Executive Summary

The Cancer Steering Committee (CSC), part of the Foundation of the National Institutes of Health (FNIH) Biomarkers Consortium (BC), brings together experts from academia, pharmaceutical companies, biotechnology companies, nonprofit organizations, the National Institutes of Health (NIH), and the U.S. Food and Drug Administration (FDA). The CSC facilitates multi-stakeholder projects; defines standards, best practices, and processes for biomarkers; and accelerates oncological drug development and patient management.

CSC projects are precompetitive, build upon existing infrastructure, and produce publicly available results. CSC projects include:

- Investigation of Serial Studies To Predict Your Therapeutic Response With Imaging and MoLecular Analysis (I-SPY TRIAL-2)
- Fluorodeoxyglucose-Positron Emission Tomography (FDG-PET) Lung and Lymphoma Trials
- Minimal Residual Disease (MRD) in Acute Lymphoblastic Leukemia (ALL)
- High-Definition Single-Cell Analysis in Metastatic Colorectal Cancer
- Advanced Metrics and Modeling with Volumetric Computerized Tomography (CT) for Precision Analysis of Clinical Trial Results (Vol-PACT).

Over the last few years, public health initiatives have focused on the importance of precision medicine. The White House Cancer Moonshot's Blue Ribbon Panel Report provides a perspective of the current state of precision medicine in oncology.

Some precision medicine efforts have focused on developing medications that target druggable genetic mutations or the immune system. In addition, researchers have also explored the utility of biomarkers to guide treatment decisions and predict treatment response.

Strategic Collaborations in Support of Precision Medicine in Oncology

A variety of strategic collaborations support precision medicine in oncology. For example, National Cancer Institute (NCI) initiatives include:

- NCI-Molecular Analysis for Therapy Choice (NCI-MATCH)
- The Lung Cancer Master Protocol (Lung-MAP)
- The Adjuvant Lung Cancer Enrichment Marker Identification and Sequencing Trials (ALCHEMIST)
- NCI Genomic Data Commons (GDC).

White House Cancer Moonshot programs include:

- The Adaptive Patient-Oriented Longitudinal Learning and Optimization (APOLLO) Network
- The International Proteogenomics Moonshot Consortium
- The Partnership for Accelerating Cancer Therapies (PACT)
- Project Genomics, Evidence, Neoplasia Information Exchange (GENIE)
- GRAIL: Circulating Cell-Free Genome Atlas Study.

Other programs that support precision medicine include:

- The Veterans Health Administration (VHA) Precision Oncology Program (POP)
- Oncology Research Information Exchange Network (ORIEN), which includes the Total Cancer Care (TCC) and Avatar projects
- Immediate Clinical Endpoint in Cancer of the Prostate (ICECaP)
- Clinical Proteomic Tumor Analysis Consortium (CPTAC).

MRD in Blood-Based Cancers

MRD is an important predictor that can promote efficiency and cost-savings in drug trials, thus expediting patient care.

For example, the FNIH MRD ALL project will evaluate existing data to determine the utility of MRD for predicting event-free survival (EFS) in pediatric and adult ALL, and standardize MRD testing across laboratories. In addition, efforts are underway to establish MRD as a surrogate endpoint in children with ALL and to improve MRD detection.

A white paper on MRD in myeloma, *The Role of Minimal Residual Disease Testing in Myeloma Treatment Selection and Drug Development: Current Value and Future Applications*, establishes the groundwork for collaborative explorations of novel clinical trial designs to demonstrate the value of incorporating MRD endpoints into prospective myeloma treatment studies.

Past and current research has also focused on druggable genetic mutations, such as:

- Multiple myeloma: *BRAF, KRAS*, or *NRAS*
- Acute myelogenous leukemia (AML): *FLT3*, *NPM12*, and *DNMT3A.* The Beat AML project will use central genomic profiling and local metaphase/interphase cytogenetics to assign newly diagnosed adults older than 60 with AML to a treatment arm.

MRD and related biomarkers could also be used for:

- Internal decisions about whether to continue a therapeutic approach or change treatments
- Identifying populations to study (e.g., patients nonresponsive to induction therapy)
- Regulatory decisions
- Treatment decisions
- Relapse predictions.

To promote the use of MRD as a surrogate endpoint, MRD data must be collected in a standardized way, using analytically validated assays. This will promote the pooling of de-identified data into a centralized database.

Imaging-Based Biomarkers

Imaging-based biomarker projects include:

- Vol-PACT—a BC project that analyzes volumetric CT imaging data from Response Evaluation Criteria in Solid Tumors (RECIST) and immune-related Response Evaluation Criteria In Solid Tumors (irRECIST) trials.
- FDG-PET Lymphoma Biomarker Qualification Project compared EFS rates of Rituximab, Cyclophosphamide, Doxorubicin Hydrochloride, Vincristine Sulfate, and Prednisone (R-CHOP) and dose-adjusted Etoposide Phosphate, Prednisone, Vincristine Sulfate, Cyclophosphamide, Doxorubicin Hydrochloride, and Rituximab (EPOCH-R) in untreated diffuse large B-cell lymphoma, and plans to develop a molecular predictor of treatment outcomes using molecular profiling.
- The Cancer Imaging Archive (TCIA): an NCI-sponsored resource of de-identified imaging data in a wide variety of cancers and phantoms.
- Quantitative Imaging Network (QIN): The NCI QIN uses superpixels as an option to segmentation.

Recommendations from committee members included:

- Encouraging researchers to share data to better determine efficacy endpoints supporting drug approval

- Leveraging existing resources, such as the TCIA and QIN
- Focusing FNIH and Vol-PACT efforts on obtaining original images to demonstrate superiority of new imaging approaches
- Discussing techniques to encourage growth of commercially available radiopharmaceuticals.

Mass and Growth Biomarkers for Precision Medicine

Another potential biomarker of treatment response, mass accumulation rate (MAR) of tumor cells, measures the rate at which individual cells change their mass. This is similar to a marker for patient response to antibiotics that measures bacterial proliferation in the presence of antibiotics. MAR will be incorporated as a complementary biomarker into the Individualized Screening Trial of Innovative Glioblastoma Therapy (INSIGhT).

Liquid Biopsy: Cancer Biology, Analytical and Clinical Validation, and Clinical Utility

Liquid biopsies can provide tumor samples when anatomic biopsies are not feasible, support a more global assessment of tumor biology, and help monitor changing cancer genetics. Biomarkers must demonstrate analytical validity, clinical validity, and clinical utility, although researchers have not reached a consensus definition for clinical utility. The Southwest Oncology Group (SWOG) S0500 trial in breast cancer was unsuccessful in demonstrating clinical utility for circulating tumor cells (CTCs), although other efforts are ongoing. Other projects include:

- High-Definition Single-Cell Analysis (HD-SCA) in Metastatic Colorectal Cancer. This project seeks to determine the correlation between CTCs from blood samples and solid biopsies taken from tumor touch preparations in patients with metastatic colon cancer.
- The Blood Profiling Atlas in Cancer, a project of the White House Cancer Moonshot, will create an open database for liquid biopsies, thereby accelerating blood profiling diagnostic technologies. Several companies, foundations, and academic institutions have agreed to share preanalytical data, and three working groups are focusing on data, samples, and technology.
- The ctDNA Reference Material Working Group was formed to design, develop, and validate reference material for ctDNA testing. The group will also develop a white paper describing preanalytical processing. A mock submission discussion is planned with the FDA to obtain guidance on addressing regulatory issues.

Clinical studies are also evaluating the use of liquid biopsies to screen for:

- *Estrogen receptor 1* (*ESR1*) mutations, as a risk factor for metastatic, hormone-receptor-positive breast cancer in patients previously treated with an aromatase inhibitor. A focus on *ESR1* mutations might promote development of selective estrogen receptor downregulators or selective estrogen receptor modulators.
- *BRAF V600* mutations, as a predictor of metastatic or unresectable melanoma.
- Androgen-receptor splice variant 7 (AR-V7) messenger RNA assay, to predict negative responsivity to androgen receptor therapies in patients with prostate cancer.
- A *T790M* mutation and tissue profiling, to assign non-small-cell lung cancer (NSCLC) patients to appropriate therapies.

Clinical Validation and Determination of Clinical Utility of ctDNA, CTCs, and Exosome Assays

The FDA does not necessarily require a demonstration of concordant results between plasma and tissue testing, although these data can help in understanding underlying processes. Urine tests are probably not useful, since they provide fragmented DNA segments.

Cancer Research in the Cancer Moonshot Era

The White House Cancer Moonshot's Blue Ribbon Panel has recommended areas of cancer research that are poised for acceleration. In addition, the NCI continues to support research in areas that do not fall under these recommendations. The NCI is consulting its advisory boards and establishing advisory groups within the NIH to determine best uses for funding.

Protein Biomarkers for Companion Diagnostic Tests

Studies comparing PD-L1 assays have found concordance among pathologists for some measures, but not all. These studies include:

- The Blueprint study, which assessed four FDA/Investigational Use Only (IUO) PD-L1 assays
- The National Comprehensive Cancer Network (NCCN) study, which assessed three FDA/IUO PD-L1 assays, and one laboratory-developed test.

However, it would be more informative to detect numbers of activated T cells instead of testing for one protein biomarker. Measuring activated T cells and other biomarkers of immune system functioning will yield important information to determine optimal therapies for each cancer patient. Once appropriately standardized, selected reaction monitoring mass spectrometry will also be useful in biomarker analyses to quantify protein measurements.

With different tests being performed at different institutions, it is unknown if those tests are comparable across laboratories. Standardization of diagnostic tests that use antibodies would address this issue.

Immuno-oncology Biomarkers: Project Opportunities

Advances in single-cell genomics allow systematic dissection of the tumor microenvironment (TME) to better determine the impact of chemotherapy on tumor immunity. Examples include:

- Single-cell RNA sequencing (scRNA-Seq), which can identify cell types, molecular states, cell interactions, spatial positioning, and cell circuits within the tumors.
- Single-nucleus RNA sequencing (sNuc-Seq), a new technology to profile RNA molecules in single nuclei, thereby overcoming challenges of small samples. The BC will propose a study using scRNA-Seq to dissect the TME of patient samples before, during, and following therapy.
- Dronc-seq, a method that combines sNuc-Seq with a massively parallel droplet-based method for profiling tens of thousands of nuclei at once. To date, 1,481 cells from 10 patients have been profiled.

A multiplex polymerase chain reaction (PCR) immunosequencing assay system provides the basis of a research use only ImmunoSeq TCR beta kit developed by Adaptive Biotechnologies. The assay enumerates primers recognizing each V and J gene segment for any given immune receptor locus and has shown reproducibility in beta testing across 10 sites. Statistical analyses can be conducted to predict patient response to immunotherapies.

T-cell transfer therapy has several advantages over other immune-based therapies for cancer. Patients can be given large numbers of highly selected cells that have been activated *ex vivo* to exhibit high avidity for tumor antigens. Identifying and targeting mutations unique to each cancer has the potential to extend cell therapy to patients with common epithelial cancers, and autologous lymphocytes that are genetically engineered to express TCRs or chimeric antigen receptors can mediate the regression of metastatic cancers.

MD Anderson's Moonshot Program's APOLLO platform is a clinical trials partnership between the NCI, the VA, and the Department of Defense to screen leukemia and melanoma patients for genomic and

proteomic information, thereby matching tumors to targeted immunotherapies. MD Anderson also participates in a clinical trial alliance that will assess predictive markers for immunotherapy in tissues from 1,483 patients with a variety of cancer types.

Researchers are also exploring how the tumor microenvironment affects tumor-infiltrating lymphocytes TILs), and whether TIL metabolic pathways be used as markers of dysfunction or to predict outcomes of immunotherapy.

A companion diagnostic test provides information that is essential for safe and effective use of a specific drug. A newer concept for companion drug diagnostics is complementary diagnostics, which are biomarker tests that aid in the risk/benefit analysis for individual patients.

Promising Biomarkers

Biomarkers should predict if a patient will respond to therapy, allow assessment of efficacy, or aid in diagnosis. Enumerating the number of mutations in a patient's tumor is a first step toward predicting patient response, since virtually all the immunotherapies previously discussed recognize mutations.

Big Data: Data Standardization, Harmonization, and Sharing

The NIH genomic sharing policy requires public sharing of genomic datasets. The hope is that data generated from precision medicine and precision oncology will increase the fundamental understanding of how to better treat patients.

Datasets currently include:

- NCI's GDC, part of the NIH Big Data to Knowledge (BD2K) initiative. Current content is from TCGA and the TARGET initiative, with additional datasets forthcoming.
- The FDA's Information Exchange and Data Transformation (INFORMED) project aggregates FDA clinical trial data using a combined manual and automated approach.
- CancerLinQ (CLQ) prospectively collects electronic health records (EHRs) from oncology patients to provide quality analytics to participating practices and identify knowledge gaps.
- The Targeted Agent and Profiling Utilization Registry (TAPUR) is a prospective phase 2 clinical trial to match genomic characteristics of tumors to the use of marketed drugs that are used off label.
- The Project Data Sphere® Cancer Research Platform facilitates the use of clinical trials-level data to answer important questions.

A proposed pilot project will leverage data collected for Centers for Medicare & Medicaid Services-approved quality measures to identify germline genetic variants associated with prostate cancer aggressiveness. This may also help identify patients who are likely to fail active surveillance and predict disease progression. The resulting model may be expandable to other diseases.

Challenges to data sharing in oncology include:

- Restricted access to data due to bureaucracy issues or issues with de-identifying data
- Lack of academic credit
- Divergent data formats
- Intellectual property issues.

Catalyzing Translational Innovation

The mission of NIH's National Center for Advancing Translational Sciences (NCATS) is to catalyze the generation of innovative methods and technologies that will enhance the development, testing, and implementation of diagnostics and therapeutics across a wide range of human diseases and conditions.

Cross-Disease Analysis of Biomarker Initiatives: Analogies, Synergies, and Approaches for Collaboration

Collaborations across disease conditions can help inform biomarker initiatives. Examples include:

- Evidentiary criteria for biomarker use in drug development: A framework was released December 6, 2016, that will help support the FDA in the development of relevant guidance for biomarker qualification. The Framework process is intended to be interactive and dynamic, and the decision to move to qualification is made in collaboration between the sponsor and the FDA. Early planning by the sponsor for the data requirements will provide a more efficient path to qualification.
- The NIH's Extracellular RNAs (exRNA) Communication Consortium seeks to understand the biology and the potential for using exRNA in biomarker and therapy development. The Data Management and Resource Repository serves a central role by housing all shared data. The steering committee is comprised of NIH investigators, external scientists, and the FDA.
- Data sharing across portfolios for biomarker development, which will help researchers learn from each other across therapeutic areas. For example, the Immunology Database and Analysis Portal (ImmPort) promotes re-use of immunological data generated by National Institute of Allergy and Infectious Diseases (NIAID)investigators. These data could inform cancer biomarker development.
- Incentivizing data collection for biomarker development research: Incentives should be created for collecting data elements at the point of care that are agnostic to specific disease areas.
- Converting data into information: Incentives are needed to help physicians more effectively enter data into EHRs, and tools are need to extract data effectively and informatively from those EHRs.