Cancer Steering Committee Annual Scientific Symposium
October 27–28 and November 3–4, 2022
EXECUTIVE SUMMARY

Day 1, October 27, 2022, 1:00 – 4:45 PM ET

FNIH Welcome
Dana Connors, MSc, Senior Science Project Manager for Cancer Research Partnerships, Foundation for the NIH (FNIH)

The FNIH was founded by Congress in 1990 to support the mission of the NIH by developing public-private partnerships (PPPs) for biomedical research. The FNIH manages partnerships from design through implementation by establishing clear governance and policies, building programs in coordination with partners, and managing fundraising efforts. The FNIH has raised over $1.5B and supported more than 600 programs. As part of FNIH, the Biomarkers Consortium (BC) works closely with research and regulatory agencies to move biomarkers through the validation and qualification process for use in drug development and patient care. BC achievements include tools developed in coordination with the FDA, guidance that has helped support biomarker development, and many publications. BC membership is diverse, representing large and small companies, trade groups, not-for-profit organizations, and patient-advocacy groups. The BC is organized into steering committees, including the Cancer Steering Committee (CSC), that form working groups and project teams to develop projects centered around biomarker development. The goal for the annual BC CSC Symposium is to develop new collaborative project ideas.

Welcome and Overview
Gary Kelloff, MD, CSC Co-Chair, National Cancer Institute (NCI)

The development of complex biomarkers faces challenges in several areas, including cancer biology, standards development, strategy integration, and pre-competitivity. The BC is focused on translational issues in these areas. Two areas that have seen growth are the development of serum/plasma biomarkers and digital pathology.

Active CSC efforts addressing liquid biopsy and other complex biomarkers include projects addressing validation of circulating tumor (ct) DNA quality control materials (QCM) and measurable/minimal residual disease (MRD) in acute myeloid leukemia (AML). The CSC also organizes the International Liquid Biopsy Standardization Alliance (ILSA). Other areas to watch in cancer biomarker development include the roles of big data and surrogate endpoints in clinical utility.

Opportunities in early detection and intervention may provide the best chance for better outcomes. These include advances in screening technology with liquid biopsies, image-guided intervention in focal disease, and drug and immune intervention. Examples are the multicancer early detection (MCED) liquid biopsy platforms and the Cancer Research Screening Network and VANGUARD study from the NCI Division of Cancer Prevention.

The CSC has two new co-chairs: Dr. Geoffrey Oxnard, Vice President, Foundation Medicine, and Dr. Emmett Schmidt, Vice President of Clinical Research, Merck Research Laboratories.

Keynote Presentation: Pairing T Cell Receptor α/β Genes, Antigen Specificity, and scRNA-seq Phenotyping Across Large Patient Populations for Cancer Immunotherapy
James Heath, PhD, Institute for Systems Biology

Dr. Heath discussed his research identifying CD8+ T cells that are specific to tumor antigens. His laboratory studies the Major Histocompatibility Complex (MHC) antigen and T cell receptor (TCR) complex in pursuit of patient-specific TCR-engineered therapies for treatment of solid tumors with immunotherapy (IO).

T cells engineered against a patient's neoantigens can target solid tumors and promote tumor killing. Clonal expansion of antigen-stimulated cells appears to promote a cross-reactive NK-like phenotype that is potentially immunosuppressive and apoptotic. This may be a mechanism to promote T cell diversity against a target and may be a general phenomenon.

Comprehensive analysis of clonally expanded T cell responses may cause the field to re-evaluate the "quality" of an immune response and how one evaluates T cells for cancer immunotherapies.

SESSION 1: Biomarkers from Real World and Other Big Data

The session covered the status and future needs to make wearable technology clinically useful. Panels discussed the role of data science and using data from public resources to create biomarkers and the role of public-private partnerships in bringing innovative products to the clinic.

Wearable Technology, Remote Sensors, and Patient Monitoring
Moderator: Mike Espey, PhD, NCI

Talk: Using Data from Wearables and Remote Sensors to Define Biomarkers for Patient Selection and Treatment Monitoring
Chris Hartshorn, PhD, National Center for Advancing Translational Science (NCATS)

Digital health technologies may lessen the impact of factors such as distance from medical centers and improve access to care for medically underserved populations. Digital health technologies may result in more objective understanding of adverse events and provide additional data to complement assays and biomarkers. Tools developed recently include wearable sensors for remote patient monitoring that can enhance understanding of perturbations, decentralize clinical trials helping to address healthcare disparities, and enable in-home testing to be the point of care for low-resource clinics.

Until recently, these technologies were used in a small number of clinical trials, due in part to implementation challenges and the need for validation. NIH funding is available for development of digital health technologies, and several initiatives for discovery science request use of digital technologies and wearables. The FDA released Draft Guidance for using digital health technologies for remote data acquisition in clinical investigations.

Panel: Wearable Technology, Remote Sensors, and Patient Monitoring
Moderator: Mike Espey, PhD, NCI
Panelists: Chris Hartshorn, PhD, NCATS; Karen Mustian, PhD, MPH, University of Rochester; Steven Hoffmann, MSc, FNIH

Ideally, digital technologies would interact as a suite of sensors and modalities that generate data to be aggregated into an accurate assessment of patient status. Given that the complexity of evaluation of the different signals, Dr. Espey asked the panel how to integrate signals to generate a clinically useful product. Dr. Mustian suggested field training to address challenges of using the technologies in multi-center trials and encouraged creation of user-friendly devices and integration of technologies into a single device to read several functions per patient.

Mr. Hoffmann described work supported by the BC in individual general health monitoring; clinical decision making; and analytical validation and clinical correlation to meet standards for drug development. The FDA and BC have hosted workshops focused on biomarker qualification, including evidentiary criteria and security, and how these differ for remote technologies. These considerations are reflected in FDA guidance. A subsequent workshop was held on patient-centric design. The development and implementation of technologies may occur in a stepwise fashion, focusing on different elements linked to different criteria for COU.

The panel discussed standards for incorporating wearable data into real world data collection. Dr. Hartshorn noted a standardized core set of metrics would be valuable for validation. The group discussed whether each patient could serve as their own control. Lastly, making resources available would be helpful for researchers implementing programs.

Predicting Patient Outcomes Using Clinical Trial Data
Talk: Can Data Science Help Cure Cancer?
Andrew Lo, PhD MIT

Dr. Lo studies the role of finance in drug development, the worth of a cancer drug, and how to make the drug development process more efficient. He discussed the MIT Project Analytics for Life Sciences Professionals and Healthcare Advocates (ALPHA) developed by his team.

Dr. Lo defined the expected value of a drug candidate in terms of the expected profits of the approved drug, the probability of success (PoS), and the cost of development. PoS has been suggested to be ~ 10-16%, but this remains unclear. To better

understand PoS, Project ALPHA used a robust data set including 20 years of information from 15,000 compounds and 5,700 companies to calculate historical PoS rates. AI tools can also be used to forecast clinical trial outcomes and the likelihood of approval using >200 features including drug classification, trial design, and sponsor. The team found that drugs with larger calculated probabilities of approval were more likely to be approved. In a collaboration, Novartis data science teams attempted to beat the MIT models using data provided by Informa. The published results show incorporation of many types of data can improve predictions.

War on Cancer is not a sustainable metaphor. However, if a price tag is put on cancer, economic incentives can be used to bring resources to bear to address cancer. With the right financing and data science, it is possible to do well for good.

Panel: Using Data from Multiple Clinical Trials to Predict Patient Outcomes
Moderator: *Andrew Lo, MIT*
Panelists: Nick Kelley, PhD, Novartis; and Sean Khozin, MD, MPH, formerly, CancerLinQ

The panelists discussed the increasing opportunities for use of data science in clinical cancer care. These opportunities include synthesis of data and literature sources, therapy and clinical trial optimization, and AI analysis of PET images. The panel discussed how far away data science is from being able to determine the probability of success for an individual patient's treatment. Roadblocks to implementation include reluctance to sharing data, incompatible workflows, and regulatory issues.

Talk: Genome-Wide Identification and Analysis of Prognostic Features in Humans
Jason M. Sheltzer, PhD, Yale University School of Medicine

Dr. Sheltzer is interested in whether genomic differences between microscopically similar tumors can explain patient outcomes, whether related biomarkers can be useful for clinical staging for aggressive therapy, and drivers of mortality in cancer. His team analyzed the complete dataset from The Cancer Genome Atlas (TCGA) using Cox Proportional Hazards modeling to identify features associated with patient outcome, linking the risk of death with genetic features of the tumor. Tumors were profiled for mutations, DNA methylation, copy number alterations (CNVs), gene and protein expression, and the genomic data for about 3 million survival relationships. They identified prognostic markers across 33 cancer types and found that mutations in common cancer genes (except p53) are rarely associated with patient outcome, while CNVs are. They found that aneuploidy strongly predicts worse patient outcomes across cancer types. The data raises the question of the value of mutated common genes as biomarkers. The group's website shares access to calculations of relationships between genes and cancer patient outcomes, and the data are published. They did not analyze markers used for therapy.

Panel: Using Data from Well-Curated "Public" Resources to Create Complex Biomarkers
Moderator: Vincent Miller, MD, EQRX
Panelists: Lynda Chin, MD, Apricity Health; Tracy Lively, PhD, NCI; Soma Ghosh, PhD, FDA; Bill Louv, PhD, Project Data Sphere; Sean Hanlon, PhD, NCI; Jason M. Sheltzer, PhD, Yale University

The panel discussed needs for complex biomarker development, standardization of data, the role of PPPs, and NCI programs and regulatory oversight.

Dr. Chin stated that standardization of clinical data requires clinical longitudinal annotation and biomarkers designed for clinical care, not research purposes. These would be complex markers defined as a set of data points that can be used to accurately diagnose patients, select therapies, and design clinical trials based on intended use. Dr. Sheltzer noted that one of the forefronts of complex biomarkers development will be development of formal definitions of amplifications, deletions, and understanding how to incorporate aneuploidy. Dr. Louv supported optimizing clinical data to increase the probability of finding biomarkers. He noted the FNIH project to determine biomarkers of cutaneous immune-related adverse events (irAEs) in IO aimed at helping patients maintain therapeutic intervention by improving irAE management. Dr. Lively noted data from PPPs are informative and these partnerships are important.

The Human Tumor Atlas Network (HTAN) is a follow-up to TCGA that encompasses different analysis methods including spatial proteomics and single-cell RNA sequencing. These approaches provide an early look at potential complex biomarkers, which must be validated and tested in biological models. This rich annotation of clinical data is widely available to the cancer community. The project includes a clinical data group to follow patients over time. Dr. Lively noted that the NCI Division of Cancer Treatment and Diagnosis supports laboratory efforts aimed at improving the efficiency of complex

biomarker development. One real-world issue is the comparability of assays from different laboratories and the difficulty in getting data, as proficiency data is not available.

Dr. Ghosh added that from the regulatory standpoint, over the last 2 years there has been an interest in complex biomarkers like tumor mutational burden (TMB). She discussed requirements for complex biomarker regulatory approval, starting with the definition and intended use (which determines the regulatory pathway), assay sensitivity and specificity, reliability of results, factors in detectability, clinical validation data, and device comparability. The FDA has been supporting reference material development with the establishment of functional comparability to clinical specimens.

Panel: Public-Private Partnerships in Support of Next-Generation Biomarker Development
Moderator: Sean Khozin, PhD, MPH, formerly CancerLinQ
Panelists: Andrew Lo, PhD, MIT; Reena Philip, PhD, FDA; Joshua Ofman, MD, GRAIL Bio

The panel discussed PPPs to accelerate development of next-generation blood and tissue biomarkers for cancer detection and screening, and for guiding treatment decisions.

While establishing analytical and clinical validation is necessary, the latter can take many forms. Many organizations are working on establishing real-world evidence in clinical practice and PPPs can play a role in demonstrating assay effectiveness at scale, expediting the accumulation of real-world evidence and approvals. The FDA is interested in using PPPs to help improve the validation and harmonization of assays. The group discussed whether the FDA could act as an anchor within a PPP to assist in validation and expedite assay reviews. There is a fear with PPPs that involving multiple public agencies will slow review, and concerns about technical obsolescence over an extended review time can arise. Dr. Philip thought a PPP facilitated by the FDA Oncology Center of Excellence to enable real-time review of emerging clinical data was a good suggestion.

Dr. Lo added that greater refinement of biomarkers and coordination among government, private, and patient-advocacy groups will speed therapy approval. Biomarkers provide economic value by stratifying patient populations with business implications, increasing the chances of success in getting the product to market. Everyone wins with the creation of sustainable PPPs to improve outcomes and the probability of success. Another advantage of PPPs is, "venture philanthropy" where non-profit entities engage in investing in for-profit organizations to advance goals. An example is the Cystic Fibrosis Foundation investment in companies to develop drugs. However, for some public health problems, such as COVID-19, the balance is how to bring innovative technologies that are safe and effective forward quickly.

Day 2: October 28, 2022, 1:00 – 4:00 pm ET

Mr. Connors introduced new CSC Co-Chair Dr. Geoff Oxnard, VP, Head of Clinical Development, Foundation Medicine. Dr. Oxnard is a practicing oncologist at Boston Medical Center and Associate Professor of Medicine at Boston University. He has a long history with the CSC, having served as a co-lead for the Vol-PACT and ctDNA QCM projects.

Keynote Presentation: Computational Pathology – The Next Revolution in Cancer Diagnosis
J. Carl Barrett, PhD, AstraZeneca

Built upon digital pathology, computational pathology has the power to improve patient selection and clinical outcomes. Traditional IHC pathology scoring has several limitations that can be improved upon by computational methods. Digital and computational methodologies are more quantitative, provide continuous data, are more objective, have greater resolution of low-level staining, and offer a better definition of spatial heterogeneity. Dr. Barrett described three elements of computational pathology significant for drug development: Quantitative Continuous Score (QCS), Spatial Proximity Score (SPS), and the Orthogonal Method.

Dr. Barrett noted that the features of computational pathology are important in developing antibody-drug conjugates (ADCs), which bind to and kill cells by homing in on specific targets. T-DXd is an example. It has three components: a humanized antibody that binds HER2, a cleavable linker, and a topoisomerase-based inhibitor stabilized via binding to the antibody. T-DXd improved outcomes for breast cancer patients termed HER2 low. To identify these patients and other similar groups, the QCS was developed using computational pathology tools. The QCS method uses supervised deep learning on whole slide digitized images of stained tissue followed by bioinformatics analysis of individual cellular data.

Clinical outcomes are then assessed. The QCS methodology can reveal patterns and heterogeneity in target expression and potentially could improve upon standard categorical scoring by pathologists.

Tumor heterogeneity introduces a challenge in predicting patient response that can be addressed by computational pathology. A SPS can be used to predict if biomarker-negative cells within the tumor will also be killed based on their distance from the positive cells. At lower levels of expression, spatial heterogeneity might matter more than categorical assignments. SPS could be one way to distinguish responders from non-responders.

The Orthogonal Method is another avenue for ADC target quantification. This method uses mass spectrometry (MS) analysis of protein abundance. Together, MS-proteomics and QCS methodologies could validate each other, enable quality control in clinical diagnostics, and allow for reinforced target prioritization.

In future work, algorithms could be applied to images as well as specimens. AstraZeneca is working with other companies to democratize the methodologies and that it will be common in a few years for pathology laboratories to select an algorithm of choice for their analyses.

Session 2. Clinical Utility of Complex Digital Pathology and Liquid Biopsy Biomarkers
Moderator: Stan Hamilton, MD, City of Hope

Talk: Digital Pathology: State of the Science
Liron Pantanowitz, MD, PhD, MHA, University of Michigan, Ann Arbor

The beginning of digital pathology—the use of imaging technology to practice pathology—stretches back to the 1990s with the development of the first "virtual microscope." Today, digital pathology is bolstered by sophisticated imaging hardware and software with numerous vendors coupled with regulatory approval for clinical diagnostic use (the FDA approved whole slide imaging in 2017). There is also a growing interest in AI tools.

From a regulatory point of view, digital pathology comprises two subsystems: the acquisition component (where the image is acquired) and the workstation (where the image is viewed). Once the system is cleared by the FDA, substituted components are considered an "off-label" product. To transition to a fully digital pathology laboratory, there needs to be a good business use case, a committed histology laboratory, integration with the laboratory information system, and a validated digital system. Once these criteria are met, the laboratory can perform a digital primary diagnosis. There are still materials that cannot easily be scanned, such as cytology slides, microorganisms, and hematology slides. The College of American Pathologists (CAP) has provided guidance on whole slide imaging validation for diagnostics.

The COVID-19 pandemic catalyzed adoption of digital pathology. Digital pathology permitted remote sign-out, virtual training, and breakdown of some of the regulatory and cultural barriers to adoption. Computational pathology is a key driver of digital pathology. AI tools are being applied to whole slide images, but it is not yet clear how to integrate AI tools into clinical practice.

Panel: Clinical Application of Digital Pathology
Panelists: Marilyn M. Bui, MD, PhD, Moffitt Cancer Center; Mike Espey, PhD, NCI; Anil Parwani, MD, PhD, MBA, The Ohio State University; Peter Sorger, PhD, Harvard Medical School

Dr. Hamilton asked the panel about the regulatory aspects of digital pathology, specifically how to address issues regarding quality assurance (QA) and quality control (QC) as digital pathology moves into the clinical setting. Dr. Bui reiterated the process of validating the whole slide imaging system presented by Dr. Pantanowitz. She emphasized the need for QA/QC to continue monitoring pathologist performance and to train technical personnel.

The panel discussed the extent to which digital pathology has been implemented in US laboratories. Dr. Parwani noted that <20% of laboratories have access to a scanner for clinical use, the majority of laboratories are not 100% digital, and most laboratories do not use whole slide imaging for cytology or hematopathology. However, for surgical pathology, many laboratories have moved to a digital work sign-out process, but <5% of those are doing primary diagnosis. There are new scanners on the horizon for hematology and cytology, and Dr. Parwani expects those numbers to increase. Asked about the cost of transitioning to this technology, he replied it costs ~$1M to operate 2 scanners 24 hours a day, scanning 600 to 1,000 slides per day. The initial funding for many of the centers has come from foundation and research grants. However, new CPT codes are being introduced, and this is increasing interest in digital pathology in private laboratories.

The audience asked the panel to provide a reference for a standardized methodology for validating whole slide imaging automated tools. Dr. Bui replied a white paper is being written on this topic, and she expects guidance to come from that. She encouraged review of white papers on the DPA website.

Dr. Espey emphasized that rigor and reproducibility are key to establishing something actionable from the information gleaned. Dr. Sorger noted that spatial profiling methods could help with reproducibility and with the financial side of adoption by providing prognostic biomarkers. Dr. Sorger emphasized the importance of productive dialogue at the level of NCI between those in digital pathology and those in spatial profiling who are unfamiliar with what colleagues in digital pathology have learned. This would then benefit standards in AI.

Dr. Hamilton and Dr. Sorger discussed the uncertainty around the longevity of a product from a start-up company. They noted the need for community and public investment to create standards and shared data. Dr. Bui added that the digital pathology community has already initiated collaborations. Transitioning from analog data to digital data is only step one, and step two is using AI to improve efficiency and accuracy. This requires quality data sets. Dr. Sorger agreed and emphasized the lack of adequate resources for quality data sets in the field. Dr. Bui called upon NIH leadership to recognize the role of digital pathology in healthcare and medicine. Dr. Parwani described NCI's Cooperative Human Tissue Network (CHTN). Dr. Bui added that Europeans are making progress in creating a large collection of images for developing high-quality AI resources.

Dr. Espey introduced the issue of scale. If digital imaging tools are used at the cellular scale, but PET, CT, and MRI are used at larger scales, is there an opportunity to bridge those scales and use the same techniques and standards to cut across imaging modalities? This is an untapped area where tools can be combined to glean predictive biomarker information.

The panel was asked if there is a commitment to adopt the Digital Imaging and Communication in Medicine (DICOM) standard for all slide imaging. Dr. Hamilton commented that radiology has had DICOM standards for decades, but it has not been done collaboratively for all image analyses.

Dr. Bui was asked if the European image database is accessible to the public, to which she replied it is only available to their users. DICOM is collaborating with CAP and DPA on standardizing digital pathology. Dr. Sorger noted more efficient file standards, including some that are cloud-based, now exist and urged the field to consider efficient data storage.

Dr. Hamilton concluded by stating there is a lot in the digital pathology pipeline, and it all starts with digital images and their availability.

Panel: Translating Liquid Biopsy into the Clinic
Moderator: Minetta Liu, MD, Natera
Panelists: Amy Moore, PhD, LUNGevity; David Gandara, MD, UC Davis, International Society for Liquid Biopsy (ISLB); Soma Ghosh, PhD, FDA, Daniel F. Hayes, MD, University of Michigan, Jerry Radich, MD, Fred Hutchinson Cancer Center

Dr. Hayes shared a presentation on "Defining Clinical Utility of a Tumor Biomarker Test or When Should a Tumor Biomarker Be Applied in the Clinic?" He listed the following factors as important to evaluating the clinical utility of a biomarker assay: analytical validity, COU, endpoint definition, magnitude of the difference in patient outcome with and without the biomarker, stakeholder decision-making, and levels of evidence. Dr. Hayes emphasized that the evaluation of the clinical utility of a tumor biomarker test requires the scientific method. Luck is not a good strategy.

Dr. Liu focused the panel on detection of MRD and disease monitoring. She asked Dr. Ghosh to share FDA perspectives on the topic. Dr. Ghosh is from the Division of Molecular Genetics and Pathology in CDRH at the FDA. Their group reviews in vitro diagnostic tests in the cancer space, including a large proportion of companion diagnostics. In the past two years, they have seen growing interest in the development of liquid biopsy tests for MCED, single-cancer early detection, screening, and detection of molecular disease in solid tumors. She noted that from a regulatory standpoint, the following elements are essential: definition of the biomarker—what factors contribute to the test result; thresholds that determine biomarker positivity or negativity; pre-analytical validation; analytical validation; and clinical validation. She encouraged engagement with CDRH early in development.

Dr. Moore, representing the LUNGevity Foundation, provided the patients' perspective. Patients are very motivated to understand if their treatment is working. LUNGevity is partnering with other stakeholders to push research forward and to work through the access and regulatory issues around liquid biopsy. Dr. Gandara, Chief Medical Officer of ISLB, stated

that liquid biopsy MRD assays for solid tumors are in transition from research to standard clinical application and emphasized the importance of assay sensitivity. Most studies in solid tumors have had small patient numbers, and the few retrospective large studies have had mixed results. Prospective studies are underway, and further engagement on the topic can advise what is needed to complete the transition of MRD assays from research into clinical care. Dr. Liu agreed with the need for community engagement to reach answers as technology quickly evolves.

Talk: Making Liquid Biopsy Reference Materials "Fit for Purpose"
Jerry Radich, MD, Fred Hutchinson Cancer Center

BCR-ABL expression in peripheral blood in chronic myeloid leukemia (CML) epitomizes biomarkers for MRD. However, lessons can be learned from what went wrong in validating this biomarker to better understand considerations for standards moving forward. Dr. Radich described the original imatinib trial, the largest clinical trial done in leukemia. Through a series of unfortunate events, only 40/500 diagnostic samples sent to the reference laboratories had sufficient RNA for analysis. Dr. Radich's team found, in an ad hoc analysis, that a 3-log reduction at the end of one year of therapy was associated with better outcomes. This finding created a new endpoint for phase 3 trials and ultimately reduced trial length from 5 to 1-3 years. He emphasized the luck involved in creating an international scale based on 40 samples and cautioned against using a similar approach. Thinking carefully about controls is critical. In biological systems the strongest signal is often reproducible noise. Dr. Hayes offered a simplified way to use the tests: If SOC is to do something, but the assay says you should not, then opt-out. If the standard of care is not to do something, but the assay says you should, then opt-in. And if the standard of care has multiple options, then there is opt-alt. The question is how big the magnitude needs to be to opt-in or opt-out, and who makes that decision. Dr. Gandara agreed and added that a negative MRD assay implies that the patient does not need more treatment, and that is a big step. Dr. Moore reiterated this is about coming together to benefit patients and improve patient outcomes. Dr. Ghosh emphasized the importance of goal alignment with clinical usefulness and the clinical context in which the assay will be used.

Panel: Clinical Implementation and the Role of Public-Private Partnership
Moderator: Geoff Oxnard, MD, Foundation Medicine
Panel: Esther Abels,Visiopharm; Stan Hamilton, MD; Minetta Liu, MD, Natera; Francisca Reyes-Turcu, PhD, FDA; David Rimm, MD, PhD,Yale

Dr. Oxnard noted the field is asking more difficult tasks of liquid biopsies. He agreed with Dr. Liu's earlier comments on the importance of definitions and semantic clarity when talking about biomarkers. Dr. Oxnard asked Dr. Liu how the group can move the bar forward. Dr. Liu reiterated the importance of defining and demonstrating clinical utility. The topic of lead time concerning liquid biopsy is also a large issue. She specifically asked at what point does identifying MRD and acting upon that information benefit patients. Dr. Liu emphasized the need for standards.

Dr. Oxnard asked Dr. Liu if there is alignment on what a good design looks like and if there is consensus on the definition of terms such as positive predictive value in MRD. Dr. Liu replied that all stakeholders need to come together to develop definitions and guide how studies are crafted moving forward. For example, the term "monitoring" could be for treatment benefit during active therapy or for recurrence. Words can be interpreted differently by different groups. This can create noise that will affect how the community develops these assays.

Dr. Oxnard invited Dr. Francisca Reyes-Turcu, a team lead at CDRH, to comment from an FDA perspective. Dr. Reyes-Turcu listed several challenges for these assays, including understanding sources of variability and the increasing complexity of applications for liquid biopsy. She stated that reference materials and methods may help in understanding the sources of variability and that FDA collaborates with other organizations on projects aimed at developing reference materials, understanding sources of variability for complex biomarkers, and developing analytical validation strategies for liquid biopsy assays. Dr. Oxnard asked if the biology of cancer (and the complexities of non-malignant perturbations) will prevent the development of standards. Dr. Reyes-Turcu reiterated how FDA looks at in vitro diagnostic devices: Is there clinical and analytical validity of the assay? Is the biomarker associated with a clinical claim? What is the assay measuring? When comparing assays, is it the same biomarker? What is the reliability and accuracy of the test? Is this being tested in the right population? Dr. Reyes-Turcu stated that all these facets are considered to understand if the test will work as intended, and that reference materials may help with understanding variabilities between assays.

Dr. Oxnard asked Dr. Hamilton for comments based on his digital pathology expertise. Dr. Hamilton foresees several problems, including difficulties that may arise with moving into AI and how it will be applied in the clinical setting; differences in approaches to characterizing tissue; challenges with pre-analytics; challenges with following evidence development guidelines; and too many methodology techniques that each need to be analyzed and validated properly.

Dr. Oxnard stated that early adopters can help learn assay flaws, but progress is stuttering. He asked Esther Abels to speak about digital pathology adoption. Ms. Abels stated that the field is growing at a slower rate than anticipated. She argued this is not due to technical challenges, unproven efficiency, reimbursement issues, or inadequate return on investment. Instead, adoption has been slow because it is not being used to its full potential for creating digital biomarkers. Ms. Abels touched on five points: interoperability—the ability to follow patients and patient data between hospitals; cooperation within industry; stakeholders understanding each other's needs; patient involvement; and use of algorithms to obtain real-world evidence. She concluded with a call to action, stating that collaborations build a strong foundation to connect all crucial elements in digital health to deliver precision medicine to patients.

Dr. Oxnard agreed on the need for collaborative effort around specific goals and invited Dr. Rimm to speak. Dr. Rimm stated that the bottom line is clinical utility and emphasized the importance of quantitative measuring over subjective reading. Dr. Oxnard asked Dr. Rimm to describe one project that would generate momentum toward utility. Dr. Rimm replied there should be quantitative testing in multiple places and encouragement to use measured biomarkers to establish clinical utility. He added that pathologists are good at analytical and clinical validity, but the challenge is utility.

Dr. Hamilton emphasized that a major problem is the financial cost to set up digital pathology. Clinical laboratories are under increasing financial pressure. Instruments, storage, and trained bioinformatics personnel are expensive, and it takes a major financial investment. Dr. Oxnard stated that this could be a motivation for PPPs — to find a cost-sharing approach to iteratively grow the field. He encouraged the submission of concepts on this topic to the FNIH.

Day 3: November 3, 2022, 1:00 – 4:40 pm ET

Mr. Connors introduced new CSC Co-Chair Dr. Emmett Schmidt, Vice President of Clinical Research, Merck Research Laboratories. Dr. Schmidt provided a brief reflection on drug development and the influence of biomarkers on the success of drug trials.

Keynote Presentation 3. Selected Regulatory Considerations – Disease and Treatment-Related Biomarkers
Marc Theoret, MD, FDA, Deputy Director, Oncology Center of Excellence

Dr. Theoret described the FDA CDER biomarker qualification process and how biomarkers, either disease-focused or treatment-related, may be applied to serve various purposes (i.e., COUs) in clinical trials leading to the FDA regulatory approval of drugs or biologics. He focused on two types of treatment-related biomarkers: response/pharmacodynamic biomarkers and selection/predictive biomarkers.

Regarding response/pharmacodynamic biomarkers as potential efficacy endpoints, he discussed the strengths and limitations of endpoints that measure direct clinical benefit such as OS, and those that are surrogate/intermediate efficacy endpoints based on radiographic evidence of tumor response. The degree of certainty of clinical benefit that an endpoint can convey decides the magnitude of treatment effect required for drug/biologic approval. He acknowledged the challenge in validating a surrogate endpoint.

On selection/predictive biomarkers, Dr. Theoret described two COUs, namely as companion or complementary in vitro diagnostic devices. He illustrated the distinction between the two using examples of the companion diagnostic PD-L1 IHC 22C3 pharmDx for pembrolizumab in NSCLC and the complementary diagnostic PD-L1 IHC 28-8 pharmaDx for nivolumab in melanoma or non-squamous NSCLC. Biomarkers with tissue-agnostic indications have been gaining interest as selection biomarkers. In October 2022, FDA released Tissue Agnostic Drug Development in Oncology Draft Guidance.

There is great interest from the FDA and external stakeholders in validating biomarkers. The FDA Biomarker Qualification Program established a multi-step iterative process to qualify biomarkers as drug development tools and encourage stakeholders to engage with the FDA.

Session 3: Applying Knowledge Across the Disease Continuum

Immune Microenvironment
Moderator: Lanny Kirsch, MD, Adaptive Technologies

Special Keynote Presentation: Lymphocytes as a "Living Drug" for the Treatment of Cancer
Steven Rosenberg, MD, PhD, NCI

Dr. Rosenberg presented research that resulted in the first cell-based gene therapy approved by the FDA, a CD19-targeting CAR-T cell. His group first reported anti-CD19 CAR-T mediated regression of lymphoma in humans. In 2012, NCI transferred the technology to Kite Pharma who subsequently conducted a multi-center trial, confirming the efficacy and resulting in FDA approval in 2017. This is a proud example of research performed at NIH that translated into a commercial product now available in US, Europe, and Asia for patients with B-cell lymphoma.

A major challenge confronting cancer IO is to develop effective IOs for patients with metastatic epithelial solid cancers that cannot be cured by any available treatment. These cancers result in 90% of cancer deaths. In searching for effective cell therapies for these cancers, Dr. Rosenburg's research group found that tumor-infiltrating lymphocytes (TIL) selecting for the CD39- and CD69- "stem-like" phenotype effectively treated melanoma. To develop a general approach across common epithelial cancers, Dr. Rosenburg's group identified somatic mutations in cancer cells that can serve as neoantigens for TIL. Adoptive cell therapies using TIL-targeting neoantigens have caused cancer regression in several epithelial cancers, such as metastatic cholangiocarcinoma, and breast and cervical cancer. In addition to targeting neoantigens highly unique to individual patients, common mutations such as Kras and p53 can also be targets for TIL selection to treat cancers. This approach has also shown success in patients with pancreatic cancer. TCRs are available for treating patients with p53 mutations. "Off-the-shelf" anti-p53 TCRs showed efficacy in breast cancer.

Panel: The TME, the ME, and the E
Panelists: Michael Khodadoust, MD, PhD, Stanford; Jerry Radich, MD; Fred Hutchinson Cancer Center; Alexandra Snyder, MD, Generate Biomedicines, SITC

Each panelist commented on how their work has influenced their perspectives on the immune microenvironment (ME). The panel shared their thoughts on whether Robert Schreiber's model of immune response to cancer treatment (i.e., elimination, equilibrium, and escape) still holds, and the future directions of IO.

Dr. Radich commented on his stem cell transplant experience to treat CML, where it was observed that immune regulation-related genes and pathways were upregulated in patients who responded to tyrosine-kinase inhibitors (TKIs) favorably. These patients did not relapse after discontinuation of TKIs. This finding suggests that in patients with an activated immune response, the immune system can continue to wipe out the cancer and prevent relapse when TKIs shift the equilibrium in favor of the immune system. This observation is in line with Dr. Schreiber's model.

Dr. Khodadoust commented that in treating T cell lymphomas with immune checkpoint inhibitors (ICIs), many biomarkers have been identified that correlate with response, especially through high dimensional genomic and transcriptomic analysis, but not a single biomarker has turned out to be clinically useful. He suggested that the next phase of biomarker development is integrating multiple aspects to generate biomarkers using a holistic approach, involving tumor characteristics, TME, and host immune system competencies and characteristics.

Dr. Snyder focuses on response and resistance to ICIs for solid tumors. On the features of the TME associated with response to checkpoint blockade, adaptive immune response is key, and suppressive cell types can be associated with non-response. However, there are important exceptions to these generalizations. For example, the "over-inflamed" phenotype can be associated with non-response. These associations may not apply to combination therapies with exception of some IO combinations. Dr. Snyder commented on whether the lessons learned are actionable, stating that the greatest opportunity for biomarkers in drug development is to inform target selection and patient stratification.

The panel commented on identifying gaps in understanding of the immune ME, and how these gaps can be addressed most efficiently. Dr. Rosenberg emphasized that lympho-depletion is critical for changing the ME because it eliminates T-regulatory cells, myeloid-derived suppressor cells and competing lymphocytes to make the ME more suitable for transplanted cells. Dr. Radich added that the bone marrow transplant setting is an ideal place to look at the interaction

between the TME and the tumor. He suggested studying factors that dictate why patients with or without graft versus host disease do or do not relapse.

Dr. Kirsch asked if the next five years will lead to the refinement of existing biomarkers (e.g., TMB or IHC of PD-1 or PD-L1) or the creation of new, complementary tools, and how they may be used in clinical management. Dr. Rosenberg replied it is not the presence of antigen or T-cells that recognize the antigen that is limiting; it is the question of why lymphocytes are not working. There is opportunity to genetically modify lymphocytes to improve their anti-tumor activities by identifying limitations to their recognition. Dr. Rosenberg anticipates this could be realized over the next five to ten years.

Imaging
Moderator: Dan Sullivan, MD, Duke
With the promise of stimulating the immune system to treat cancer comes interest in ways to measure treatment response, one of which is imaging. Dr. Mahmood provided an overview on imaging to measure IO response.

Talk: Challenges and Opportunities for Imaging Immunity
Umar Mahmood, MD, PhD, Massachusetts General Hospital, Harvard Medical School

Dr. Mahmood discussed strategies to assess IO response including imaging tumor anatomy using CT, MR, and ultrasound; imaging tumor metabolism by FDG-PET; examining tumor biopsy; assessing immune modulation; imaging immune cells; and imaging immune cell activity. Imaging assessment of response to IO is confounded by pseudo-progression because immune cell infiltration into a tumor in response to therapies cannot be distinguished from tumor growth by anatomical or metabolic imaging. Efforts are under way to find novel PET tracers to assess response to immune therapies, leading to a number of human trials. Examples include $[^{18}F]$-FHBG imaging of reporter gene HSV-TK in CAR-T cells for glioma therapy, $[^{18}F]$-FAraG and $[^{18}F]$-clofarabine imaging for activated T cells, and $[^{89}Zr]$- pembrolizumab for PD-1 imaging.

Dr. Mahmood discussed his group's work using $[^{68}Ga]$-GZP to image granzyme B activity, a common downstream pathway for activated T cells. The agent is potentially useful in assessing tumor response to all killer T- cell therapies, including ICIs, CAR-T cell therapy for solid tumors, and tumor vaccines. Regions of pre-treatment granzyme B uptake on PET are associated with response, indicating the agent is potentially useful in predicting tumor response to IO.

Panel: Novel Imaging Technologies
Panelists: Gregory Goldmacher, MD, PhD, MBA, Merck; Nola Hylton, PhD, UCSF; John Waterton, PhD, University of Manchester, UK, Bioxydyn; Wolfgang Weber, MD, Technical University of Munich

Dr. Sullivan asked for pharma perspectives on challenges of applying novel PET imaging tracers in drug trials. Dr. Goldmacher sees tremendous promise in imaging the biology of the TME directly, non-invasively, and longitudinally to assess treatment effects. However, from the point of view of those who run multi-center trials, there are logistical and operational challenges which complicate using tracers at scale. These challenges include: lack of capacity to make an investigative tracer on site for some phase 1 trials; hurdles with supply and distribution networks for multi-center trials; and lack of GMP compliance (many small or academic sites do not pass the GMP compliance audit). Scaling adds financial costs as well. There is a need for specialized expertise to handle radioactive blood samples and a large amount of data is required to validate imaging endpoints. It takes some time to accumulate data to compare the results of these tracers with gold standard imaging to use these as endpoints for drug approval. In the near future, tracers are most promising in small, early trials to measure pharmacodynamics, potentially for go/no-go decisions.

Dr. Sullivan asked Dr. Weber to comment on his experience with CAR-T cell imaging. Dr. Weber stated that studying the distribution and function of CAR-T cells using reporter gene PET probes is an exciting opportunity. CAR-T cells are genetically engineered, so there is a realistic opportunity to incorporate reporter genes. The challenge is learning how to do this in a way that does not affect the CAR-T cells or trigger an immune response against them. He is optimistic these obstacles can be overcome.

Dr. Sullivan transitioned to the challenge of reproducibility in multi-center clinical trials. He asked Dr. Hylton, a leader of the I-SPY 2 trial, about managing reproducibility. Dr. Hylton discussed her experience using breast MRI. The measure of tumor burden using breast MRI was designed into the longitudinal model of I-SPY 2 as part of the process for adapting to response measures of different drug arms. Controlling and standardizing across multiple centers requires constant

monitoring, constant review of data, and engagement of every trial component to ensure protocol compliance and high-quality data. While the drugs are being tested, the biomarkers are being fine-tuned. Consequently, the imaging resolution, contrast, and other system specs must be designed with biomarker goals in mind. This may differ from the optimal diagnostic specifications of extracting the most numerical information from each voxel in the image.

Dr. Sullivan commented on the enormous undertaking of standardization and the resistance in the health care system to standardization. He asked Dr. Waterton, an expert in the field of imaging biomarkers, for his thoughts on the potential for using biomarkers in routine clinical care. Dr. Waterton framed the use of new imaging biomarkers as a way to identify which drug should be chosen for a patient or to identify which patients are unlikely to respond to a drug. This raises three challenges for developing imaging biomarkers as companion or complementary diagnostics: getting efficacy data from biomarker-negative patients, which are necessary to validate biomarkers that are predictive rather than prognostic; having biomarkers available worldwide; and ensuring tracers and imaging biomarkers remain available in every jurisdiction for as long as the drug is on the market.

Dr. Sullivan asked what needs to happen over the next five years to improve the likelihood of imaging biomarker success. Dr. Goldmacher commented that novel PET tracers are more suitable in small scale, early-stage clinical testing to identify drug efficacy signals. New methods of quantitative analyses (e.g., radiomics, tumor growth kinetic modeling) on routine clinical images by CT and MRI hold promise for imaging biomarkers that are more practical in late-stage drug development trials. It will provide more confidence in imaging biomarkers if an early-stage PET biomarker correlates with a late-stage CT or MRI biomarker. Dr. Weber cautioned that while it is interesting to investigate MRI or CT radiomic signatures that are invisible to the human eye, these signatures have not yet reproducibly shown that they predict outcomes. The panel agreed that there is a need to incentivize standardization of methodologies and systematic data collection in addition to innovation, especially in academic settings. Public-private partnerships can play an important role in this area.

Applying Knowledge from Other Therapeutic Areas
Moderator: Hartmuth Kolb, PhD, Janssen

Talk: Lessons Learned for Cancer from Across the Disease Continuum
Hartmuth Kolb, PhD, Janssen

Neuroscience takes inspiration from oncology in using precision medicine to facilitate drug development using biomarkers. Given that both the brain and cancer are influenced by the immune system, there are opportunities for cross-disease development of tools. An example is using click chemistry to develop new PET tracers, which can be used in a disease-agnostic fashion for patient selection, response monitoring, and safety evaluation.

Panel: The Potential for Cross-Disease Application of Tools
Panelists: Eric Hostetler, PhD, Merck; Umar Mahmood, MD, PhD, Massachusetts General Hospital, Harvard; Marty Pomper, MD, PhD, Johns Hopkins; Gary Ulaner, MD, Hoag

Dr. Hostetler introduced the context in which imaging tools are used in neuroscience and lessons learned in imaging at Merck. 21 PET tracers have been developed for neuroscience applications, but none has been applied outside neuroscience. In neuroscience, PET tracers are used to understand drug target engagement and as pharmacodynamic biomarkers in phase 2 trials. He emphasized that operational simplicity is a key consideration in implementing imaging biomarkers in clinical trials. He discussed several considerations when repurposing neuroscience imaging biomarkers in oncology, including biomarkers for target engagement and for pharmacodynamic effect. He commented that the bar for novel imaging in oncology clinical trials is high, and development of imaging biomarkers should focus on the contexts where blood or urine biomarkers fall short.

Dr. Mahmood discussed T cell imaging for assessment of cancer therapy response, irAEs and autoimmune disease. He offered several examples of T cell imaging to assess response to IO, including imaging cell surface proteins, imaging reporter genes, and visualizing granzyme B. PET imaging is quantitative, and this allows for comparisons of results among multiple trials. He offered evidence that granzyme B can be used as an early biomarker for response to IO. In a cross-disease application, granzyme B imaging offers a method to monitor irAEs as well as autoimmune diseases.

Dr. Pomper spoke about PET for precision imaging, providing examples of repurposing an imaging agent to monitor a target in different organ systems. [^{18}F]-DCFPyL PET imaging can guide treatment by distinguishing between localized and metastatic prostate cancer. He described generation of CD19-specific CAR-T cells co-expressing a mutant version of prostate-specific membrane antigen (PSMA) which can be detected by the "reporter" PET imaging agent [^{18}F]-DCFPyL to monitor these CAR-T cells and heterogeneity of response to cell therapy. Another application of such agents is to image neuroinflammation, a potential serious side effect of CAR-T cell therapy. Dr. Pomper's research team developed the compound 11C-CPPC, an imaging agent targeting CSF1R, a protein upregulated in microglia during neuroinflammation. This agent was able to image other disorders with an inflammatory component. A modified version of the compound was able to image tuberculosis in a murine model.

Dr. Ulaner discussed the cross-disease application of immunoPET. Using radiolabeled HER2 antibody [^{89}Zr]- pertuzumab, his team revealed that PET imaging could find HER2-positive metastases in 15% of patients who tested negative by prior IHC, resulting in change in clinical management of these patients. [^{89}Zr]-daratumumab, which targets CD38, visualized myeloma missed by other imaging modalities. Over 100 FDA-approved antibody products are now in clinical use with more in development. These antibodies could potentially be radiolabeled and used in immunoPET imaging, providing a target-based tool that can cross from oncology into other disease types.

Session 4: Platform Trials: Challenges and Opportunities

Panel Discussion
Moderator: Laura Esserman, MD, MBA, UCSF
Panelists: Donald Berry, PhD, Berry Consultants; Hossein Borghaei, DO, Fox Chase Cancer Center; Laura van't Veer, PhD,UCSF; Jane Perlmutter, PhD, MBA, Gemini Group

Platform trials are a type of clinical trials in which multiple interventions are evaluated simultaneously using a common control arm. They have been shown to accelerate learning; are efficient, flexible, and collaborative; and can become an engine for discovery. This session focused on responding to challenges in platform trials.

Experience with Changes in the Standard of Care Over Time
Platform trials offer the advantage of simultaneously testing new agents without generating multiple new protocols. However, challenges do occur, one of which is a change in the SOC during the course of a trial. Dr. Berry described how this was addressed in I-SPY 2, an adaptive Bayesian platform trial in neoadjuvant breast cancer patients. I-SPY 2 has tested over 20 agents on experimental arms using common control arms. The SOC for HER2+ patients changed during the study with the approval of pertuzumab for neoadjuvant breast cancer in 2013, prompting a change of the control arm. They initially developed the "time machine" method and eventually evolved to using a dynamic control to adjust for changes in SOC without jeopardizing the continuation of the trial and data integrity.

Lung-MAP is an umbrella platform trial in patients with NSCLC. Dr. Borghaei shared his experience with the trial, in which SOC changed during the trial when ICIs were approved for NSCLC in 2015 as second line treatment following chemotherapy. This approval led to switching ICI monotherapy from experimental arms to control arms and catalyzed the design of studies with an ability to pivot mid-study to adapt to the changing landscape of lung cancer treatment.

Power to Advance Molecular and Imaging Biomarkers in the Context of Platform Trials
Dr. van't Veer discussed development of predictive biomarkers in the I-SPY 2 trial across 10 cancer therapies targeting diverse biology. Using the wealth of data containing comprehensive multi-omic molecular characterization of tumors and the diverse array of drugs targeting different molecular pathways, her research team combined five response-predictive biomarkers to create response predictive subtypes (RPSs). Patients with breast cancer have been stratified by receptor biology, but the RPS approach considers the various biologies of tumors to prioritize the best-performing drugs for a patient's tumor biology. RPSs are being prospectively evaluated in I-SPY 2.2.

Diversity, Equity, and the Role of Advocacy
Dr. Perlmutter discussed the role and importance of advocacy in platform trials. She described how advocates participate, from preplanning to planning to execution, to ensure patient centricity in every aspect of the trial. Examples include participation in all working groups, DSMB and external advisory groups; providing extensive input on all patient-facing

materials; designing the I-SPY patient website; and reviewing concepts, abstracts, and manuscripts. There are currently 18 advocates in the trial. They are mostly breast cancer survivors and older women. They welcome additional advocates and provide training and mentoring to new members.

Transition from an organ of origin approach to cancer to a common biology approach using biomarkers
Drs. van't Veer and Borghaei commented that some biologies are specific to tumor type, but immune modulation works in many different cancer types. For immune modulation-based therapies, a basic understanding of molecular pathways of activated T cells and response in tumor cells will allow for more unified biomarkers among different cancer types.

Improving equitable trial enrollment
Dr. Esserman stated that I-SPY 2 has a diverse group of patients that reflects the population of the US as a result of carefully selecting trial sites that serve diverse populations. Educating, training, and involving investigators that look like their patients is critical. Dr. Perlmutter added that their advocate group has focused on including diverse advocates, retaining diverse patients, and generating informational materials that are sensitive to diversity.

Commonalities of disease development across disease types and how such knowledge can help treat these diseases
Dr. Berry emphasized the need to look at both organ of origin and common biomarkers across diseases in considering treating patients. This holistic approach presents a huge statistical and scientific challenge. An example is the inflammatory nature and immune system associations shared between cancer and many other diseases. Dr. Esserman added that every challenge is an opportunity, and large amounts of data from platform trials can advance the field. She encouraged investigators to incorporate biomarkers in their trials to produce more data to help generate knowledge.

Day 4: November 4, 2022, 1:00 – 4:00 pm ET

Steven Hoffmann, FNIH BC Director, recounted the growth of the BC CSC Symposium over the past decade and recognized the efforts of the FNIH staff and collaborators. He highlighted Dr. Kelloff's years of outstanding leadership.

Dr. Kelloff noted that progress is accelerating in cancer research. The field of pathology is changing; big data is being utilized; standardization is underway; and human molecular genetics and genomics advances have made patient stratification and precision medicine possible. Human carcinogenesis is a multi-year process, usually preceded by pre-cancer, which means there is an opportunity for early intervention. A sampling of research areas that factor into early intervention include screening technology, image guided intervention, drug intervention, immune-prevention, and early disease analysis efforts.

Keynote Presentation: Addressing Cancer Disparities and More

Doug Lowy, MD, NCI

Progressing cancer prevention and screening will help address cancer disparities. When developing and testing new technologies, the potential impact on health disparities must be considered as early as possible. Cancer disparities in low- and middle-income countries need more attention.

Evidence of Progress and Remaining Disparities
In the past 20 years, cancer mortality rates have decreased faster for Black men than for people of other racial or ethnic backgrounds; however, overall mortality rates among Black men and women remains higher than those of White men and women, and American Indian/Native American populations have not benefited from overall improvements in cancer mortality. Some cancer types, such as uterine, have larger health and mortality disparities (Clarke et al., 2022). Cancer death rates are 12% higher in rural counties with persistent poverty than other urban US counties. Trends in uterine, lung, and cervical cancer provide an opportunity to examine health disparity challenges. Lung cancer incidence and mortality have been decreasing, partly due to IO. Yet, Black patients get molecular testing less frequently than White or Asian patients (Kehl et al., 2019) and have been underrepresented in IO clinical trials (Herbst et al., 2020) and in IO uptake.

Cervical cancer has a higher incidence in Hispanic women, which is reflected in disparate mortality rates. Staggering differences in incidence and mortality rates between North America and Africa highlight the need to consider health disparity challenges on a global scale. Of three approaches to cervical cancer–vaccination, screening, and treatment of invasive cancer – the former two, for HPV interception, have not been utilized well in low and middle-income countries due to cost and logistics. Ongoing research aims to establish single dose HPV vaccination as the standard of care for a

long-term, high-level of protection. In the US, women who are uninsured or on public insurance do not get screened as often as women on insurance.

Technology Development and Health Disparities
Clinical trials must be equitable. Technology can play a major role in perpetuation of disparities, and a system should be in place to ensure the under-insured receive high-level evaluation and appropriate treatment. Dr. Mark Schiffman at NCI is working on a cost-effective, high quality "see and treat" approach for cervical cancer screening that could be used in low- and middle-income countries.

Cancer Moonshot
Cancer Moonshot 1.0, which began in 2016, has supported promising research and is under consideration for continued support. A new Cancer Moonshot has four goals: invest in a pipeline of new interventions for cancer prevention, interception, and treatment; expand clinical trials to speed evaluation of candidate interventions in diverse populations; increase implementation research to ensure equitable delivery of current and new SOC; and increase diversity of the cancer research and care workforce to resemble the communities served.

There has been substantial increase in minority enrollment in clinical trials through the NCI Community Oncology Research Program (NCORP), NCI's National Clinical Trials Network (NCTN), and the Connecting Underrepresented Populations to Clinical Trials (CUSP2CT) program. NCI is leading discussions among multiple stakeholders on equity, diversity, and inclusion in early phase clinical trials. The Cancer Moonshot next phase is jumpstarting three programs from NCI: Cancer Moonshot Scholars, Telehealth programs, and Multi-Cancer Detection. Dr. Lowy encouraged the cancer research community to continue to progress towards addressing health disparities by being inclusive in research and the workforce.

Dr. Hawk commented that NIH and NCI have led data collection, reporting, and responses with intention, drive, and specific actions, which advanced the participation of women and minorities in its research portfolio. He asked whether the NCI would investigate other significant drivers of cancer-associated inequities, such as poverty, underinsurance and unequal access to treatment, and the scalability of such efforts. Dr. Lowy noted that TCGA was skewed toward White patients, and efforts are ongoing to democratize cancer databases. Other efforts from private philanthropy would aim to address the underinsured or uninsured, with lessons learned about what works. Dr. Krol, FDA, commented that the FDA has been developing guidance on this topic in recent years and encourages sponsors to read that guidance as a critical step to increase ethnic diversity in clinical trials. Dr. Srivastava added that the HTAN is emphasizing fair representation in precancer and cancer atlases of the community it serves.

Session 5: Expanding Early Diagnostics into Early Detection & Cancer Prevention/Interception
Moderator: Ernest Hawk, MD, MPH, UT MD Anderson Cancer Center

Talk: Early Detection Research Network (EDRN): A National Infrastructure for Biomarker Research
Sudhir Srivastava, PhD, MPH, Chief of the Cancer Biomarkers Research Group, NCI

Effective biomarkers are needed for risk assessment, early detection, and therapy, to reduce mortality; however, only a few receive regulatory approval each year. The EDRN's stringent biomarker development process aims to bring robust, reproducible, quality-assured biomarkers into clinical use, via separate entities for biomarker development, reference, validation, and a hub and spoke model of biomarker research with coordination among topic-specific programs and inter-agency agreements. The program aims to improve diagnostic performance, develop precancer biomarkers, characterize precancer in the HTAN Precancer Atlas, use AI and ML approaches for improving risk stratification and pathological uncertainty, build biomarker and biospecimen resources, and provide big data and informatics through the EDRN website.

Talk: Multi-Cancer Early Detection Through Multi-Biomarker Class Testing
Paul Limburg, MD, MPH, Chief Medical Officer for Screening, Exact Sciences

MCED screening is a feasible and advantageous approach for early cancer detection, potentially leading to curative therapies and favorable clinical and economic outcomes. A large-scale prospective interventional study, DETECT-A, evaluated the diagnostic performance of MCED testing with Exact Sciences' assay, and showed that cancers were detected in multiple organs, the majority of which have no screening options. Development has accelerated for the Exact Sciences prototype MCED assay which uses three- and four-biomarker test configurations. MCED testing can minimize disparities related to cancer screening; however, barriers could include areas of low insurance coverage and high out-of-pocket costs.

Talk: Integrating Cancer Risk Assessment & Prevention/Interception in High-Risk Cohorts
Eduardo Vilar-Sanchez, MD, PhD, University of Texas MD Anderson Cancer Center

Dr. Vilar-Sanchez's work involves patients who have hereditary diseases that predispose them to colorectal cancer (CRC). CRC risk is categorized in three broad categories: average, increased, and high-risk patients with hereditary CRC syndromes. Polygenic risk scores (PRS) stem from decade-long meta-analysis efforts in genome-wide association studies, and aid in quantifying and stratifying risk by percentile in the general population. Risk modeling integrates PRS with environmental factors, lifestyle factors, and family history and SNPs, towards the goal of new cancer prevention and immune interception strategies for the highest risk populations. Research in Dr. Vilar-Sanchez's group focuses on two high-risk populations – Lynch Syndrome (LS) and Familial Adenomatous Polyposis (FAP).

LS is characterized by pan-cancer genetic predisposition, with high risk for colorectal, endometrial, and ovarian cancers. In LS carriers, the pathogenesis of cancer involves activation of the immune system. Modification of the immune response is hypothesized to be a powerful chemoprevention and immune interception strategy. In a cancer prevention pivotal study (CAPP2), aspirin showed a cancer incidence difference between the aspirin and placebo cohorts in LS carriers. Naproxen (NSAID) had a better safety profile, and likely acts through activation/regulation of the immune system. Neoantigens can teach the immune system to recognize mutations present in the pre-malignant and early stage of disease. Nous-209, an adenoviral vaccine strategy, will be tested in a cancer prevention trial in LS carriers.

FAP predisposes individuals to CRC, with a lifetime risk of 100%. Effective prevention includes risk-reducing colectomies, yet patients develop duodenal cancer and small bowel tumors. The current SOC for duodenal cancer with FAP/familial FAP is sulindac (NSAID) plus erlotinib (EGFR inhibitor). Ocaliva is a novel cancer preventive agent for FAP, under trial, to determine treatment effect on duodenal burden.

Talk: Key Questions Related to Advancing Early Cancer Detection via MCEDs
Ernest Hawk, MD, MPH, UT MD Anderson Cancer Center

EDRN's framework for novel cancer test development has included Phase 1 to Phase 3 testing. NCI and industry are embarking on Phase 4 testing to demonstrate clinical utility of novel cancer tests in asymptomatic individuals with unknown cancer status. Leaders in the field of cancer testing came together to define idealized MCED test characteristics. Key criteria include safe, simple and inexpensive sample collection; sensitivity for early-stage detection; high specificity; provider and public acceptance; proven clinical validity and utility; and complementary benefit to current screening measures. A GRAIL-sponsored modeling study of MCED test performance suggests that there could be a reduction in incidence and in all-cancer 5-year mortality, showing possible benefit in a real-world setting if added to SOC.

Key questions to address when designing MCED clinical studies include whether tests should be used in high- or average-risk populations, and as additional or complementary screening; whether the endpoint is convincing, and the test used safely with well-defined downstream diagnostic processes; and how the test could affect health disparities. Diverse audience engagement during the MCED test development process is key to addressing barriers to cancer screening and issues of acceptability, access, and affordability.

Requisite frameworks should support MCED introduction for population health benefit. Industry engagement should complement the work of regulatory agencies in the identification of safe and effective MCED tests. Industry has advocated for transparency and collaboration, government and legal frameworks incentivizing early detection and prevention, and global and systems-level thinking. As 75% of the world's cancer deaths occur in low- and middle-income countries, an international perspective is critical to advance equity. NCI has enhanced commitment through the Cancer Screening Research Network to evaluate MCED tests and identify those having the greatest safety and effectiveness.

Panel: Near-Term Prospects for MCEDs to Advance Cancer Early Detection & Interception
Panelists: Danielle Krol, MD, FDA; Ruth Etzioni, PhD, Fred Hutchinson; Peter Bach, MD, DELFI Diagnostics

Dr. Krol commented on data components needed to create a compelling case for the FDA or other regulatory bodies. Proper study design with an intended population is critical for universal screening tests. Important components in MCED test development include a well-conducted analytical and clinical validation study, appropriate statistical analysis, and proper patient selection. She advised starting with higher-risk populations, screening asymptomatic patients, and broadening eligibility criteria to reduce disparities in cancer screening.

Dr. Bach spoke on the choice of high-risk versus average-risk populations. DELFI Diagnostics is an early detection company using circulating DNA to find cancer. There is a distinction between screening for a single cancer versus multiple cancers because the parameters and clinical utility of those tests are fundamentally different. For MCED tests, when clinical benefit is unknown, there is a need to start in a high-risk population to enrich pre-test probability of diagnosis for proof of concept.

Dr. Etzioni commented on which cancers should be screened by liquid biopsy. Not enough is known about the natural history of many cancers to know if early detection in each cancer type will clinically benefit patients. She suggested that the field focus on getting answers about the cancer prior to moving on to a screening program. Identifying and focusing on high-risk populations is important. The field should learn from the past (in reference to early detection studies in ovarian cancer that did not lead to clinical benefit) and that the ability to detect does not mean benefit.

Dr. Krol seconded the importance of learning from the past. She touched upon several challenges of MCED tests, including MCED test complexity, safety concerns (overcoming overdiagnosis and risk/benefit of unnecessary invasive procedures), the replacement of current screening methods due to the convenience of liquid biopsies, and questions surrounding endpoint validation. It is ultimately about safety and the standing question of whether MCED tests will lead to invasive diagnostic workups that are expensive and not feasible for many people.

Dr. Etzioni reiterated that these tests will lead to expensive follow-up procedures and emphasized the need to understand what happens after the test, and whether imaging can find the cancer in a non-invasive way, with equity and accessibility being key factors throughout the diagnostic process. Dr. Krol agreed and stated a hope that a simple, non-invasive procedure could benefit patients who are reluctant to go for more expensive follow-up scans, with a potentially quicker follow-up with the help of the system.

Dr. Bach added that democratizing access to the traditionally underserved is beneficial if the test has a clear follow-up path. The healthcare system can be an impediment to technological advancement. The behaviors associated with lung cancer tend to skew toward poorer, harder to reach populations, and liquid biopsy, if it performs as intended, can reach traditionally underserved communities. The biology of the tests mitigates the over diagnosis problem but creates another problem—namely that the signal preferentially picks up more aggressive cancers, which means the test is selectively sensitive. Using stage-distribution shifts as a therapeutic-like surrogate endpoint for screening tests could be foundationally weak. From a population standpoint, when most people can only be harmed by a test because they do not have disease, but a few can benefit, it is vital to measure the magnitude of that benefit and what it means for mortality.

As a clinician, Dr. Krol sees potential in early detection tests. From the regulatory perspective, any new technology is going to have challenges, and the FDA is happy to be a part of the discussion. Dr. Bach stated that with potential from this transformational space comes the obligation to do the right kind of research. Dr. Etzioni emphasized this is an opportunity to learn. She asked the FDA to lean on past lessons and take advantage of the decades of scholarship in screening among the community and think about diagnostic performance in the context of disease dynamics. She emphasized the need for a public data resource to learn about test performance and the natural history of cancer.

Concluding Remarks

Dr. Kelloff reiterated the importance of the concepts discussed during the meeting and thanked the new CSC co-chairs, Drs. Schmidt and Oxnard. He acknowledged panel members, session speakers, keynote speakers, the BC, the CSC, and many others at FNIH. Dr. Kelloff closed the Symposium with the sentiment that there is plenty of work to do in 2023.