CSC Annual Scientific Symposium
December 3 – 4, 2020

Meeting Summary

Meeting Introduction and Overview

The Foundation for the National Institutes of Health (FNIH) Biomarkers Consortium (BC) Cancer Steering Committee (CSC), led by its co-chairs Dr. Gary Kelloff (National Cancer Institute) and Eric Rubin (Merck) annually convenes more than 200 experts from academia, pharmaceutical companies, biotechnology companies, not-for-profit organizations, NCI, FDA, and other federal agencies to review advances in the field of biomarker and regulatory science and to strategize the development of new public-private partnerships for biomarker development. The CSC Annual Scientific Symposium, held virtually this year, highlighted cutting-edge science, identified critical areas of biomarker research need, and fostered collaborations designed to inform the field of exciting new advances. Having recognized that there is a need for biomarkers at all phases of cancer (from diagnosis through treatment and maintenance), this year's symposium systematically evaluated each phase of disease and treatment in terms of the challenges of applying and implementing biomarkers and identified potential regulatory hurdles. The sessions provided insight into difficult-to-detect tumor types and highlighted the importance of public-private partnerships, with updates from ongoing precompetitive BC-CSC projects. The keynote speakers, representing academia, NCI, FDA, and the pharmaceutical industry, provided valuable insight into recent innovations in biomarker use for drug development and patient care.

Keynote: "Oncology Center of Excellence: Current Efforts and Future Directions" – Julia Beaver (FDA Oncology Center of Excellence and Center for Drug Evaluation and Research Office of Oncologic Diseases)

The FDA Oncology Center of Excellence (OCE) was created as part of the 21st Century Cures Act and leverages the combined skills of regulatory scientists and reviewers from 3 FDA centers (Center for Drug Evaluation and Research [CDER], Center for Biologics Evaluation and Research, and Center for Devices and Radiological Health [CDRH]) to support an integrated approach to clinical evaluation of drugs, biologics, and devices to modernize and streamline the review and approval process and expedite the development of products for oncologic and hematologic malignancies. Project Orbis and the Real-Time Oncology Review program are among those initiatives undertaken by OCE that are bearing fruit. In addressing the impact of COVID-19, the FDA is adjusting its regulatory approaches to allow more flexibility in the conduct of oncology trials, including decentralizing trials, expanding inclusion/exclusion criteria, and learning from real-world data (RWD). Dr.

Beaver noted that on the precision oncology front, OCE continues to encourage biomarker development and incorporation of biomarkers in clinical trial designs. Biomarkers have potential value across the full spectrum of cancer drug and device development and clinical care, and have resulted in successful drug approvals, for example, as patient selection biomarkers in lung cancer and in immunotherapies such as PD-1/PD-L1 antibodies. OCE is advancing regulatory science and policies of rare molecular subsets in disease, tissue-agnostic approvals, and use of biomarkers derived from circulating tumor DNA (ctDNA).

Keynote: "Biomarker Qualification" – Christopher Leptak (FDA CDER Biomarker Qualification Program and BC Executive Committee)

Dr. Leptak spoke on how biomarkers are developed for regulatory use, specifically within the context of a biomarker qualification effort, and the elements of a successful biomarker development effort for qualification. Depending on the purposes in drug development, a biomarker is classified into one of 7 "**B**iomarkers, **E**ndpoint**S**, and other **T**ools" (BEST) categories in the context of disease and therapy: susceptibility/risk, diagnostic, monitoring, prognostic, predictive, pharmacodynamic/response, and safety biomarkers. The utility of a biomarker in drug development is determined by its context of use (COU). In biomarker qualification, the COU describes the biomarker category and how the biomarker impacts the clinical trial or drug development program. The conceptual framework for biomarker development for regulatory acceptance includes a need statement, COU, benefit/risk assessment, and evidentiary criteria. The COU dictates what evidence is needed to support the claim, and also demonstrates the value of the biomarker to clinical development. The specific COU for a biomarker drives the extent of evidence needed for qualification, which falls under 2 broad domains: analytical validation and clinical validation. Analytical validation is to establish performance and acceptance characteristics of the biomarker assay; clinical validation is to establish that the biomarker acceptably identifies, measures, or predicts the concept of interest.

The 21st Century Cures Act increasingly places FDA as an active participant in drug development, broadens FDA's traditional regulatory role, and formalizes a 3-step submission process for biomarker qualification: Letter of Intent (LOI), Qualification Plan, and Full Qualification Package (FQP). A transparent process is put in place so all stakeholders are aware of tools in development, the stage in the biomarker qualification process, and FDA determinations/recommendations to provide opportunities for a shared learning culture. The review of submissions is a 3-tiered process and is completed within a specified timeframe. The acceptance decision for each submission is based on scientific merit. There are opportunities for qualification submitters to engage with FDA throughout this process, at pre-LOI, post LOI, and before the FQP submission, on general or specific topics relevant to a qualification submission.

Session I: Biomarkers in Early Diagnosis

The session on early diagnosis covered initiatives to improve and advance early cancer screening and detection strategies as well as clarification of cancer biology, focusing on some of the opportunities and challenges, in order to provide earlier opportunities for intervention and better chances to improve survival.

Dr. Geoff Oxnard (Foundation Medicine) chaired the session. He introduced the importance of biomarkers for early detection by pointing out that circulating free DNA (cfDNA) analysis from noninvasive liquid biopsies is now a reality, as it is used in noninvasive high-risk pregnancy testing and has been adapted for genotyping advanced cancers (as ctDNA) with FDA-approved assays, so why not use it for cancer detection and screening? ctDNA assay-based cancer detection is likely to identify higher risk (shedding) cancers and improve outcomes in these patients. Approaches that are focused on detection alone, without considering biology or actionability, i.e., how to manage patients when the cancer signal is detected. To improve outcomes in these patients, a concerted diagnostic/therapeutic paradigm may be needed.

Dr. Nickolas Papadopoulos (Johns Hopkins University) noted that the goal is to identify and detect cancers early, because current therapies, such as immunotherapies, have a better chance of successful outcome with earlier detection and lower tumor burden. He highlighted the liquid biopsy test, CancerSEEK, a multi-analyte DNA and protein assay developed to complement other screening tools to detect multiple cancer types at early stage disease. The Johns Hopkins team evaluated an early version of the CancerSEEK assay in a prospective, interventional study, DETECT-A, of 10,000 women between 65 and 75 years old, enriched with ovarian cancer and comorbidities. The study showed that the multi-cancer blood test can be used to detect cancers in patients not known to have cancer, help enable treatment with intent to cure for some patients, complement standard of care (SOC) screening, and with positron emission tomography-computed tomography (PET-CT) imaging, detect cancer locations with specificity. Given these results, the next step is to run randomized prospective interventional trials in target populations to assess risk/benefit, demonstrate cost effectiveness, reduce morbidity, and establish clinical utility. The overall vision of the group is to prevent advanced tumors by integrating such tests as part of routine screening and management.

Dr. Minetta Liu (Mayo Clinic) focused on early detection of malignancy through multi-cancer screening tests that perform at population scale and serve as an adjunct to existing screening paradigms. The idea is that the greater value is in a single test to detect multiple malignancies. This test should provide specific and sensitive detection of clinically relevant malignancies at the earliest stage possible, detect the early stage cancers across all major tumor types, identify the cancers that will impact survival while avoiding detection of premalignant and benign tumors, and determine the tissue of origin.

Dr. Liu collaborates with GRAIL Inc. in clinical trials of multi-cancer tests and described the company's approach to developing the Galleri multi-cancer test, which interrogates ctDNA methylation patterns. The Circulating Cell-free Genome Atlas (CCGA) Study using Galleri includes 3 sub-studies for discovery, training, and validation of the test. Sub-studies 1 and 2 have been completed and 3 is ongoing.

Sub-study 1, Discovery, evaluated methods for assessing ctDNA, determining that a whole genome sequencing (WGS)-targeted methylation panel assay outperformed a next-generation sequencing (NGS)-targeted panel and WG bi-sulfate sequencing assays. Sub-study 2, Training/Validation, showed the ability of the methylation assay to determine cancer, noncancer, and tissue-of-origin classes for localization of the signal. Sub-study 3 will entail further validation. GRAIL is also sponsoring the current PATHFINDER Study, an interventional study to evaluate the use of Galleri in clinical practice, with the results returned to the provider and patient.

Dr. Liu then described additional studies with new technologies that employ the tissue and cancer specificity of alterations. These include the DNA MeDIP-seq, a genome-wide bisulfite-free plasma DNA methylation profiling assay, and Delphi DNA, which uses low-coverage genome-wide analysis of DNA fragmentation profiles. She concluded by stating that blood-based detection of cancer at the time of a clinical diagnosis is feasible with over 99% specificity, including a general cancer signal as well as tissue localization. The current NGS-based assays can detect selected mutations, targeted methylation, differentiated methylation, methylated regions, and cfDNA fragmentation patterns. There is potential to further improve sensitivity by assessing multiple alterations and/or circulating proteins from the same plasma sample.

Dr. Catherine Marinac (Dana Farber Cancer Institute and Harvard Medical School) outlined the case for early screening and detection for treating and reducing mortality for blood cancers such as multiple myeloma (MM). MM has well-defined, asymptomatic precursor conditions stages that include monoclonal gammopathy of undetermined significance (MGUS) and smoldering myeloma. Clinically similar patient subgroups appear to have very different rates of progression. High-risk Individuals with MGUS and smoldering myeloma are prime candidates for myeloma prevention efforts. However, there currently are no biomarkers of disease progression, and it cannot be predicted which patients with these premalignant conditions will progress to myeloma within their lifetime and who will not. Thus, there is need for screening is to identify those with a form of the disease requiring intervention vs. monitoring. Testing for early detection of precursor MM in high-risk individuals would be easy to implement, as currently employed blood tests also pick up precursor conditions.

The PROMISE Study was initiated in 2019 to capitalize on the areas of opportunity and address some of the obstacles. This study is the first nationwide effort to detect MGUS and smoldering myeloma in a higher-risk cohort of individuals who are black or of African descent, or who have a family history of a blood cancer such as myeloma. The goal is to screen and then prospectively follow this higher-risk cohort of individuals. The first objective is to identify novel biomarkers of disease progression and refine current prediction algorithms and risk stratification efforts to guide clinical follow-up; importantly, this objective decreases the diagnostic uncertainty that can be a great source of anxiety among patients who are currently incidentally diagnosed with these conditions. Liquid biopsies are used to identify genomic abnormalities that may predict progression. The PROMISE team is also interested in in the impact of the immune system and immune dysregulation on the risk of progression. The second objective of the study is to generate

new tools to both prevent and interpret patterns that can help make intervention the SOC in this patient population.

Screening is a relatively streamlined process, employing a remote infrastructure whereby individuals sign up to be tested using an online platform and receive directions for providing samples for central testing with a combination of serum protein electrophoresis and serum free light chain assays. Patients with positive results are followed prospectively until progression to overt MM, with the collection of clinical information as well as blood and tissue throughout the study period. A sensitive matrix-assisted laser desorption ionization time-of-flight mass-spectrometry (MASS-FIX) mass spectrometry assessment of monoclonal proteins was added to the protocol, which can detect these proteins before they are picked up on standard assays. The investigators have found an almost 3-fold higher positivity rate in higher-risk patients using mass spectrometry than using traditional testing paradigms. Mass spectrometry may be over-diagnosis, but it does enable the identification of a subset of patients with light chain glycosylation who are at risk for amyloidosis, a condition that can lead to life-threatening organ dysfunction.

Finally, to be more widely adopted, screens of high-risk individuals need to be accompanied by actionable interventions to prevent progression and establish biomarkers of disease progression, which is still a challenge. Dr. Marinac's team is launching several intervention trials, including one of metformin. In addition, they hope to use cfDNA liquid biopsy analyses to help risk-stratify patients. However, patients early in their disease course, such as those with MGUS, often don't have enough tumor fraction in the blood, limiting liquid biopsy analyses as an option.

Dr. Sanford Markowitz (Case Western Reserve University) discussed strategies and challenges in non-endoscopic detection of esophageal neoplasia. While esophageal cancer (EAC) incidence is the fastest-growing among solid cancers in the US with a 5-year survival rate of <20% and a death toll that exceeds ovarian cancer, the challenge is that it is rarely detected early. However, detection and ablation of the dysplastic precursor lesion, Barrett's esophagus (BE), can prevent EAC. BE occurs in the distal esophagus, and as premalignant neoplasia does not shed ctDNA. As more than 90% of BE goes undetected and endoscopic screening is not widely accepted, the goal was to develop a biomarker-based method for non-endoscopic detection of BE.

To meet this challenge, Dr. Markowitz's group developed a methylated DNA biomarker panel. They found that methylated vimentin (mVIM), a colon cancer marker, is 90% sensitive and specific in esophagus cytology brushings for detection of BE, as is CCNA1 gene methylation (mCCNA1) using a genome-wide BE screen. These were tested in combination in the EsoGuard panel and found to be negative in biopsies of other common upper-GI pathologies.

In order to test the distal esophagus for the biomarkers, the group developed the EsoCheck device. The biomarker panel is incorporated into a capsule-sized inflatable, tethered balloon (Joe, Amitabh, Sandy Swallowable Sampling [JASSS] balloon) as a comfortable non-endoscopic method to sample the area of interest. The deflated balloon is swallowed and

then inflated in the stomach and pulled back to sample the distal esophagus. The balloon has a structured surface brush for collection of surface cells and is deflated for retrieval. In a clinical trial with 156 patients, the performance of the balloon device was shown to be equivalent to endoscopic brushings. The device was licensed to Lucid Diagnostics, commercialized as EsoCheck, and obtained FDA 510(k) approval. The EsoGuard test panel was awarded the FDA breakthrough device designation. Clinical trials are ongoing to define performance.

The challenge of overdiagnosis remains in distinguishing BE that will or will not progress. To address this, a collaboration with Drs. Papadopoulos, Bert Vogelstein, and others was established to develop a molecular assay for surveillance of BE patients. High aneuploidy is a feature of progressive BE, and progressed dysplastic, aneuploid clones can be identified by testing the brushing using a method to recover DNA from brushings, followed by polymerase chain reaction (PCR) analysis. The group worked out a Barrett Aneuploidy Decision (BAD) Classifier. BAD is in validation trials to demonstrate that identification of "Not-BAD" vs. "Very-BAD" BE allows molecular surveillance and prevention of overdiagnosis and overtreatment of patients detected by BE screening.

In the discussion following the presentations, Dr. Liu was asked about her view of the relationship between CTCs (circulating tumor cells) and ctDNA. She noted that she is working on a manuscript describing analysis of CTC-derived DNA as well as cfDNA from the same tube of blood. Although there are many similarities, there are some alterations identified in the CTCs that are not detected in cfDNA. It may be just a question of sensitivity. She believes that CTCs have a role and may have a different biology.

Dr. Papadopoulos was asked which cancer is going to be most impacted by blood-based detection tools, or in the multi-cancer space where is the biggest opportunity? He responded that studies are needed, as it is not known. But the hope is that the most benefit will be derived by earlier detection of cancers for which SOC or screening tests do not currently exist. Dr. Liu pointed out that another potential benefit is that the multi-cancer tests may broaden the population of screened individuals by including those that don't comply with current screening recommendations.

Dr. Marinac was asked whether they are seeing MGUS progress and whether, when characterizing the cells, they are seeing somatic cellular alterations. Are there germline alterations in the cells with evolution, or is that part of what is being investigated when looking at these high-risk individuals to figure out who's getting bad MGUS? Dr. Marinac replied that when we think about the continuum from MGUS to myeloma, the smoldering myeloma patients are the much more genetically mature cohort that have many of the driver alterations that are seen in overt MM. Similar somatic alterations can be seen in the MGUS phase, but it is more variable, so the key is the study that Dr. Mark Bustoros (Dana Farber) has presented on somatic alterations in the smoldering phase.

Dr. Markowitz and Dr. Papadopoulos were asked about the desired specificity for detection of the conditions they presented, especially given the risks of over-diagnosis already mentioned (i.e., risks of finding disease not needing treatment). They responded that this

becomes a clinical question. The answer is highly disease-specific and depends on the risks of the intervention, the clinical application, the patients, and the type of cancer.

Session II: The Challenges in Diagnosis and Monitoring

This session was chaired by Dr. Lansing Taylor (University of Pittsburgh Drug Discovery Institute).

The first speaker, Dr. Evis Sala (University of Cambridge), talked about novel approaches to improve treatment monitoring in ovarian cancer. High-grade serous ovarian carcinoma (HGSOC) is characterized by extreme genomic complexity and development of resistance to chemotherapy, so remains a major clinical problem with an incidence/mortality ratio that is similar to lung and pancreatic cancer. Dr. Sala discussed treatment response assessment in this disease. Currently, Response Evaluation Criteria in Solid Tumors (RECIST) and CA-125 measurements are widely used, but RECIST measurements are not suited to the confluent multisite heterogenous disease typical in HGSOC and do not distinguish differential responses, either within or between sites of metastasis. The fact that there aren't robust and biologically validated imaging biomarkers for HGSOC leads to poor assessment of treatment response in routine clinical practice and clinical trials. To address these issues, Dr. Sala and colleagues have developed next-generation computed tomography (CT) imaging approaches that involve automated sub-segmentation and quantitative extraction of radiomic features. The radiomic information is derived from sonogram, CD raw data, and images that are reconstructed agnostic to the platforms from different clinical centers. These features are integrated with clinical information, CA-125 measurements, and ctDNA features to capture tumor heterogeneity and improve prediction of responses to treatment in ovarian cancer. Dr. Sala demonstrated that this analyses was optimized through training and validation sets. In a neoadjuvant chemotherapy setting, this approach was used in combination with imaging-guided biopsies to precisely sample the tissue prior to chemotherapy. Application of the integrated data led to better distinction than previous methods between true responders and patients who responded poorly to chemotherapy. The group has integrated image acquisition and analysis into their clinical practice, adding PET-magnetic resonance imaging (MRI). In future planned studies, this work will be expanded to multicenter trials and imaging will be refined to understand the biology of the imaging habitats created on the basis of radiomics features. This information will be used to predict clinical endpoints.

The second speaker, Dr. Jingying Xu (Parker Institute for Cancer Immunotherapy [PICI]), talked about a novel T cell receptor-based cell therapy for H3.3K27M-mutated diffuse midline glioma. These brain tumors are seen mostly in children and young adults, are hard to resect, and have a dismal progress with a median overall survival (OS) of 9–10 months with current treatments. H3.3K27M is a driver mutation, which makes it an attractive target for therapy development. Dr. Hideho Okada (University of California San Francisco [UCSF]) had successfully established a CD8+ T-cell clone specific for H3.3K27M. From this CD8+ T-cell clone, full-length cDNA was obtained and expressed in a retroviral vector. Primary HLA-$A2^+$ T cells transduced with this vector could efficiently lyse HLA-$A2^+H3.3K27M^+$ glioma cells in culture. Adoptive transfer of TCR-transduced T cells also significantly suppressed the progression of glioma xenografts in mice (PMID: 29203539). Based on these preclinical data, PICI, in collaboration with UCSF, developed a manufacturing process to produce clinical-grade engineered CD8+ cellular therapy product appropriate for autologous transfer (Cytotherapy 2019). IND-enabling studies with this

product are ongoing, and a Phase 1 clinical trial in collaboration with the human Pacific Pediatric Neuro-oncology Consortium is planned for 2021. One unique aspect of this trial will be the use of the immunotherapy response assessment in neuro-oncology (iRANO) criteria for tumor assessment, which combines immune-related response and response assessment specifically for neuro-oncology. Biomarker studies using samples collected from tumor tissue, blood, and stool will include immune profiling, single-cell RNA sequencing, TCR sequencing, and whole genome sequencing. These data, together with clinical metadata would be fed into a platform called CANcer Distributed Learning Environment (CANDLE), a deep-learning artificial intelligence (AI)-based model that will enable data integration and enable potential new discoveries.

In the next presentation Dr. Ralph Weissleder (Harvard Medical School) described an alternative to standard image-guided intervention using biopsy guns that provides more rapid and highly multiplexed analysis of single cells in tissue. The procedure involves fine-needle aspiration (FNA) with a much smaller needle to obtain individual cells or cell clusters from a lesion of interest and has a 10-fold lower complication rate. Typically, several needle passes are performed to obtain 10,000 cells, with tumor cells representing 10–30% of the cells collected. The needles pass through the entire 3-D space in multiple directions, and thus are able to sample the entire tumor space. Cytologic analysis can usually be done during the same day. The new platform technology is important for 3 major applications: 1) same-day, rapid diagnostics, such as for fast turnaround-time requirements in hospitals and in global health applications; 2) to analyze cancer cell pathways, such as for same-day clinical trial drug eligibility testing; and 3) for immune oncology, to obtain serial profiling of the tumor microenvironment, as opposed to just a single snapshot at the beginning of the therapy.

The Weissleder laboratory has developed a pipeline for efficient automated clinical single-cell diagnostics including cell harvesting, applying cycling chemistries to analyze 10–40 molecular targets/cell, automated instrumentation, analysis, and report generation, ideally within the same day. Dr. Weissleder described the cycling chemistry platform that uses the multiplexing technologies developed in the Weissleder laboratory: SCANT and the more rapid FAST technology, which uses tri-linkers to attach fluorochromes to monoclonal antibodies. Quenchers are attached adjacent to the fluorochrome to rapidly quench stained sections, followed by restaining with a different set of antibodies. The laboratory has validated a number of antibodies for use in this system to target cancer pathways.

Dr. Weissleder described applications and clinical trial results of rapid cellular analysis in point-of-care settings in breast cancer and in immuno-oncology treatment of head and neck squamous cell cancer with serial monitoring, where the sample analysis could be reported within 1 hour of collection. Dr. Weissleder ended by stating that serial, deep cellular profiling of protein targets is possible in clinical FNA samples, and the FAST/SCANT chemical cycling methods can be used for up to 40 targets per cell. FNAs have a higher technical success rate and a much faster turnaround time then traditional biopsy staining procedures.

The last speaker of the session was Dr. Patrick Brown (Johns Hopkins University Kimmel Cancer Center) who spoke about modern tools for diagnosing and monitoring childhood acute lymphoblastic leukemia (ALL). Diagnostics in ALL uses molecular (to detect chromosomal translocations) and cellular (flow cytometry to identify B- vs. T-cell ALL and markers expressed) methodologies, which have implications for treatment. Molecular and cellular methods are also key in assessing response to treatment. Monitoring initial response to therapy has important implications in treatment decisions, while periodic monitoring post-induction therapy is important to identify relapse. The development of flow cytometry and genetic sequencing has led now to more refined techniques for monitoring minimal residual disease (also known as measurable residual disease [MRD]). Flow cytometry is based on the identification of aberrant cellular markers expressed on the surface of the leukemic cell. Molecular methods for measuring MRD are based on tracking rearranged immunoglobulin (Ig) or T-cell receptor genes in leukemic B or T cells. The sensitivity of PCR-based MRD assays is 10^{-5} cells, while the sensitivity of NGS-based technologies is 10^{-6} cells. MRD is highly prognostic and can be used to stratify patients based on risk and also direct treatment regimens. For example, patients who have MRD may be candidates for novel therapies (e.g., blinatumomab). While MRD-based information has been extensively used in clinical trials, how this marker can be incorporated in routine clinical practice is unclear. MRD measurements, especially by flow cytometry, can be challenging to measure and standardize, particularly when patients are being treated with CD19-directed therapies. While NGS assays are highly sensitive, the clinical significance of low level MRD positivity (0.0001%) is unclear. Lastly, the clinical need for measuring MRD during remission and the clinical significance of detecting it remains unclear, and prospective trials may be needed to address this.

Dr. Taylor moderated the discussion for this session and started by presenting the overarching concept of monitoring spatial and temporal information as measures of heterogeneity in cancers. For solid tumors, this represents monitoring changes in time and space, while in hematologic malignancies, it is primarily changes in time. Dr. Sala talked about the value of CT imaging to correlate pathology samples with the tumor microenvironments as a way of addressing heterogeneity. On the subject of imaging, there was a question about using MRI contrast agents to track autologous T cells in the area of T-cell therapeutics. Dr. Sala noted that there may be opportunities to apply computational powers with machine learning/deep learning algorithms to perform virtual biopsies, which can provide information on the areas and lesions for further biopsies.

On temporal spatial 2-axis sampling and FNAs, the question was asked if heterogeneity was evaluated through a control such as a freshly sized tumor and sampled in 2 axes in multiple locations. Dr. Jonathan Carlson (Harvard Medical School), Dr. Weissleder's colleague, responded that correlative studies on excised tumors processed in a whole biopsy or whole excised fragment, both in mice and in patients, have shown good concordance between the 2-axis FNA samples or the multi-axis FNA samples with overall tissue. Spatial conventional profiling of tumor regions to evaluate the relationship between the FNA sample and any local heterogeneities on the millimeter scale or the subtextual scale within mouse or patient tumors, is yet to be evaluated in detail, and is an area of interest. In the context of cross-fertilization processes, Dr. Sala noted that the pancreas can be imaged well with multi-sequential MRI, and habitats can be derived as with ovarian cancer. Using external and internal metrics to cross match would be a productive area to pursue. The

addition of ctDNA to the prediction model for progression-free survival (PFS) could not improve the model because the location of heterogeneity was not accounted for. Chemical interrogation at the origin of tissues or biomarkers, without physical sampling, is another area of interest and could be a fertile ground for future research.

Beyond looking at dichotomous states (i.e., biomarker + or – cells), Dr. Taylor wondered if modern tools (flow cytometry and the SCANT platform) and/or automated cellular phenotyping algorithms could be used to identify subpopulations or transitional/hybrid cells. Dr. Brown noted that for acute leukemias, cellular heterogeneity within a leukemic population is detectable by flow cytometry and has treatment implications. For example, a tumor with a CD19-dim population may not respond robustly to CD19-directed antigen therapy. Addressing this question from a different point of view, Dr. Carlson noted the importance of using a platform that enables longitudinal monitoring and repeat sampling to characterize as many parameters and subpopulations as possible, with a nuanced approach to understanding the natural evolution of the cells profiled.

The next issue discussed was with regard to lessons learned from ALL and whether they can be translated to other malignancies such as acute myeloid leukemia (AML). Dr. Brown talked about the challenges in MRD detection in AML because it is technically difficult to distinguish a leukemic cell from the background bone marrow environment. Multiple-parameter flow cytometry and some AI-based technologies are now being used by Dr. Michael Loken and colleagues (University of Washington) to overcome these challenges. Risk stratification is now possible through these efforts. All the techniques discussed in ALL are applicable in AML, although the latter is a multistep process, with initiating mutations occurring decades before clinical presentation of AML. Thus, targetable points are challenging to pinpoint.

Finally, the utility of imaging to support FNAs and augment multi-omic biomarkers was discussed. There may be opportunities in the future to use novel technologies coupled with image-guided ways to find biology in specific areas of interest.

Session III: Case Study on Diagnosis and Treatment Challenges: Cancer-Associated Cachexia

This session was chaired by Dr. Roberto Calle (Pfizer), who is also the cochair of the BC Metabolic Disorders Steering Committee (MDSC). Cancer-associated cachexia is an interdisciplinary area of research being pursued jointly by the MDSC and CSC. The speakers in this session highlighted the recent efforts of this cross-functional group.

The first speaker, Dr. Jennifer Goldsack (Digital Medicine Society), talked about digital monitoring, obtained through the use of wearable devices such as Fitbit monitors, and how it could be applied to cachexia. Her talk focused on digital measurements or sensor-generated data that are processed by algorithms to yield clinically meaningful information in the service of human health. FDA-approved remote monitoring products and digital tools are increasingly being used in routine health care and clinical research. There are about 155 unique digital endpoints (including 47 primary endpoints) currently being used in clinical trials of drugs, biologics, and devices. In the case of cancer-associated cachexia, digital monitoring has the potential to provide comprehensive information about patients (beyond what can be gleaned by a physician during a routine clinical visit) that could be used to make clinical and treatment decisions to ultimately improve the lives and outcome of these patients. Explaining the types of digital measurements that would be useful in this context, Dr. Goldsack mentioned gait as a powerful and meaningful high-quality measure of cachexia. A composite measure that includes activity tracking and respiratory rate to complement

gait could serve as a digital companion to measure cachexia. The speaker proposed that the V3 framework (PMID: 32337371) could be used to evaluate whether a digital tool is a fit-for-purpose measure. This framework has 3 steps: verification (how does the digital tool perform using a set of prespecified criteria?), analytical validation (is high-quality data obtainable?), and clinical validation (is the data clinically meaningful?). The modular nature of V3 distributes the evidentiary and documentation requirements across disciplines and organizations and provides for the exchange and coupling of sensor technologies and algorithms based on the context of use. In summary, the V3 framework, while serving as a guide for developers of digital measurement tools, provides a basic set of criteria to enable collaborations focused on bringing forward clinically useful evidence-based remote monitoring technologies to function more efficiently.

The second speaker of the session, Dr. David Thomas (Broad Institute), spoke about the goals of the MDSC and CSC cross-functional Markers of Cachexia in Oncology (MARCO) project. Cancer-associated cachexia is a devastating disease of systemic wasting and multi-organ dysfunction accompanying aggressive cancers, directly leading to profound morbidity and reduced response to primary disease therapies. Cachexia can occur in early disease and correlates with cancer aggressiveness. It is distinctly informative and a good indicator of survival. Dr. Thomas noted that the current consensus criteria for defining cachexia based on weight loss is imprecise, variable, and represents a late manifestation of the disease. There is a need for a precise set of metrics (prognostic, diagnostic, and response biomarkers) and clinically relevant endpoints to expedite drug development and improve treatment outcomes. The MARCO project intends to incorporate several key features, such as high-resolution objective cachexia measurements, to complement classic measures of body weight along with molecular and cellular profiling (blood plasma, markers, tumor genomics) to identify early biomarkers of cancer-associated cachexia. These measurements will be correlated to the cachexia phenotype (measured and monitored using contemporary methods) and ultimately linked to clinical outcomes. The project includes an initial systematic literature review to identify putative biomarkers followed by a retrospective biomarker discovery phase that would leverage existing large clinical trials such as Lung Cancer Master Protocol (Lung-MAP) and BIOmarkers in Patients with Pancreatic Cancer (BIOPAC). Potential biomarkers identified through these efforts will be validated in a phase 2 prospective trial design within the Lung-MAP protocol. The project will solicit FDA feedback on biomarker qualifications and clinical outcome assessment.

During the discussion, Dr. Goldsack talked about regulatory acceptance of remote monitoring devices. She noted that while regulatory colleagues are receptive to digital measures, an FDA guidance document on remote monitoring devices may help to resolve some of the uncertainties. Dr. Teresa Zimmers (Indiana University School of Medicine) noted that cachexia is under-studied, and that the MARCO project has the potential to address the unmet need in this therapeutic area. Dr. Thomas talked about autophagy as a pathophysiologic response to cachexia. Although more research is needed to measure autophagy at a systemic level, he stated that there may be opportunities to use it to complement other measures of cachexia.

Session IV: Case Study on Measurable Residual Disease and the Importance of Early Remission Detection

This session highlighted ongoing efforts aimed at applying MRD in AML and MM trial design and drug development. Chairing the session, Dr. Ola Landgren (University of Miami) emphasized the importance of MRD negativity in MM. A large body of literature, including a meta-analysis from his group (PMID: 27595280) , established that MRD negativity is associated with longer PFS and improves overall survival in MM. Dr. Landgren summarized several recent developments in his laboratory focused on the development of NGS-based methodologies in MM. First, in a large, single-institution study including 438 samples from 251 patients, Dr. Landgren and colleagues found a concordance rate of 92.9% (at a 10^{-5} sensitivity level) between NGS and flow cytometry in terms of predicting clinical outcome (PMID: 33217553). Furthermore, clonal Ig CDR3 (complementarity-determining region) sequences identified at baseline were found to be reliable biomarkers for long-term tracking of the malignant clone, rendering NGS as an optimal strategy for routine clinical use (PMID: 31571261). Besides tracking Ig rearrangements, NGS could also be used to address focal copy number aberrations (CNAs), and to identify frequently mutated genes, further suggesting that this technology is highly suitable for modern clinical applications.

The second speaker of the session, Dr. Jerry Radich (Fred Hutchinson Cancer Research Center), addressed the role of MRD in AML. As with other hematologic malignancies, the detection of MRD in AML is a direct measure of disease burden (and thus, treatment efficacy) and is the strongest predictor of relapse. The challenge of MRD application in AML is that it is technically more difficult to measure and standardize when compared with other hematological cancers. Teams from academia, industry, and government centers interested in the promise of MRD in AML have developed a collaborative project under the CSC that aims to develop, validate, and integrate molecular diagnostics focused on quantitating MRD into AML trials and therapy. The overall goal of the project is to use MRD detection in AML as an informative measure for trial design and drug development. This project will bring together critical players and resources to begin a process whereby new technologies can be efficiently tested against the established benchmarked method (flow cytometry). This effort will integrate with the current NCI AML Precision Medicine Initiative (MyeloMATCH) to bring appropriate technologies to prospective trials. This project will also leverage collaborative efforts between FDA, MyeloMATCH, and pharmaceutical companies to establish testing standards and design clinical trials in order to establish MRD as a surrogate endpoint for drug development. MRD assessment methodologies based on duplex sequencing, digital PCR, and single-cell genomics show promise and would most likely be moved forward for rigorous testing.

Continuing with the theme of MRD in MM, Dr. Dan Auclair (Multiple Myeloma Research Foundation) highlighted recent collaborative efforts initiated by a BC CSC working group. In 2017, this group published a landmark paper (PMID: 28428191) on the role of MRD in improving MM patient care and enhancing the development of new therapies. Current efforts are focused on generating a white paper, with broad input from international academic clinical researchers and caregivers, FNIH, FDA, biotechnology, and pharmaceutical industry representatives, to provide a framework on how MRD and clinical data could be collected during clinical trials to help standardize correlative analysis between differences in MRD dynamics and response. The intention is for trial sponsors to be able to incorporate the findings of this group into ongoing or planned trials, without compromising or interrupting their primary trial's objectives. The planned paper also illustrates the current value of MRD to inform clinical patient care using real-world cases of patients in different settings, including smoldering, newly diagnosed, and relapsed/refractory MM. In each case, the white paper summarizes what is known and key questions to be addressed, such

as the use of MRD status to inform induction, consolidation, and maintenance therapy in MM. In summary, these collaborative efforts will assure that therapeutic advances in MM translate to FDA approval of novel treatments and continued improvement in outcome.

The 3 talks were followed by a short discussion moderated by Dr. Landgren with participation from Drs. Radich and Ken Anderson (Dana-Farber Cancer Institute). Emphasizing the crucial role played by the immune system in eliminating tumors, discussants stressed the value of evaluating the immune/non-tumor repertoire in conjunction with MRD as an important correlate of clinical outcome. In terms of future applications, Dr. Anderson saw the value of MRD in regulatory and clinical settings. He stated that MRD could be used to support new drug approvals both in newly diagnosed and relapsed/refractory settings, but also noted that it is important to use this marker in routine clinical practice. In the case of AML, how MRD can be used in clinical practice remains unclear, partly because it is hard to salvage MRD positive AML even by transplant. There is a need to understand the underlying biology to help distinguish patients who can clear MRD versus those who can't. Targetable pathways to convert an MRD positive patient to MRD negative need to be addressed.

In summary, the value of MRD in predicting clinical outcome is clear. However, rather than defining MRD dichotomously with an arbitrary cutoff, future efforts could be aimed at using it as a continuous variable in trial design and clinical practice.

Session V: Roundtable: Real-World Impact of Regulatory Advancements

This session featured presentations from 5 speakers, reflecting the perspectives of oncologists, patient advocates, FDA regulators, and cancer research foundations on the regulatory advancements to accelerate cancer drug development for patients, and the challenges remaining. The presentations were followed by a roundtable discussion.

Dr. Mark Stewart of Friends of Cancer Research (Friends) provided an overview of several initiatives of Friends that help inform regulatory advancements leading to real-world impacts on patients. Among those is breakthrough therapy designation, which provides a mechanism to expedite the development of drugs that have preliminary evidence demonstrating that the drug has substantial improvement over other therapies. American Society of Clinical Oncology (ASCO) and Friends have collaborated over the past several years to develop recommendations for broadening eligibility criteria for clinical trials, leading to release of five FDA guidance documents. Lung-MAP is an example of using the Master Protocol mechanism for more efficient cooperative trials. The Tumor Mutational Burden (TMB) Harmonization project brings multiple stakeholders together to help facilitate standardization and develop best practices for TMB. A more recent project, the ctDNA for Monitoring Treatment Response (ctMoniTR) project, with participation of FDA and other partners, has produced promising results for ctDNA correlation with survival.

Dr. Merry-Jennifer Markham (University of Florida/UF Health Cancer Center) spoke on the need for targeted therapies for broader populations of patients with gynecological cancers to benefit more patients. To date, the targeted therapy poly (ADP-ribose) polymerase (PARP) inhibitors are the primary drug that has changed the clinical practice for women

with ovarian cancer. Biomarkers are increasingly important in the care of patients with various kinds of cancers, but there is a long way to go with many cancers, especially in the treatment of women with gynecologic cancers. Dr. Markham shared the journeys of 2 cancer patients and their quests to find clinical trials they could be eligible to enroll in for their diseases, with the unfortunate outcome that 1 died, never having had an opportunity to receive a novel therapy because she did not meet the inclusion criteria for clinical trials. Biomarker-driven therapies and diagnostics have benefited many patients, but a large portion of patients who do not respond to existing treatment remain unable to be matched to a clinical trial. The cancer community—researchers, clinicians, regulators, drug developers, and patient advocates—need to continue to work toward the goal that every patient who walks into an oncologist's office has the option to participate in a clinical trial for treatment of his or her cancer.

Dr. Susan L. Weiner (Children's Cancer Cause) spoke on the needs and unique challenges in biomarker development for pediatric oncology. Because pediatric tumors are rare, there is little commercial interest, and industry has never seriously invested in childhood cancer research. Despite the advances in cancer research, biomarker development in pediatric oncology lags behind. Recent advances in technology, data infrastructure, and the pediatric regulatory environment offer multiple opportunities to advance understanding of pediatric oncology biomarkers and to bring precision oncology into the clinic for children. Data on new potential therapeutic opportunities for children will substantially increase in the coming years as a result of the Research to Accelerate Cures and Equity (RACE) for Children Act, enacted in August 2020. The potential to bring precision pediatric oncology into the clinic is more exciting now than ever, but a mechanism or structure is needed. A partnership of all the stakeholders in the childhood cancer community and a commitment of substantial support from industry would be critical. Additional resources from NIH and from large academic centers constructed as open access data commons should be part of this partnership. Over the past decade, the efforts from patients and family advocates as stakeholders have resulted in the passage of new legislations and increases in research funding to improve pediatric oncology research and patient care, and their continued involvement is crucial to realizing the vision of precision oncology for children.

Dr. Michelle Tarver (FDA, CDRH) spoke on the CDRH 2018–2020 strategic priority and collaborative communities. A collaborative community is different from a task force, which is usually initiated by a government entity to tackle an acute issue of a single concern for a limited duration. A collaborative community is convened by an external partner, and FDA may be a member of the community, contributing like other members. A collaborative community has a broad scope to address a long-standing issue and requires sustained engagement by stakeholders to advance the effort. It may have multiple deliverables for the various work streams for a sustained period of time. To provide guidance to stakeholders, CDRH lays out the best practices for establishing and maintaining collaborative communities. Potential outcomes of a collaborative community include tool development, peer-reviewed publications, research agendas and projects, white papers, studies informing health-care coverage and reimbursement decisions, best practices, templates or frameworks, and improved relationships among stakeholders. CDRH has developed criteria for considerations for participating in a collaborative community, and has a simple process

to receive, review, and act on an invitation from an external stakeholder to engage in a collaborative community. CDRH currently participates in 6 collaborative communities with a broad range of topics, and recently joined 3 others. Some of them have started to produce results, including the Collaborative Community on Ophthalmic Imaging and the International Liquid Biopsy Standardization Alliance.

Dr. Stacey Adam (FNIH) shared FNIH experience on the Accelerating COVID-19 Therapeutic Interventions and Vaccines (ACTIV) partnership, which was launched in April 2020 in response to the COVID-19 pandemic. The mission of this project is to develop a coordinated research response to speed COVID-19 treatment and vaccine options. The ACTIV partnership consists of 4 fast-track focus areas, consisting of working groups and subgroups, with membership of both public- and private-sector representatives to oversee tactical operations on vaccine evaluation, preclinical treatment development, clinical trial capacity, and clinical testing. The Master Protocol clinical trial design was established and implemented in clinical trials to accelerate the clinical evaluation of promising therapeutic candidates. Thus far, the ACTIV partnership has evaluated more than 500 available agents and prioritized the most promising agents for further study; it assessed, designed, and harmonized 5 Master Protocols; selected clinical trial networks best suited to execute these Master Protocols; and supported NIH efforts to launch them. Five ACTIV protocols for phase 2 and 3 trials have been launched to date. To optimize the resource utility, ACTIV established clinical population prioritization schema. ACTIV conducted the media campaign and engaged with communities to reach and recruit patients. The rapid design and deployment of ACTIV Master Protocols benefited tremendously from FNIH's prior experience with Master Protocol designs, such as Lung-MAP. ACTIV demonstrated once again the effectiveness of partnerships to move things forward in a time of great need.

Roundtable Discussion

The roundtable discussion centered around challenges and barriers for drug development, especially for gynecologic and pediatric cancers, which face more hurdles than some of other cancers. Also discussed were the need for making clinical trials more accessible to patients, and the important role multi-stakeholder partnerships can play to tackle these difficult issues. The experiences gained from the COVID-19 response and the infrastructures built may also help the cancer community in the future.

What are the possible reasons that it has been challenging to find effective targeted therapies and biomarkers for gynecologic cancers? One of the challenges is that these diseases are not talked about publicly as much as other cancers, such as breast cancer or colon cancer. There are barriers and stigma to overcome with gynecologic cancers, which may also have impacted advocacy efforts.

What are the barriers and challenges that prevent patients from participating in clinical trials? How can these be overcome? Stringent eligibility criteria prevent many patients from participation. Broadening eligibility criteria for certain parameters, such as age and lab results, has been helpful to some degree to get more patients on trials. Other real-world barriers include patients' lack of financial and logistic resources. A holistic approach is

needed to ensure that trials are practical and that the eligibility criteria balance scientific rigor and the needs of real-world patient populations. It is important to involve patients and patient advocates in the trial development from the beginning, and to educate patients about clinical trials and how to participate as clinical trials are being developed and rolled out through the regulatory processes.

In forming partnerships to tackle more challenging questions, how do we get stakeholders together to collaborate to share data or other resources? Working toward a common goal of high clinical relevance that aligns with each member's needs and creating an environment where everyone trusts each other is the first step toward sharing data, ideas, and solutions. Partnering with all stakeholders, including FDA, may produce results of broader impact to the field and reduce investment risk. In the case of pediatric drug development, a safe harbor organized by a foundation is a suitable mechanism where precompetitive programs take place and all stakeholders share risk.

How do we translate the results from these partnerships into accelerating real advances for patients faster? In response to COVID-19, many barriers to advancing clinical studies have been removed. We can build on this, be creative, and continue advancing these areas post-COVID-19, including use of electronic health records (EHRs) and the decentralized clinical trial setup. For these initiatives to happen, resources and funding are necessary from individual collaborators and from other sources, such as the federal budget.

There is currently no COVID-19-related trial for which children under 13 are eligible. What incentives are needed to bring pediatrics to the forefront for cancer or other diseases? For COVID-19, it is likely that such a clinical trial will happen naturally. One of the biggest challenges in cancer is that the trials need to be international, but the regulations are not concordant across the regulatory agencies, raising serious challenges in efficiently managing the trials. Additionally, benefits and risks need to be carefully weighed before radical therapies are introduced to children. The model of decentralized trials may be tested in a small consortium environment to evaluate how and under what circumstances decentralized trials would work for future studies to accelerate the development of pediatric oncology indications. The current regulation in the RACE for Children Act is essentially repurposing adult drugs for children. But there is a core of pediatric tumors that is unique to children. There needs to be a strategy, a regulation, and an incentive apparatus to address the gap where there is no associated adult market for agents.

Will the infrastructures developed for COVID-19 programs be maintained for future use? ACTIV took advantage of and repurposed the existing clinical networks, including networks for HIV/AIDS, other infectious diseases, and cancer. It linked existing networks and brought new community sites into these networks. These infrastructures and clinical networks built for COVID-19 patients will be maintained and could be repurposed for future use. Additionally, communication tools developed for the COVID-19 pandemic would be useful for outreach to hard-to-reach cancer patients within the cancer community to complement the existing cancer outreach programs. It is critical to get into diverse communities through making connections with local community organizations to reach patients.

Keynote: "Some Cancer Research Advances, Challenges, and Opportunities" – Douglas Lowy (NCI)

The theme of Dr. Lowy's talk was applying what was learned from the COVID-19 pandemic to positively impact cancer screening, research, and treatment. Although the pandemic has affected the progress of most cancer research and delayed clinical trial accrual and reporting of outcomes, it has also led to the widespread adoption of telemedicine and greater flexibility in clinical trials, which, if efficiently harnessed in the future, could better serve underserved communities, and seamlessly integrate with clinical practice. Although cancer screening rates fell in 2019, integration of cancer screening efforts with SARS-CoV-2 immunization programs and supporting research to enable home cancer screening may represent public health opportunities to overcome the backlog and delays caused by the pandemic. Improved data collection using modern technologies and the use of RWD will aid in understanding the impact of cancer treatments. For example, the NCI Surveillance, Epidemiology, and End Results (SEER) Program, in collaboration with the US Department of Energy, is developing natural language processing and real-time automated extraction of data elements to increase patient-level data in SEER. These technologies could improve the utility and relevance of the SEER database by linking cancer outcomes with treatment.

Keynote: "Towards a World Without Disease" – William Hait (Johnson & Johnson)

The "world without disease" effort focuses on prevention, interception, and early curation of disease to restore good health, with the hope of "immorbidity," a new term coined by Dr. Hait and colleagues. Immorbidity is defined as "aging in total freedom from disease or sickness." Advances in healthcare have increased longevity; however, the incidence and impact of accumulating disease burden has also increased, and interception of disease means stopping the process of disease causation. In the cancer drug development paradigm, there is a paucity of clinical trials for the in situ and prevention space, attributed to myths of increased costs of chronic drug use and irrecoverable costs of development, unachievable safety benchmarks, and approval hurdles. Addressing the issues of insufficient diagnostics to identify individuals at greatest risk, and the lack of validated targets or surrogate endpoints, can bolster investments in premalignancy research. There is regulatory precedent for approvals based on surrogate endpoints, along with substantial clinical benefit and favorable risk-benefit profiles, rather than overall survival alone, which makes up for long and costly clinical trials. For prostate cancer, FDA convened the Oncology Drugs Advisory Committee, from which came the potentially approvable surrogate endpoint of "metastasis-free survival." Apalutamide approval for non-metastatic castrate-resistant prostate cancer was based on this, as a primary endpoint. For type 1 diabetes, interception can occur before insulin dependence, with beta cell synthesis and release of insulin and precursor C-peptide as an FDA-approved surrogate and biomarker of disease progression. For the lung cancer initiative, the chronic inflammation pathway to disease is intercepted with canakinumab and showed decreased lung cancer incidence. Pulmonoscopy for premalignant nodules, and removal, can also aid interception.

Session VI: Biomarkers Consortium Project Updates

Dr. Joe Menetski and Mr. Steve Hoffmann (FNIH) provided an overall introduction to the BC. Dr. Menetski spoke about how the structures and foundational work that the BC put in place have made the BC consistently successful since its inception in 2006 in fulfilling its mission and goals. The public-private partnership research collaborations created and managed by the BC during the past 13 years have made significant contributions to the field of cancer research in multiple aspects, and the number of BC member organizations is steadily growing. The BC specializes and thrives on complex collaborations that cannot be achieved through other mechanisms. The Advanced Metrics and Modeling with Volumetric CT for Precision Analysis of Clinical Trial Results (Vol-PACT) project sponsored by BC is a great illustration of a complex project that contains many moving parts. The BC has established a structure throughout the life cycle of a project with governance, policy management, program management, fundraising and relationship management, project management, and intellectual property management. A successful project has a focus on the group goal, has a true partnership with all stakeholders, and is based on the best science. To reduce the barrier to success, BC efforts are devoted to the foundational work in the front end anticipating and addressing potential issues so that once the project is started and running, it is streamlined. Beyond individual projects, private-sector members of the BC, BC Executive Committee, and Steering Committees are valuable resources for member institutions to generate additional collaborations.

Mr. Hoffmann shared the BC experience regarding criteria for successful projects. The main characteristics that make BC projects successful include the following: addressing significant unmet scientific and medical needs with solid scientific and rational design, leading to significant improvement in the drug development process; focusing on critical gaps and impact on public health/patient care; having goals that are achievable in a specific time frame; leveraging pre-existing resources whenever possible; generating required funds and stakeholder support; having synergism and not duplicating other initiatives; and benefiting from a multi-stakeholder approach. Most success occurs in projects that focus on the BC mission to validate and qualify biomarkers and to develop drug-development tools that impact regulatory decision making. The BC worked closely with FDA to establish an evidentiary framework on biomarker qualification and uses this framework to guide projects. The goals and impact of BC projects depend on the stage of biomarker development, with the understanding that FDA biomarker qualification is a high bar; therefore, not every project is designed to achieve that goal. Projects can have other deliverables, such as creating tools to optimize clinical trial decision-making, producing guidelines, and improving disease definitions. These considerations are reflected in the current CSC project portfolio and the collaborative projects across BC steering committees. Two examples that illustrate the profound impact of the foundational projects under the BC are the kidney safety project, which led to FDA qualification of the first clinical safety biomarker, and the sarcopenia project, which developed the first evidence-based definition of sarcopenia, allowing prediction of meaningful patient outcomes. The Vol-PACT and ctDNA reference standards projects follow the same path.

Drs. Larry Schwartz and Tito Fojo (Columbia) reported on the progress of the Vol-PACT project and outlined the proposed next steps. This collaborative effort was initiated in 2016, with participation by investigators from 5 institutions and 10 pharmaceutical company partners who provided financial support as well as access to Digital Imaging and Communications in Medicine (DICOM) images and clinical data from 12 completed phase 3 trials that were intended to support FDA drug approvals for various oncology indications, including colorectal cancer, renal cell carcinoma, non-small cell lung cancer (NSCLC), and melanoma. The project aims to develop novel imaging-based phase 2 clinical trial endpoints in solid tumors to improve prediction of phase 3 outcomes by the current RECIST method. It employs 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 prediction by 3 different approaches: tumor growth kinetic modeling, partly conditional modeling, and radiomic signatures. Metrics developed by all 3 approaches outperformed RECIST in predicting survival, and some of these metrics can be generalized across different cancer types. Three publications have been produced from this project, and more are in development. After successful completion of this phase of the project by the end of 2020, the project team is looking to move to the next phase of metric development by building on these findings to further develop and refine these metrics toward prognostic, response, or surrogate biomarker(s) that can achieve biomarker qualification through the FDA biomarker qualification program as a clinical trial endpoint.

Dr. Robert McCormack (Independent), the next speaker of the session provided an update on the ctDNA Quality Control Material (QCM) Project, which was initiated in 2019. Although the potential for clinical use of ctDNA has been demonstrated across multiple cancers in different clinical settings, the absence of well-validated QCM for ctDNA testing causes inconsistencies in interpreting and translating ctDNA results into clinical actions. The project aims to characterize 3 sets of QCM to assist in advancing the clinical validity and utility of ctDNA measurements. The project plan was presented by Dr. Mickey Williams (NCI), who explained the objective and provided a status update for each of the 3 phases of the project—Phase I, Performance Evaluation; Phase II, Functional Characterization; and Phase III, Clinical Pilot. In Phase I, QCM with 14 clinically relevant mutations representing single nucleotide variants (SNVs), insertion/deletions (indels), translocations, and copy number variants (CNVs) were sourced from 3 QCM commercial manufacturers with variant allele frequencies (VAFs) of 5%, 2.5%, 1%, 0.1%, and 0%. The 3 QCM mixtures were tested in 2 allele-specific droplet digital PCR (ddPCR) and 3 (amplicon and hybrid capture) NGS assays across 4 laboratories. Each of the 4 laboratories assayed each blinded aliquot in quadruplicate to assess assay sensitivity, specificity, linearity, and precision for the specific variant loci. The selection of the variants for the QCM was based on input from a large group of experts in the field and included SNVs, indels, CNVs, and translocations. The specific variants were chosen because they are known to be clinically relevant, analytically challenging, and found in multiple different cancer histologies.

The 2 ddPCR assays in this study reported VAF values close to the reported measurements from the 3 QCM manufacturers for all variants. Most SNVs and indels, but not translocations, tracked closely to the expected NGS-measured VAFs. Two NGS assays

reported lower VAF than expected for all translocations in all 3 QCM mixtures. *ERBB2* copy number amplification and detection varied across assays. The data from the 0.1% VAF level demonstrate drop-outs in all assays across all variant types, suggesting that the 3 different QCM could serve for testing of assay limits of detection (LODs) with associated confidence claims for the specific variants. In conclusion, the results of this validation study indicate that the QCM are suitable for determining performance characteristics of a laboratory's ctDNA reagents and technology, though unique interactions with a specific laboratory's assay system and/or specific QCM may require testing of multiple QCM to find the best-suited reagents for accurate result interpretation.

Phase II of the project, expected to start in Q1 of 2021, will evaluate the comparability of QCM performance to clinical samples. This a 2-part study design in which part 1 will test QCM and real clinical samples (near the LOD of the ctDNA assay) in an NGS assay using variants *EGFR L858R* (SNV), *EGFR Ex19del* (indel), *ERBB2* (CNV), and *ALK* (fusion). Part 2 will test the quantitative range of different assays (probably 2 NGS panels and 1 ddPCR) by comparing the linearity of dilutions of the contrived QCM with real clinical samples. Normal human donor plasma will be used as the diluent for the clinical samples, given the large amount needed for the experiments, and the fact that the origin of most of the cfDNA in both heathy individuals and cancer patients is from leukocytes undergoing apoptosis.

In Phase III of the project, expected to start in Q2 of 2021, these QCM will be first used as positive/negative controls for ctDNA genotyping and then tested against clinical samples to demonstrate comparable performance. Regarding timeline, Phase I testing is complete and a manuscript summarizing the results will be submitted for publication shortly. Phase II is scheduled to start in Q1 of 2021 and Phase III in Q2 of 2021.

Dr. Daniel Hayes (University of Michigan), the last speaker of this session, reviewed the history and evolution of concepts for bringing tumor biomarker tests (TBTs) into the clinic over the last 15 years. This involved efforts by several investigators to standardize criteria for validating TBTs. While exciting new technologies for TBTs have been developed, the roadmap for bringing them into the clinic can be challenging, and the clinical utility of TBTs remains unclear in several instances. For example, a TBT may be approved or cleared by the FDA without clear demonstrated benefit for patients; moreover, unapproved laboratory-developed tests may not be evaluated by any regulatory body with the exception of the Centers for Medicare & Medicaid Services under Clinical Laboratory Improvement Amendments, even though they provide important information. Addressing this issue, Dr. Steven Teutsch and colleagues first proposed the 3 critical semantics for TBTs (PMID: 18813139), which included analytical validity, clinical validity, and clinical utility; these were widely adopted. The FNIH BC efforts to characterize QCM greatly support the first piece of crucial evidence, i.e., analytic validation. In order to determine if a tumor marker has clinical utility, Dr. Dan Sargent (Mayo Clinic) and colleagues proposed a prospective clinical trial design (PMID: 15774793) in which the tumor biomarker's clinical utility for a specific use is the main objective of the study. To generate criteria equally rigorous but logistically more acceptable, Dr. Hayes, with Drs. Rich Simon (NCI) and Soonmyung Paik (Yonsei University), suggested "prospective retrospective" analyses using archived specimens to generate high levels of evidence for a TBT (PMID: 19815849); the

criteria have been adopted in guidelines from organizations including ASCO and CAP. In an effort to address the inconsistent regulatory environment, Dr. Hayes collaborated with other representatives across the spectrum to generate a set of proposals to address the inconsistencies (*Hayes, DF, et al., Sci Transl Med 5:196cm6, 2013*). Addressing the other issue of clinical utility, In collaboration with Drs. Michaela Dinan (Duke University), Gary Lyman (University of Washington), and Richard Schilsky (ASCO), developed a tiered system of reimbursement determination based on the relative value of a TBT (*Dinan, MA, et al., JCO Precision Oncology 1-10, 2019*). Concluding his presentation, Dr. Hayes noted his recent manuscript *Hayes, DF, Journal of Clinical Oncology, in press*) discussing important considerations including context of use, endpoint, and the magnitude of effect within the endpoint that would be necessary to determine clinical utility of a TBT.

Keynote: "Learning from Every Patient: The ASCO Research Enterprise" – Richard Schilsky (ASCO)

Dr. Schilsky talked about the ASCO research enterprise, which encompasses 4 domains: research policy and practice; member surveys data library; pragmatic clinical trials (Targeted Agent and Profiling Utilization Registry [TAPUR]); and generating RWD. In the area of research policy and practice, ASCO has worked on policies and recommendations regarding clinical trial design, oversight, reporting, translation, and execution. Of note, ASCO has collaborated with Friends of Cancer Research and FDA in broadening eligibility criteria to make clinical trials more representative of the intended patient population. The ASCO data library includes content from ASCO meetings, survey data regarding oncology practices, and annotated glioblastoma clinico-genomic data. CancerLinQ is a big-data platform that collects, analyzes, and makes available electronic health records from participating practices across the country. It is driven by the vision of learning from every patient with cancer and uncovers unseen patterns in patient characteristics and outcomes with a goal of revealing opportunities to improve the quality of care. The COVID-19 in Oncology Registry is another real-world initiative of ASCO to assess the impact of the COVID-19 pandemic on cancer patients. In the area of clinical trials, TAPUR is ASCO's pragmatic clinical trial to evaluate molecularly targeted cancer drugs and collect data on clinical outcomes.

Keynote: "Update of mCODE" – Monica Bertagnolli (Dana-Farber/Brigham and Women's Cancer Center)

In the second keynote presentation of this session, Dr. Bertagnolli spoke about the Minimal Common Oncology Data Elements (mCODE) initiative developed through a working group convened by ASCO that included oncologists, informaticians, researchers, and experts in terminologies and standards. mCODE refers to a core set of common data elements for cancer that is standardized, computable, and clinically applicable in every electronic patient record with a cancer diagnosis. The data elements are structured around 6 distinct domains: patient, laboratory/vital, disease, genomics, treatment, and outcome. mCODE is managed through a community called Common Oncology Data Elements eXtensions

(CodeX) whose mission is to accelerate interoperable data modeling and applications, leading to step-change improvements in cancer patient care and research. As a pilot use case for mCODE, a collaborative project called ICARE is being developed by The MITRE Corporation, ASCO, and the NCI to integrate clinical data captured via the electronic health record with data obtained during conventional prospective cancer clinical trials to validate the use of mCODE as a tool for clinical research. Future efforts are aimed at expanding mCODE beyond oncology to create a universal taxonomy of disease that can be used broadly by the clinical community. As a step toward that goal, mCOVID and mCARD are data elements being developed for COVID-19 and cardiology.

Session VII: Data-Driven Problems and Data-Driven Solutions

This session highlighted initiatives that attempt to leverage the power of big data. The session chair, Dr. Shawn Sweeney (American Association for Cancer Research [AACR]), established the underlying theme of learning from every person/patient to solve problems using big data and highlighted the CSC initiative of drafting a guidance document to address issues related to data access, integration, and quality.

The first speaker of the session was Dr. Bill Louv (Project Data Sphere [PDS]), who talked about PDS, an open-access, data-sharing platform created through a nonprofit initiative of the CEO Roundtable on Cancer. Dr. Louv discussed the focus and mechanics of this initiative. Attempting to maximize the use of clinical trial data, this initiative provides a secure platform for researchers to access de-identified patient-level clinical data to catalyze patient-focused cancer research and accelerate the development of new therapies. SAS provides secure data mining and machine learning tools within the PDS environment. In close collaboration with FDA's OCE, 4 data-driven research programs (Rare Tumor Registries, Immune-Related Adverse Events, External Control Arms, and Images and Algorithms) have been initiated to foster collaborative research communities and address pressing issues in cancer research.

Dr. Sweeney, the second speaker, emphasized the need for "end-to-end learning health care systems" to ensure the success of precision oncology. The critical requirement for large amounts of data to fuel health care systems provided the impetus for Genomics Evidence Neoplasia Information Exchange (GENIE). A publicly accessible international cancer registry of RWD assembled through data sharing between 19 leading cancer centers across the world, GENIE aims to improve clinical decision making by linking clinical genotypes to outcomes. Several open-source technologies allow GENIE to share and analyze data safely and securely both internally and externally. The Synapse platform from Sage Bionetworks provides data versioning and provenance control and serves as the primary data hub for the consortium. The open-source Research Electronic Data Capture system enables clinical data to be captured in a relatively consistent format. All data are exported into cBioPortal for data genomics, an open-access platform for data visualization and analysis. PRISSMM (Pragmatic Implementation of Phenomic Data Standards for Curating Outcomes of Cancer Treatment) is an AI tool to extract real-world outcomes from retrospective RWD. To accelerate the speed of clinical data collection, GENIE recently created a collaboration of 9 pharmaceutical companies to work precompetitively to generate deep clinical annotation on specific cohorts.

The third speaker, Dr. Frank Meng (Boston University School of Medicine and VA Boston Healthcare System), shed light on the US Department of Veterans Affairs' (VA's) efforts

aimed at data aggregation, curation, and sharing. The VA system of data capture is enabled by an advanced scalable clinical information system (Veterans Health Information Systems and Technology Architecture), while the VA Informatics and Computing Infrastructure facilitates analyses of VA data in a secure environment. Data-related initiatives undertaken by the VA include efforts by the Cooperative Studies Program to capture data for clinical trials and other epidemiological studies, the Million Veterans Program to collect germline sequencing data and patient reported demographics, and the National Precision Oncology Program to collect tumor tissue sequencing data for tailoring oncology treatment based on individual patient characteristics. Data-sharing efforts undertaken by the VA include the Research Precision Oncology Program, which provides a mechanism for patients to consent to broad data sharing for research purposes, and the Applied Proteogenomics Organizational Learning and Outcomes Network to incorporate proteogenomics into patient care. The application of big data requires a workforce with an in-depth understanding of data science and informatics. Meeting this need, the VA, in collaboration with NCI, has initiated a Big Data-Scientist Training Enhancement Program focused on training a new generation of "hybrid" clinical scientists empowered with the ability to use data in clinical research. This program creates an in-house data science capability with the goal of increasing the utility of the data being shared with external investigators and clinicians.

The last speaker of the session was Dr. Diana Merino Vega (Friends of Cancer Research). Dr. Vega spoke about ctMoniTR, a multi-stakeholder initiative involving academia, industry, and FDA that seeks to standardize ctDNA assessment and accelerate the collective understanding of ctDNA as a treatment-monitoring tool. The first phase of the project addressed the feasibility of pooling and harmonizing ctDNA data from patients with NSCLC treated with an immune checkpoint inhibitor, with the goal of determining whether promising trends observed in smaller data sets could be replicated in larger, more robust data sets. The criteria used for data collection included the presence of tumor response and outcome data, with a minimum of 2 ctDNA measurements (1 at baseline and 1 or more follow-up samples) reported as variant allele frequency. Data from a total of 200 patients enrolled in 5 studies comprised of a total of 7 cohorts were aggregated and analyzed. Results indicated that ctDNA measurements could predict clinical benefit with checkpoint inhibitors in patients with advanced NSCLC, suggesting that it could potentially serve as a candidate surrogate marker. Future efforts will focus on validating this association in different clinical settings. The long-term objective of the project is to drive regulatory innovation for more efficient drug development and to improve patient care.

During the discussion session moderated by Dr. Sweeney, Dr. Vega listed strategies to promote collaboration between different stakeholders. A common understanding of the problem being solved and an overall goal in sight were identified as important factors. Dr. Vega also highlighted that involving all parties in the design and statistical analyses helps make the various parties more amenable to data sharing, and that ensuring data security and establishing expertise in terms of data analyses is also key. With an abundance of AI tools, Dr. Louv felt that the challenge is not how to analyze data, but rather how to gather more data. Dr. Sweeney noted the importance of the data being fit for purpose; not all data can answer all questions and it is important to interpret the context of the issue being addressed.

Identifying Intellectual property as a potential barrier in data sharing, Dr. Louv felt that the reticence around sharing data is not limited to for-profit companies but is also an issue with academic institutions who want to publish the data before they are willing to share it broadly. While these reservations are understandable, they need to be balanced against the greater good of sharing data, since combining and aggregating data may allow certain inferences to be made that may not be possible otherwise. In an attempt to identify potential solutions to overcome some of the issues surrounding data sharing, the participants discussed federated data systems, particularly for sensitive data (e.g., clinical, genomic, and imaging data). With this approach, users are able to apply their algorithm to analyze the data but the data never leave the firewall. Given that institutions have a huge responsibility to protect clinical data, it was suggested that they may be more open to federated approaches for sharing data.

Prospective vs. retrospective studies was the next topic discussed. The general consensus was that retrospective studies can be analyzed in a timely manner, and that they contain a large amount of historic data, although harmonizing the data could be challenging and some key information could be missing. These issues can be fixed, and standardized data can be collected in prospective studies, but these studies require more time. In essence, both prospective and retrospective studies are useful, although each provides a different lens on a tough problem.

The discussion session ended with the participants expressing their views on sustainability in data-sharing initiatives. Dr. Louv suggested a community or group of like-minded entities could serve as data stewards while recognizing that this endeavor could be resource and capital intensive. As a patient advocate, Dr. Vega talked about the need to have mechanisms to ensure data privacy and suggested that explaining to patients how their data is being used and what mechanisms are in place to protect their privacy may make them more comfortable with sharing their data.