsy
Chairs: Mickey Williams, Frederick National Laboratory for Cancer Research, and Robert McCormack, independent

Dr. Williams introduced himself and Dr. McCormack, noting they co-lead the CSC QCM project, and gave a brief overview of the project before introducing the session speakers and discussion panel.
Dr. McCormack added his welcome, noting the talks cover liquid biopsies from bench to bedside.

Clinical Benefit of Comprehensive Genomic Profiling of Cancer Patients as Standard of Care
Erin Cobain, University of Michigan

Dr. Cobain introduced her talk with the rationale for using precision medicine strategies in oncology, i.e., that tools such as NGS are widely available to identify actionable mutations and deliver targeted therapies based on these mutations. She noted that along with DNA sequencing, tumor RNA profiling enhances the detection of oncogenic gene fusions and mutational signatures and helps identify the tissue of origin. She said that it could be worthwhile for all patients with advanced cancer to undergo comprehensive tumor NGS, given that positive results could match to a treatment, and the relatively low cost of testing. Dr. Cobain closed by describing the complementarity of tissue and liquid (ctDNA and CTCs) biopsies for NGS testing.

Technological Challenges for Efficient and Sensitive Detection of Cancer Biomarkers in Liquid Biopsies
Mike Makrigiorgos, Dana-Farber Cancer Institute, Harvard Medical School

Dr. Makrigiorgos described a novel approach for detecting cancer-relevant alterations in liquid biopsy – the Alu-PCR-microsatellite instability (MSI) tracer. The approach is based on the multitude of repeat elements per genome (e.g., the millions of Alu elements), which increase targets by orders of magnitude, and are PCR-accessible with a single reaction. Inter-Alu PCR captures poly-A sites that are susceptible to MSI changes and can be used to assess MSI status, an FDA-approved biomarker for predicting positive response to immunotherapy. The Alu-PCR-MSI tracer is a sensitive, rapid, and inexpensive technique for detecting MSI+ tumors in the plasma for several cancers. Applications include MRD tracking for MSI+ cancer patients, MSI status assessment for immunotherapy, and early cancer detection in high-risk groups.

Precision Cancer and Immuno-Oncology Strategy Using Liquid Biopsy in Clinical Studies
Lillian Siu, Princess Margaret Cancer Centre

Dr. Siu discussed the potential role of ctDNA in precision medicine and immunotherapy clinical trials in advanced disease settings. She illustrated the clinical applications of ctDNA to TMB. She noted that ctDNA could differentiate pseudo vs. actual progression in patients on immunotherapy. Response can be described by integrating changes in ctDNA and radiologic imaging of target lesions to define 4 "sensitivity groups," including patients with emerging resistance and potential pseudoprogression. She concluded that as ctDNA applications are developed, it is important to collect data on these applications in clinical settings for correlation with long-term clinical outcomes; consensus and standardization are also critical.

Measurable Residual Disease in Acute Myeloid Leukemia – in 10 Minutes!
Jerry Radich, Fred Hutchinson Cancer Research Center

Dr. Radich noted that most AML patients respond to therapy and then relapse; 75% of patients go into relapse with MRD as a measure of disease burden. He indicated that accurate assessment of MRD will improve patient outcomes, influence clinical study design, and allow for rapid measurement of drug response.

Duplex sequencing is a new and better method for measuring MRD. Duplex sequencing libraries are made from both DNA strands, and mutations are called only if complementary base pairs are detected. This results in lower noise and better sensitivity than other NGS techniques, increasing single-base resolution to find rare mutations. Dr. Radich noted digital droplet PCR with higher sensitivity than analog PCR could also be used with NGS to identify mutations at diagnosis and for MRD. He ended by noting the clinical, technical, and biological questions around MRD measurements that remain to be answered.

Minimal Residual Disease (MRD) Assessment by Circulating Tumor DNA (ctDNA) in Colon Cancer
Sakti Chakrabarti, Medical College of Wisconsin

Dr. Chakrabarti discussed work showing that ctDNA-guided adjuvant therapy in colon cancer is an exciting novel paradigm. Studies have led to the conclusion that ctDNA has high specificity and positive predictive value; one study found that all patients with ctDNA detected postoperatively had recurrence. However, a single postoperative negative ctDNA result will miss some patients with MRD, thus serial

testing is necessary. ctDNA-guided MRD assessment in colon cancer has high specificity and positive predictive value, and ctDNA is a promising novel risk stratification tool.

Liquid Biopsy for Early Cancer Detection
Minetta Liu, Mayo Clinic

Dr. Liu reviewed blood-based assays for possible use as multi-cancer early detection (MCED) screening tests. Some of the assays discussed are still in development, including CancerSEEK, PanSeer, and cfMeDIP-seq, with Galleri commercially launched. All but the CancerSEEK assay measure methylated ctDNA, and CancerSEEK assays 16 mutated genes and 8 protein biomarkers.

Dr. Liu concluded that blood-based cancer detection at clinical diagnosis is technically feasible with high specificity for cancer signal and tissue localization. The sensitivity of current DNA-based assays may be improved by assessing multiple alterations or circulating proteins from the same sample. Clinical considerations include what population to target, the role of the oncologist and primary care provider, and a need for a molecular tumor board or multidisciplinary triage.

Discussion

Discussion on the talks in Session 1 started with Dr. Radich, who stated that one of the first goals of the new FNIH MRD in AML project is addressing the use of reference materials to determine if different assays are detecting the same amounts of material. The significance of mutations in "normal" people as they age without cancer was raised (e.g., clonal hematopoiesis). Dr. Radich noted that healthy people could tolerate these mutations, but these mutations are higher risk in leukemia patients. Dr. Liu commented on the unique organ-specific methylation patterns in cells and the expectation that hematopoietic cells will not be different. She noted that many detection strategies look at factors other than mutations, e.g., whole genome bi-sulfate sequence methylation, providing tissue-of-origin signals. Commenting on the use of ctDNA in clinical practice, Dr. Chakbarti gave examples of ctDNA in assessment of MRD outside of clinical trials, noting that low-risk stage 3 patients benefit more from monitoring than from up-front adjuvant chemotherapy.

Roundtable Discussion
J. Carl Barrett, AstraZeneca (Moderator); Sakti Chakrabarti, Medical College of Wisconsin; Daniel Enderle, Exosome Diagnostics; Soma Ghosh, FDA; Dan Hayes, University of Michigan; Lanny Kirsch, Adaptive Biotechnologies; Lillian Siu, Princess Margaret Cancer Centre

Dr. Barrett commented that it is challenging to use reference materials when methylation patterns vs. mutations are measured, so any work addressing that problem would be helpful. Regarding ctDNA in clinical practice, Dr. Barrett asked what level of evidence would be needed to decide a threshold for using rising ctDNA to warrant changing a therapy? The panelists responded that the biggest pushback is that clinical trials have not yet shown that acting on a blood-based factor will affect survival. Lacking this information would result in cycling through therapies without knowing if changes would impact survival.

Dr. Kirsch cited studies in hematopoietic malignances demonstrating that serial measurements with highly validated cellular assays can be used to assess not just tumor burden but tumor biology and doubling time. The length of progression-free survival correlates with doubling time, and whether that can be extrapolated to or verified using cfDNA is still a question.

Dr. Enderle noted that any detectable RNA is in exosomes and can be extracted with the DNA and proteins for assay. Dr. Chakrabarti noted that in his studies baseline samples are taken to determine ctDNA; if ctDNA is not detected pre-surgery, it will not be valuable for post-surgery monitoring.

Day 2, October 29, 2021

Welcoming Remarks
Eric Rubin, Merck, CSC Co-chair

Keynote: Caring for Every Patient, Learning from Every Patient: Empowering Clinicians and Engaging Patients
Monica Bertagnolli, Dana-Farber Cancer Institute

Dr. Bertagnolli addressed the data patients and clinicians need to make life-altering decisions and focused on strategies for acquiring it through clinical trials. Questions that need to be addressed include: How can we bring clinical trials to more patients who need them? Why focus on clinical trials? What data are missing?

A "learning environment" such as the Moonshot Learning Health program ensures that the latest discoveries can be applied to patient care models to reach individual patient treatment goals. Randomized clinical trials (RCT) provide the highest level of evidence needed for this effort; however, there are not enough people in clinical trials to represent the broad cohorts that are seen in clinic, and there aren't enough trials to provide adequate data sets for those in marginalized groups, in rural areas, with comorbidities, and in nonstandard treatment groups. Some treatments, such as chemotherapy for lung cancer, are studied more than others (i.e., surgery and radiation therapy). More trials are needed that reflect real-world use, the populations seen in the clinic, and the different modalities used to treat them. The American Society of Clinical Oncology (ASCO) Targeted Agent and Profiling Utilization Registry (TAPUR) Study is an example.

Data are being pulled from electronic health records (EHRs) into the clinical database to address the need for more clinical information. However, there are problems with this approach. Data interoperability is one issue, as research requires the standardized format of case report forms (CRFs). CancerLinQ, ASCO's real-world data (RWD) initiative, has data from multiple EHRs and brings together multiple representations of the same data point. Data "missingness" is also an issue since not all clinical data are collected in the EHR. Data essential to understanding outcomes such as pathology, imaging results, treatment intent, surgery, and radiation therapy may be missing. There is also significant resistance to sharing EHR data related to implementation of the Health Insurance Portability and Accountability Act, data security, patient consent, researcher as "owner," and commodification of data. Dr. Bertagnolli introduced the NIH All of Us Research Program as a large-scale research project that requires sharing data across multiple systems (especially the EHR). All of Us is collecting information from a wide variety of sources on 1 million Americans.

The Minimal Common Oncology Data Elements (mCODE) is one solution to the interoperability issue. mCODE is a core set of data to be collected on every cancer patient to allow valid comparisons across study groups, across the entire healthcare system, and to enable comparisons between RWE/observational studies and clinical trials. Several other initiatives support the collection and dissemination of standardized clinical data, such as the Integrating Clinical Trials and Real-World Endpoints (ICAREdata) initiative; MITRE's GLYPH to communicate with and consent patients and collect

patient-reported outcomes (PROs); and the Patient Engagement Portal (PEP), another communication tool.

As final thoughts, Dr. Bertagnolli stated that reaching the goals of precision medicine requires merging clinical and research data to create a new way of classifying and reporting on disease. FDA is moving towards integrating RWE into regulatory decision-making. Data sharing is becoming commoner with interoperable EHR data being more widely available in programs such as PCORnet, ICAREdata, CancerLinQ, Flatiron, Syapse, and COTA, and shareable using Health Level 7 (HL7), Fast Healthcare Interoperability Resources (FHIR), and mCODE standards. Advances in technology have enabled new ways to mine data through natural language processing, ML, and wearables.

In response to a question about ensuring acceptance of mCODE, Dr. Bertagnolli stated that it is integrated into the HL7 standard and is on course to be widely accepted and implemented. Common Oncology Data Elements eXtensions (CodeX) is the FHIR development community for mCODE. Anyone who wants to use mCODE can join CodeX and develop and use it.

Session 2 – Data Sharing: Perspectives, Requirements, Resources, Progress
Chairs: Bill Louv, Project Data Sphere, and Hisham Hamadeh, Genmab

Dr. Hamadeh noted in his introduction that we are producing unprecedented amounts of data, especially in cancer. To maximize the value of this data, we need to recycle it by raising awareness about it and making it accessible to other investigators and analysis systems. Through this discussion and the examples presented in this session, the hope is to make responsible data sharing the default for clinical studies.

APOLLO Use Case
Craig D. Shriver, Walter Reed National Military Medical Center, Uniformed Services University

Colonel Shriver discussed how the Applied Proteogenomics Organizational Learning and Outcomes Consortium (APOLLO) program integrates secondary use opportunities for the collected data with the goal of data aggregation, analysis, and sharing with the NCI Genomic Data Commons, Proteomic Data Commons, and the Cancer Imaging Archive. Data are collected in a closed system of Department of Defense (DoD) sites, data standards are in place system-wide, and the system is oriented towards cancer as a readiness issue for the military. The data for all APOLLO projects is processed through APOLLO's Data Tumor Sharing system for upload to the cloud for partner analysis. The protocol work and data flows are shared with the Institutional Review Board (IRB) so that every piece of data can be tracked, and essential data sharing agreements are in place to ensure the data flow to NCI's archives. To be successful, it is important that all processes and data elements are standardized across all DoD networks and laboratories, leveraging existing electronic infrastructure. Genomes of active-duty service members cannot be shared, so they are secured at a higher level.

ctMoniTR Use Case
Nevine Zariffa, NMD Group, Consultant to Friends of Cancer Research

Ms. Zariffa opened her discussion of the Circulating Tumor DNA for Monitoring Treatment Response (ctMoniTR) Project by noting that the impetus for this effort was to define the relationship between ctDNA levels and what happens to patients after the start of their cancer therapies. This could only be done through aggregating data. To begin the effort, the research questions were identified, "data

sharing" was defined, and the work was designed around the data sharing definition. The approach was to start small (step 1) with the data in front of them and then tweak the processes regarding working with the data, other institutions, and other colleagues when broadening the target data sets (step 2).

Ms. Zariffa identified challenges for enabling sharing. The first issue was data harmonization. This effort required resources from all disciplines where data were to be pulled and analyzed. This collaboration and harmonization of data allowed for discovering the relationship between decreased ctDNA and increased OS. First, statisticians who understand the data were brought together to identify and begin addressing the challenges. Then, all the other experts on the team came together to finalize the data analysis plan, data dictionary, etc. The team met with each sponsor so they could approve their data and the mapping dictionary to ensure that the data comparison was "apples to apples."

For data sharing, it was determined that the best approach was to centralize all patient-level data, harmonization, and analysis. Sharing only summary data or allowing each sponsor to conduct its own analysis (federated) and then contribute the data, raised too many issues around standardization, quality, and completeness. Once the data-sharing approach was drafted in accordance with the statistical analysis plan, then the sponsors weighed in, and the data-sharing approach was altered as necessary. The project is strictly supervised and organized, with several independent assessments along the way and a learning mindset so that all voices can be heard and all ideas considered.

Data Sharing from SEER Perspective: Challenges and Lessons Learned
Lynne Penberthy, NCI

Dr. Penberthy, of NCI's Surveillance, Epidemiology, and End Results (SEER) Program, described surveillance (cancer registry) data and how it differs from other research and clinical data. The goal is to monitor cancer trends and support research in the diagnosis, treatment, and outcomes of cancer. SEER data are shared extensively; however, there have been some challenges recently. One is the re-identifiability of the data because of rare tumors and increased amounts of data on each patient. The increase in computational power further enables re-identification. Re-identification can cause issues with SEER reaching its goal of representing, in near real-time, patient disease trajectory from diagnosis to death. The solution to re-identifiability is to implement a tiered system of access with potential for IRB oversight and a centralized authentication and authorization process (the NIH eRA Commons system). SEER also wants to prevent inappropriate use of the data. The tiered approach defines data available at each tier and the authentication and authorization steps required to access the data at each level. The lessons learned from these efforts are that evolving data ecosystems require flexible processes for controlling data release. The key is to understand the researchers' needs and provide data to meet those needs through authentication/authorization schemes, data product schemes, and data use agreements.

NCI Human Tumor Atlas Network Data Sharing
Bruce Johnson, Dana-Farber Cancer Institute

The Human Tumor Atlas Network (HTAN) is an NCI Cancer Moonshot initiative to construct 3-D atlases of human cancers' dynamic cellular, morphological, and molecular features as they evolve from precancerous lesions to advanced disease. Dr. Johnson introduced the HTAN Data Sharing Policy as being consistent with and building upon NCI Cancer Moonshot's policies. It includes mandating an open and collaborative environment with opportunities for the scientific community to use the data while maintaining each subject's privacy and confidentiality, as well as protecting the researcher's intellectual

property and allowing for appropriate recognition of contributors and users of the data. Released data are broken into 4 levels, with levels 1 and 2 representing raw or minimally processed data, while levels 3 and 4 represent fully processed data. All levels have publication limitations.

Dr. Johnson spoke about HTAN's metadata standards that enable data-sharing, a process to update the standards, and a data release process to ensure quality data are uploaded and described properly in the HTAN system. The data are made available/accessible via the HTAN Data Portal, as are the tools with which users can view the data. The first set of HTAN atlases is available on bioRxiv. Current HTAN efforts focus on providing data sets and understanding which data the community wants and discovering how they want to use them.

Digital Pathology Use Case
Stan Hamilton, City of Hope

Dr. Hamilton defined digital pathology as incorporating the acquisition, management, sharing, and interpretation of pathology information, including slides and data, in a digital environment. There are clinical, training, and research uses for digital pathology that leverage the ability for the physical specimen to be in one place and the data about that specimen sent anywhere for review, analysis, and research. The barriers to acceptance of digital pathology include cost of conversion (hardware, software, training), interoperability of software, workflow integration, reluctance by pathologists, and the situation that technology still needs enhancement. Even with these issues, digital pathology analysis is moving forward with the application of machine learning, deep learning, augmented intelligence, and algorithms for digitized pathology specimens to identify new ways to determine a patient's prognosis more accurately.

Roundtable Discussion
Monica Bertagnolli, Dana-Farber Cancer Institute; Robert Grossman, University of Chicago; Sean Hanlon, NCI; Jerry Lee, University of Southern California; Tracy Lively, NCI; Wendy Rubinstein, FDA; Kate Sasser, Genmab

The roundtable focused on the primary challenges of data sharing. First is the large amount of work required to make data sharable. Interoperability requires a considerable effort to make systems that were originally proprietary capable of sharing readable data . This could be addressed by adopting a solid set of interoperability and semantic standards across the board. Digital Imaging and Communications in Medicine (DICOM) for imaging is one such standard. Digital pathology needs this type of effort to share its data universally; however, it must first become the standard for pathology labs. If standardization approaches can be repeated, they can be developed into best practices for designing multisource studies. Understanding the data is also key to leveraging data sharing, as you cannot write machine-learning algorithms or AI without understanding data against which you are writing

A second challenge is providing incentives for sharing, for example by recognizing those who make meaningful inferences from shared data or rewarding those whose data are referenced more frequently. Cancer Moonshot incentivizes sharing data early and often, which makes the provider more likely to receive new funding opportunities. It was suggested that researchers should add a line item in their NIH proposals to cover the costs of sharing. All NIH-funded projects will be subject to a new data sharing policy in 2023. One way to incentivize data sharing in the private sector is for regulatory agencies to define types of data sets (e.g., RWE) that are needed for approvals, which will help move

discoveries through approvals faster. Additionally, if regulatory agencies recognized the value of some curated databases (e.g., ClinGen and OncoKB), then data shared from them might be used for faster approvals.

A third challenge is data reuse which is a key goal of interoperability; however, questions were raised about procedure and research standards reuse across different signals to minimize efforts. Given that statistical plans and research may differ for different signals, it may only be possible to standardize the planning approach. Reuse was also stressed in the FAIR data standard where data satisfy the requirements for findability, accessibility, interoperability, and reusability. Curated databases may be used to share data, but publications are still the primary way that knowledge is shared.

Patient data belongs to the patient; however, involving patients means empowering them to ask questions, understand the research, know their future opportunities, and keep them updated on research progress as long as their data are being used.

Day 3, November 8, 2021

FNIH Welcome
Dana Connors, FNIH

Mr. Connors welcomed the meeting participants and described the structure and membership of the Biomarkers Consortium. He then outlined the Biomarkers Consortium project development process, noting requirements for the projects—for example, they must address scientific and medical needs, lead to significant improvements in the drug development process or patient care, and have goals that are achievable within a few years' timeframe.

Meeting Introduction and Overview
Gary Kelloff, NCI, CSC Co-chair

To introduce the remaining sessions of the Symposium, Dr. Kelloff recapped the uses of biomarkers in clinical cancer research and patient treatment. Particularly, he noted the possibilities and benefits of using biomarkers as surrogate endpoints for clinical trials and obtaining FDA approvals. In preparation for Session 4 on imaging biomarkers, he commented on the advantages of imaging biomarkers in that they can sample the entire tumor burden, be measured noninvasively, and be used for serial monitoring. He also noted their utility for screening drug interactions with molecular targets and measurements of drug biodistribution.

Keynote—Breaking Down Silos: Strategic Partnerships & Initiatives to Advance Cancer Research
Tony Dickherber, Center for Strategic Scientific Initiatives, NCI

Dr. Dickherber discussed partnerships for the nascent Cancer Grand Challenges (CGC), provided an update on NCI programs generated from the Cancer Moonshot, and commented on NCI interest in liquid biopsy platforms for early cancer detection.

The CGC award framework is a new collaboration with Cancer Research UK (CRUK) to co-fund approximately 4 awards every 2 years starting in fiscal year 2022. A CGC Scientific Committee solicits recommendations on challenge setting and funding, and a Joint Steering Committee of CRUK and NCI leadership makes final decisions. Dr. Dickherber described the 9 current CGCs in detail, including

background history for context and what the funding committee is looking for in the applications (https://cancergrandchallenges.org/). They have received 169 expressions of interest from 31 countries.

He described progress toward implementing the goals of the Cancer Moonshot. For example, for goal 1, to accelerate progress in our understanding of cancer, NCI has established the Immuno-Oncology Translational Network (IOTN), HTAN, and initiatives to address health disparities, the Participant Engagement and Cancer Genome Sequencing Network (PE-CGS), Accelerating Colorectal Cancer Screening and Follow-Up Through Implementation Science (ACCSIS) to address colon cancer disparities in incidence and mortality, an AI colorectal cancer screening implementation project, and the Patient-Derived Xenografts Development and Trial Centers Research Network (PDXNet). NCI has addressed Goal 2, to enhance data sharing by requiring all Cancer Moonshot publications to be freely and publicly available, and primary data to be broadly and immediately shared through the Cancer Research Data Commons.

Lastly, Dr. Dickherber addressed a recent focus on liquid biopsies for MCED. He noted that detecting low-abundance markers is challenging and setting up clinical trials for detection is very difficult and expensive. NCI initiated a working group in summer 2021 to better understand the role NCI can play in ensuring rigorous scientific methods are employed in the development of MCED tests, and to understand the challenges and opportunities regarding the potential of these approaches. Current knowledge of MCED assays focuses on diagnostic and analytical performance; the clinical utility of widespread implementation of MCED is unknown and presents novel implementation challenges.

Dr. Dickherber was asked how much coordination is occurring between the NCI Early Detection Research Network and CRUK. Dr. Lynn Sorbara, NCI, Division of Cancer Prevention (DCP), noted DCP is actively engaged in the initiatives, and there is a long history of collaboration with CRUK. Questions around data sharing included one that asked for any insights about how industry can support compliance and quality of shared data and what the Moonshot expiration in 2023 means for these initiatives, especially data sharing. Dr. Dickherber was not aware of any plans to issue follow-up funding. Industry might provide support to organizations such as the Biomarkers Consortium and BloodPAC, where information is being shared.

Session 3: Patient-Focused Session: Biomarkers, Screening, and Eligibility for Clinical Trials
Moderator: Vishal Bhatnagar, FDA, Office of Cancer Excellence (OCE)

Dr. Bhatnagar stated FDA, OCE's mission to achieve patient-centered regulatory decision-making in cancer therapy, which includes the patient perspective across the drug development continuum, in early and late-stage trials, through rigorous symptoms and function measurements, and patient-reported and general outcomes. A redefinition of tolerability includes longitudinal assessment of patient-reported symptomatic AEs to inform decision making (FDA, June 2021). Project Patient Voice is an OCE-created, publicly available pilot website that disseminates data from clinical trials used to support approvals. This important tool can aid provider-patient conversation at the onset of treatment.

Precision Medicine and Broadening Eligibility Criteria
Ed Kim, City of Hope National Medical Center

Dr. Kim discussed the BATTLE trial (Biomarker-based Approaches of Targeted Therapy for Lung Cancer Elimination), an early personalized medicine effort that used biomarkers to evaluate targeted therapies in NSCLC. By 2021, therapy directed by molecular subset stratification such as *EGFR* (including *exon18*,

exon20) and *ALK*, *ROS-1*, *PD-L1*, *BRAFv600E*, *RET fusions*, *MET exon14*, *NTRK* fusions, *KRAS G12C* fusions has enabled >65% of patients as targeted therapy candidates with increased effectiveness, tumor shrinkage and control, and quality of life. Lung cancer therapy has been transformed in the past 15 years with TMB and *EGFR T790M* (post EGFR - tyrosine kinase inhibitor [TKI] therapy) additionally recommended with larger biomarker panels used in the locally advanced setting and then eventually in the early stage and prevention settings. Dr. Kim urged complete evaluation and staging of patients with these biomarkers. Despite these advances, the "treatment paradox" exists. With the median number of eligibility criteria (37 per trial), only 1/20 patients are eligible for a clinical trial vs. the 16/20 eligible for an approved treatment. Treatments must be assessed in a real-world population; ASCO's Modernizing Eligibility Criteria project, begun in 2012, aims to implement a new culture where patient exclusion happens only when safety warrants, and trials are fit to patients through active discussion of trial design and FDA pre-IND meetings. The NCI Cancer Therapy Evaluation Program (CTEP) Generic Protocol template was modified per recommendations from FDA, ASCO, and Friends of Cancer Research. New, updated FDA guidance documents were issued between 2019-2020, which address eligibility for patients with brain metastases, minimum age, human immunodeficiency virus (HIV)/acquired immunodeficiency syndrome (AIDS) and hepatitis B/C infections, organ dysfunction, and prior and concurrent malignancies. Washout periods and concomitant medications, prior therapies, laboratory reference ranges and test intervals, real-world population analysis, and performance status recommendations were evaluated and published. The TAPUR Study was the first in the country to adopt all these eligibility criteria.

The discriminatory way protocols are written can limit access to underserved and rural populations. The downstream consequences of not modernizing eligibility criteria are many. These include increased numbers of studies to boost enrollment, increased burden on clinical staff, disengaged clinicians, long protocols with expanded eligibility criteria, and only marginally effective drugs that may not receive approval. Broadening eligibility criteria has benefits, including fewer protocols and greater numbers of studies with expanded opportunities for patients and real-world population enrollment. Trial staff can work with "on treatment" patients with expedited registration and approvals of active drugs. Published studies show that former exclusion criteria could limit benefits for patients, such as patients with HIV/AIDS and hepatitis B/C infections. In another example, patients with brain metastases were not included in studies of TKIs, although TKIs are effective in treating systemic disease.

Judy Johnson, Lung-MAP Patient Advocate

The Lung Cancer Master Protocol (Lung-MAP) was launched in 2014 and is a unique, collaborative PPP clinical trial that uses state-of-the-art genomic profiling to match patients to new, investigational treatments for NSCLC. One advantage of Lung-MAP is that patients have easy access to targeted therapy sub-studies and when matched, can enroll faster in independently operated sub-studies upon progression or are offered immunotherapy in a non-match sub-study. The PPP includes NCI, the NCI Clinical Trials Network (led by SWOG), FNIH, Friends of Cancer Research, FDA, Foundation Medicine, pharmaceutical companies that provide study drugs, and several lung cancer advocacy organizations. SWOG patient advocates serve as members of the study team from concept development throughout the clinical trials life cycle. A second advantage of Lung-MAP is that it includes all NSCLCs, with over 900 trial sites at academic and community treatment centers (>50% enrollment), including rural areas. Since May 2021, patients can use a previous FoundationOne CDx result instead of a new tissue biopsy. Several advancements are in progress, including a newly opened sub-study for *KRAS G12*, a matched *RET+* and non-matched immunotherapy-resistant or refractory sub-study, and new concepts in development and under discussion around immunotherapy for lung cancer.

Jane Perlmutter, Gemini Group (Breast Advocate, Associated with I-SPY 2)
Much data supports the treatment paradox, but biomarker-driven trials can be more accessible and benefit patients through innovative Master Protocol designs. Innovation in the I-SPY 2 TRIAL (Investigation of Serial Studies to Predict Your Therapeutic Response with Imaging And moLecular Analysis 2) and TAPUR Study, such as continuous learning, Bayesian adaptive trial designs, investigational agents for potentially curable disease, agnostic tumor site of origin, and off-label use of FDA-approved agents based on tumor biology, has enabled the enrollment of 1500 and 2500 patients across 20–30 and 150 sites, respectively. I-SPY 2 has collected much data that showed that agents targeting traditional breast biomarkers have neither elicited durable responses nor have been efficacious for every patient and have lacked predictive specificity, necessitating a transition to a more diverse set of biomarkers (immune, DNA repair-deficient, luminal/basal) with a target endpoint of complete pathological response (pCR) and goal of double pCR , a proven predictor of non-metastases disease-free survival.

Suparna Wedam, FDA
FDA has been working for several years to reevaluate clinical trial eligibility criteria to ensure that patients entering clinical trials reflect patients who will eventually receive approved treatments. Published guidance addresses the inclusion of subgroups or populations that are often excluded, such as adolescents, older adults, patients with organ dysfunction, and disease-specific groups such as males with breast cancer. FDA is aware that eligibility criteria can impact disparities and clinical trial participation and can be significant barriers for certain demographic subgroups due to a high prevalence of comorbidities. Project Equity and Project Community are OCE initiatives that push for greater diversity and equity in clinical trials. The FDA cannot require sponsors to follow broadened eligibility criteria in protocols; however, they routinely suggest reevaluating the eligibility criteria at all phases of the iterative drug development process. Alternate trial designs, such as expansion cohorts or companion protocols, can be offered to minimize the risks of severe AEs in vulnerable or inherently ill patient groups, yet allow for their inclusion to obtain safety and efficacy data in these subgroups, while not impacting them the study's primary endpoint. FDA highlights incentives like expanded labeling for indications and reduced post-marketing requirements when an expanded trial population is incorporated.

Mark Stewart, Friends of Cancer Research
There are perceived dangers of broadening eligibility criteria for patients with more risk factors, including safety for the patients and difficulty in demonstrating the safety and efficacy of new investigational agents. An evaluation of the new CTEP protocol template, intended to operationalize these criteria, showed a varied range of compliance based on eligibility criteria from high (liver function) to low (new or progressive brain metastases). While there was progress, most trials did not implement the criteria or address investigator discretion in determining their use. Encouraging adoption of the ASCO/Friends of Cancer Research recommendations involved a multi-pronged approach. This began with a multi-stakeholder group and the representation of diverse perspectives in the clinical trial ecosystem, engagement of trial sponsors in discussions, and working with FDA for proposed language to inform guidance. Presenting strategies to mitigate the risks of broadening the patient population could include prespecified analysis plans, stratified analyses by patient population and eligibility criteria, expanded cohorts, and adaptive trial designs that leverage interim analyses.

Discussion

Dr. Howard Fingert asked about models of the modern usage of biomarkers, making it safer to optimize risk-benefit in a broader eligible population. He followed up with another question on biomarker qualification and validity in the context of therapeutic decision-making for optimal patient care decision-making. Dr. Kim responded that biomarker-directed therapy has changed the way eligibility needs to be assessed if we want meaningful change. A biomarker-eligible population allows us to evaluate risk-benefit. Dr. Wedam added that in the era of precision and targeted therapies, prior therapy criteria could be rigidly limiting, especially when the scientific rationale of the biomarker-driven trial benefits those patients. Further, biomarker-based decision-making depends on the biomarker, tumor biology, mechanism of action, and scientific reasoning before it is used for inclusion or exclusion of patients. Dr. Bhatnagar added that patient-reported data and tolerability are also relevant to patient care in this context.

Dr. Bhatnagar asked about the potential role of RWE for biomarkers, screening, and eligibility. Dr. Wedam replied that RWD is used to characterize the natural history of subpopulations, add context to evidence generated in controlled clinical settings, to complement drug safety and effectiveness for subpopulations, and to collect post-marketing or PRO data for underrepresented populations. The challenge is the quality of the data in addressing regulatory questions or its use as a supplement when the gold standard is clinical trial data. Dr. Stewart added that standardized data elements, methodology, clinically meaningful endpoints, and aligning definitions across health data vendors could inform the utility of the evidence generated and ensure reliability and reproducibility in supporting regulatory decision-making.

Ms. Johnson noted that PRO data should be compared to Common Terminology Criteria data, and Ms. Perlmutter commented that patients want better treatments, and RWE can provide information about this.

Session 4: New Imaging Endpoints
Chairs: Janet Eary, NCI, and Marc Theoret, FDA, OCE

This session had 4 presentations, followed by a panel session. The focus was on various imaging modalities and imaging biomarkers as novel clinical endpoints in various applications across the development paradigm such as dose finding, dose optimization, enrichment with selection of patients most likely to respond, response monitoring, and efficacy assessment. Biomarkers are paramount to continued success of developing novel therapeutics for patients with cancer efficiently and expeditiously. Imaging biomarkers can play a key role in this process.

***Advanced Metrics and Modeling with Volumetric Computed Tomography for Precision Analysis of Clinical Trial Results (Vol-PACT*)**
Larry Schwartz, Columbia University

Dr. Schwartz summarized the results of the FNIH Vol-PACT project and proposed next steps. The project aimed to develop novel imaging-based phase 2 clinical trial endpoints in solid tumors to improve the prediction of phase 3 outcomes using the current response evaluation criteria in solid tumors (RECIST) method. It employed a comprehensive approach to quantitatively measure the total tumor burden of all lesions (target, nontarget, and new lesions) and assess radiomic features of these lesions at the pixel level. The measurement data were used as input to generate metrics for survival (OS) prediction by 3 different approaches: radiomic signatures, tumor growth kinetic modeling, and partial conditional modeling. Vol-PACT has developed baseline radiomic signatures, and signatures derived from baseline

and follow-up computed tomography (CT) scans in NSCLC, melanoma, or colorectal cancer. These signatures outperform RECIST in predicting survival of patients treated with targeted and immunotherapy and have been validated with external data, suggesting that they may be generalized across different cancer types and drug classes. Using tumor growth kinetic modeling, the tumor growth rate "g" value predicted OS in NSCLC and renal cell carcinoma. Built on these promising results, the next phase of Vol-PACT (phase 3) proposes further development and validation of radiomic features and tumor growth rate "g" as regulatory endpoints for accelerated approval or regular approval in rare cancers.

MRI-based Biomarkers for Response - Adaptive Treatment of Breast Cancer
Nola Hylton, University of California, San Francisco

Dr. Hylton shared her perspective on the use of magnetic resonance imaging (MRI)-based biomarkers for response-adaptive treatment of breast cancer. I-SPY 2 is a response-adaptive phase 2 trial testing novel agents as neoadjuvant treatment for locally advanced breast cancer. It was initiated in 2010 and is widely regarded as a pioneer of the "platform" trial design. Drugs "graduate" from I-SPY 2 when they reach a Bayesian predictive probability of achieving 85% success in a subsequent 300-patient phase 3 trial. The study uses functional tumor volume (FTV) derived from standardized breast dynamic contrast-enhanced MRI to adjust patient randomization ratio and estimate probability for pCR prior to surgery. A multivariate model incorporating serial FTV measurements at baseline and follow-up time points was able to predict pCR in the full cohort and in a subgroup of patients with certain characteristics. Additional models were also developed for treatment de-escalation or early escalation. Furthermore, multi-feature MRI analysis combining 4 MRI features (FTV, longest diameter, sphericity, and contralateral background parenchymal enhancement) improved pCR prediction over any individual feature. The investigators are incorporating MRI-guided early escalation/de-escalation algorithms in the design of the next phase I-SPY 2.2, to commence early 2023 and aiming to maximize every patient's chance of reaching pCR.

Framework for Molecular Imaging Probes as Biomarkers
David Mankoff, University of Pennsylvania

Dr. Mankoff provided an overview of molecular imaging biomarkers that can potentially guide cancer drug development and patient care, focusing on breast cancer patients treated with endocrine therapy. In this cohort, as a predictive biomarker, quantitative uptake of 18F-fluoroestradiol (FES) as a measure of ER on positron emission tomography (PET) at baseline predicted response to hormonal therapy in breast cancer. In another series, reaching a quantitative threshold of the FES PET uptake was required to demonstrate the minimum amount of target presence that is sufficient for successful tamoxifen therapy in patients with ER+ advanced breast cancer. Molecular imaging biomarkers have also shown utility in detecting whether the drug has reached the target and blockaded the receptor binding of the native ligand and the dose required to achieve ER blockade by ER antagonists (e.g., tamoxifen and fulvestrant). As a pharmacodynamic (PD) biomarker, fluorodeoxyglucose (FDG) PET, which images elevated glycolysis that typically occurs in tumors, can be a generic imaging PD biomarker to detect response to a wide range of cancer therapies. PD markers can be specific to a target; for example, progestin analog, 21-18F-fluorofuranylnorprogesterone (FFNP) which images progesterone receptor can be a PD marker to ER endocrine treatment response.

Whole Body/In Vivo Assessment of Immune Response by PET
Andrea Thiele, Boehringer Ingelheim

Dr. Thiele presented a proposal on behalf of the FNIH BC CSC Immune Response Imaging (IRI) Working Group on developing imaging-based biomarkers for assessment of immune response in IO clinical trials. The IRI Working Group is developing a portfolio of existing and novel PET ligands targeting features of the tumor microenvironment (TME), e.g., targeting cells, pathways crucial for confirming drug mechanisms of action and PD response, filling data gaps through precompetitive projects, building a platform for strategic collaborations, and developing an implementation strategy to collect clinical evidence to validate these molecular imaging biomarkers for specific contexts of use (COUs) in oncology drug development. Currently, many PET ligands are in development, but very few are validated and can be relied upon for drug development and patient care decision making. The proposal intends to develop evidence to fill data gaps by dedicated clinical studies toward qualification of a PET ligand as a PD/response biomarker in a specific COU for immunotherapy through the FDA biomarker qualification process.

Roundtable Discussion
Bob Gillies, Moffitt Cancer Center; Greg Goldmacher, Merck; Alexander Guimaraes, Oregon Health & Science University; Rich Wahl, Washington University in St. Louis

The topics discussed and conclusions of the panel are as follows:

Standardization to improve imaging biomarker reproducibility and adoption of imaging biomarkers for general use. Standardization of imaging acquisition and analysis is essential to achieve reproducible imaging readings so that they can be interpreted with confidence. RSNA/QIBA Profiles and NCI-recommended protocols provide guidance in this regard. Continued support in investigating the sources of imaging biomarker variability and ways to reduce it is important. This standardization would also facilitate the general adoption of imaging technologies in the community hospital settings outside major advanced imaging centers or major medical centers.

Imaging biomarkers in early and late stages of drug development. Novel molecular imaging tracers such as those for imaging TME may be more suitable for early drug development. Standard CT and MRI are more widely available and practical in later stages of drug development. PET tracers might be used in early drug development and to train radiomic signatures derived from CT or MRI for later stages of drug development.

Using existing imaging data and collaboration to generate novel biomarkers. Pharmaceutical companies have CT and MRI data from clinical trials that could be used to develop and test novel imaging biomarkers. Collaborations between pharmaceutical companies and others would be helpful to test the new tools in existing CT and MRI datasets and then in prospective trials. However, it is challenging to have pharma share data externally, and we must be creative to incentivize data sharing.

Alignment with regulatory authorities applying imaging biomarkers in oncology drug clinical trials. Although many PET tracers have been developed, evidence is lacking that they are reliable biomarkers for clinical trial decision-making. We need to understand and be aligned with the regulatory authorities on the minimum data package that is required to validate these biomarkers before they can be applied as biomarkers in oncology drug trials.

Day 4, November 9, 2021

Welcoming Remarks
Eric Rubin, Merck, CSC co-chair

Keynote: On Growth and Challenges in Checkpoint Blockade
David Fabrizio, Foundation Medicine

Mr. Fabrizio spoke on the current challenges in precision medicine, mainly that these challenges are multi-modal due to growing biomarker complexity, which can impact patient response. He highlighted some examples of the complexity, such as TMB, where TMB-high as opposed to TMB non-high is an independent predictive marker of overall response (ORR) to immunotherapy; novel immunotherapy resistance (e.g., serine/threonine kinase 11) that confers resistance to immune checkpoint blockade; mono immunotherapy vs. chemo immunotherapy and their clinical impact due to dissimilar genomic associations; changes in ctDNA levels that can be associated with patient response to therapy or that can predict risk of recurrence; and the differences between TMB and blood TMB (bTMB) and their association with ORR and how bTMB relates to tissue TMB.

Mr. Fabrizio commented that personalized immunotherapy should address the cancer immunity cycle, which is composed of 3 arms: immune potential (biomarkers that likely elicit an immune response), immune activation (genes that mount an immune response), and immune resistance (e.g., percentage of human leukocyte antigen [HLA] loss of heterozygosity, which is associated with poor OS to checkpoint inhibitors in NSCLC). He stressed that the immune-oncology signature is multi-modal, encompassing the cancer immunity cycle. The future of precision medicine involves identifying which combinations of these arms provide better insight into clinical decision-making. Immunotherapies should be based on science-driven product development focused on discovering new pieces of the immune-oncology puzzle, taking into consideration the following:

- Harmonization of efforts with multiple stakeholders focusing on definitions, validation, requirements, and clinical applications

- Rethinking new clinical trial designs that don't necessarily limit complex variable biomarkers to their categorical definitions, e.g., biomarkers that support the continuous model vs. the discover-and-validate model based on a single cutoff, and noting that the same cutoff in different tissue types may correlate with a different patient response rate

- Development of a clear and concise medical reporting strategy, which remains a challenge concerning continuous variable biomarker complexity

- Assessing other clinical variables in the cancer immunity cycle with the combination of T-cell exhaustion markers (exhausted T cells cannot perform their antitumor function) and their integration in clinical trials

Fireside Chat

Moderator: Stacey Adam, FNIH. Dr. Adam interviewed Doug Lowy, Principal Deputy Director of NCI and Jeff Siegel, FDA, Office Director, Office of Drug Evaluation Sciences

Dr. Adam asked about the advantages of developing biomarkers now and into the future. Dr. Lowy replied that the significant advantage of biomarkers, such as mutations associated with TKI or fusion proteins, is their use in predicting response, as CDx or surrogate endpoints, which can be reached faster than survival or other traditional endpoints. Genomic profiling and TMB have brought us far. The future will see expanded use of protein biomarkers, such as protein phosphorylation as surrogate biomarkers. The benefit of surrogate biomarkers is illustrated by human papillomavirus (HPV) vaccine initial approvals, which utilized surrogate biomarkers (viral infection) and high-grade cervical dysplasia as the main endpoints. The vaccine strategy elicited substantial prevention, correlated with viral infection; however, it took several years longer to attain the dysplasia endpoint. With increased events and shorter time to events, biomarkers can aid the development of third- and fourth-generation vaccines and biosimilars.

Dr. Siegel noted that the Office of Drug Evaluation Services oversees qualification of clinically accurate assessment tools and biomarkers for use in clinical trials across all therapeutic areas. Validation for COU, whether for patient care or clinical trial applications, is at the forefront of the biomarkers effort; however, mechanistic understanding of biomarkers is equally as important. The virtual cycle of biomarker discovery, COU, information on disease biology, and applied biomarkers can inform and benefit patient care. For example, liquid biopsies are used to monitor ctDNA as evidence of response and can also provide insight into resistance mechanisms so therapies can be improved or possibly changed. Surrogate endpoints are also important to several therapeutic areas, including reliable prediction of relapse to determine when to transition patients to a different treatment. Dr. Siegel cautioned that the evidentiary burden required to apply surrogate endpoints in a clinical development program reliably can be high. Choosing a COU for a biomarker with less evidentiary burden, such as a prognostic, response, or monitoring biomarker with demonstrable value in predicting outcome and applying it in a clinical trial to further qualify is useful.

Dr. Adam noted that biomarker qualification is a focus of consortia projects. Pertaining to technologies, such as liquid biopsy and NGS, Dr. Adam asked Dr. Lowy and Dr. Siegel to elaborate on imaging, MRD, and the potential future of these and other aspects highlighted during the CSC symposium.

Dr. Lowy said the NIH supports several approaches for MRD. Over the past 20 years, a significant advance has been in the number of oncology therapeutics available; however, secondary or acquired resistance still represents a major bottleneck in therapy. Efforts to detect resistance and intervention-changing treatments can be helpful regardless of the biomarker used. Liquid biopsies for cancer screening, as Dr. Liu described, are an experimental approach with considerable potential for identifying asymptomatic disease. Advances in cancer treatment and liquid biopsy for screening looking at early disease will hopefully garner success.

Dr. Siegel agreed that liquid biopsy and MRD are important areas for the future, in addition to imaging biomarkers and molecular imaging techniques used to better understand tumor burden in response to treatment. Assessing CD8+ and activated CD8+ prior to or after immunotherapy for prediction or measure of response can provide insight about mechanism of action and increase the number of patients who can benefit from immunotherapy. For many of these technologies, there are significant implications for benefit and risk because of AEs or risk of progression, for patients who may or may not

have been treated if not for that technology. Ensuring these technological tools are precise, accurate, and standardized, and understanding the risk/benefit, are critical to realizing their potential for cancer patients.

Dr. Adam asked for comment on the FDA qualification program in the context of multiparametric biomarkers and incorporating NGS and other technologies. Dr. Siegel said this could be complex but could be done in an evidence-based manner. FDA seeks to understand the biomarker and why it is put together the way it is, to understand applicability, accuracy, and reliability. Fora multi-parametric biomarkers, it is important to understand the contribution of each component to its use. Early interaction with FDA is key to assessing the evidence needed. A public workshop on multi-parametric biomarkers is planned for spring 2022.

Dr. Adam asked Dr. Lowy to comment on what NCI initiatives exist to obtain the level of evidence that Dr. Siegel suggested. Dr. Lowy provided the example of the Childhood Cancer Data Initiative, and its component that addresses the one-third of children who develop cancer but are not in clinical trials. Standardizing data from these children can comparatively enable the identification of best practices. The abundance of objective measurements in oncology contributes to precise and highly reproducible data, and the opportunity for progress with surrogate biomarkers is vast.

Dr. Adam spoke of the Biomarkers Consortium aiming to foster collaboration across many disease-focused areas, including cancer, inflammation and immunity, metabolic disorders, and neuroscience, and asked Dr. Siegel and Dr. Lowy to comment on incentivizing cross-cutting biomarker efforts. Dr. Lowy noted this would be a win-win, since one field can't address all the needs on its own. Dr. Siegel said that the different areas often borrowed tools from one another, and that collaborative work and its application across therapeutic areas is desired. Collaborative work and cross-application could begin with biomarkers that have undergone analytical validation in one therapeutic area, so additional evidence needed for cross-disease applications could be considerably less.

Session 5: Growth and Challenges in Checkpoint Blockade
Chairs: Alex Snyder, Two River, and Helen Chen, NCI

The speakers in this session discussed the progress of precision medicine, tumor immunotherapy, and future challenges.

TMB and Beyond: Understanding Genetic Predictors of Immunotherapy
Timothy Chan, Cleveland Clinic

Dr. Chan stressed that immune checkpoint therapy has been able to produce dramatic results and improved treatment outcomes for patients with different types of cancer. He stated that TMB-high (TMB >10 mutations/megabase) is a good genetic predictor for an antitumor response and explained that the success of immunotherapy is due to patient genotype as well as tumor genetic diversity. On patient genotype, he spoke about the importance of HLA diversity, which can measure the potential for antigen presentation to T cells, the T-cell receptor (TCR) repertoire, and the ability to induce signal 1 (activation of T cells via the TCR) in the initiation of an antitumor response. For example, high HLA genetic diversity (immune peptidome) predicts better response against cancer and infectious disease. However, tumor cells are complex due to differences in the tumor landscape and their transcriptome, such as mutations in immune checkpoint blockade components. He

concluded his talk by stating the importance of immune genetic diversity (immune peptidome) in the personalization of immunotherapy and stressed the harmonization of TMB in different cancers.

irAEs–Building a Resource for Analysis Across Disease Targets
David Fox, University of Michigan

Dr. Fox introduced his talk by defining what immunotherapy-related AEs (irAEs) are and how they impact many organs (e.g., skin and gastrointestinal tract). He stressed that a major challenge is the ability to define and classify irAEs, as some classifications are not all-encompassing, and irAEs manifest in many types of organs and organ systems**.** He emphasized the need to better define and understand irAEs to develop better strategies to treat them. He recommended that to develop therapies to treat irAEs, one must be able to identify and classify distinct clinical syndromes, which include the following:

- New approaches to immunotherapy that avoid autoimmunity
- Definition of which toxicities mirror known autoimmune diseases, and which are new conditions
- Establishing the genetic and epigenetic base for susceptibilities to irAEs
- Developing and optimizing specific, mechanism-based treatment for specific syndromes, and reducing use of higher corticosteroid doses.

Dr. Fox gave an example of the potential treatment of irAEs when targeting CD6, a protein that is expressed by most T cells and 60% of natural killer cells. The function of CD6 is to mediate T-cell trafficking across endothelial barriers, and it is implicated in the pathogenesis of various heart diseases. He showed the ability of an anti-CD6 Ab (UMCD6) to block CD6 and its ligands (CD166/CD318) to alleviate inflammation in a murine model of experimental autoimmune encephalitis. Furthermore, Dr. Fox stressed the importance of finding novel biomarkers such as CD6 in the categorization of irAEs, and as a new target in cancer immunotherapy to lead to better treatments.

Investigating Mechanisms of Response to Immune Checkpoint Therapy: Moving Towards Combinatorial Biomarkers to Reflect Both Tumor Cell Status and Immune Microenvironment
Padmanee Sharma, MD Anderson Cancer Center

Dr. Sharma identified specific mutations that correlate with better patient response. One such candidate is AT-rich interactive domain-containing protein 1A (ARID1A). Patients with an ARID1A mutation are associated with higher TMB and lower transforming growth factor β expression and are better responders to anti-PD-1 therapy in metastatic bladder cancer. Mutated ARID1A was associated with improved immune response and increased production of interferon-γ, an important antitumor cytokine. Dr. Sharma also talked about the importance of the immune microenvironment (e.g., C-X-C motif chemokine ligand 3 [CXCL13]) in correlating patient response to immunotherapies. Currently the predictive potential of ARID1A and CXCL13 is being studied in clinical trials with subjects with metastatic or surgically unresectable bladder cancer (cohort 1) and any other cancer (cohort 2) with a documented ARID1A mutation treated with nivolumab. The future of immunotherapy will involve combination treatments that consider the TME and mutations.

Roundtable Discussion

Theresa LaVallee, Parker Institute for Cancer Immunotherapy; Priti Hegde, Foundation Medicine; Fred Hirsch, Mount Sinai; Rob Iannone, Jazz Pharmaceuticals; Elad Sharon, NCI

The roundtable discussion was focused on the challenges and barriers to precision medicine in IO. The main takeaways from this discussion are listed below:

- Precision medicine is challenging due to many factors that involve the cancer immunity cycle, growing biomarker complexity, and resistance.
- Harmonization across industry-academic-government partners is essential to achieve consistent biomarker definitions, clinical application, and benefits.
- A lack of harmonization procedures across partners may lead to bias.
- Precision medicine is complicated by irAEs and understanding irAEs by systematic categorization will help us learn how to treat and avoid them.
- There is a need to identify new approaches to cancer immunotherapies that avoid the induction of autoimmunity.
- There is a need to identify and define specific mutations that correlate with patient response.
- There is a disconnect between great science, which can identify biomarkers predictive of clinical benefit, and how these biomarkers can be applied and translated into the clinic.
- Cross-disciplinary interactions will inform and develop treatment strategies derived from multiple fields.
- The challenge *and* future of immunotherapy depend on identifying and optimizing standardized biomarkers with combination therapies.