The Honorable Richard C. Shelby  
Chairman  
Subcommittee on Defense  
Committee on Appropriations  
United States Senate  
Washington, DC 20510

Dear Mr. Chairman:

The enclosed report responds to House Report 115-219, page 282, accompanying H.R. 3219, the Department of Defense Appropriations Bill, 2018, concerning the establishment of a task force on research for metastatic cancer of all types, with a focus on clinical and translational research aimed at extending the lives of advanced state and recurrent patients.

In 2017, the 16-member Metastatic Cancer Task Force planned and conducted a two-day Operational Meeting to inform this report to Congress. Twenty-seven internationally-recognized experts in metastatic cancer were invited to speak on the state of research and treatment in their areas of expertise; each focused on the state of the science, research gaps, major barriers, and recommended collaborations and initiatives. By analyzing these testimonies, the Task Force identified seven areas around which the lives of patients with metastatic and recurrent cancer could be extended: Clinical Trials, Diagnostics, Biology of Disease, Therapies, System Infrastructure, Patient-related Factors, and Survivorship and Palliative Care. This report details the specifics of the testimony in those areas; it also provides 29 conclusions and 27 recommendations from the Task Force.

Thank you for your interest in the health and well-being of our Service members, veterans, and their families. A similar letter is being sent to the other congressional defense committees.

Sincerely,

Stephanie Barna  
Performing the Duties of the Under Secretary of Defense for Personnel and Readiness

Enclosure:  
As stated

cc:  
The Honorable Richard J. Durbin  
Vice Chairman
The Honorable Kay Granger  
Chairwoman  
Subcommittee on Defense  
Committee on Appropriations  
U.S. House of Representatives  
Washington, DC 20515

Dear Madam Chairwoman:

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Sincerely,

[Signature]

Stephanie Barna  
Performing the Duties of the Under Secretary of Defense for Personnel and Readiness

Enclosure:
As stated

cc:
The Honorable Peter J. Visclosky  
Ranking Member
The Honorable William M. "Mac" Thornberry  
Chairman  
Committee on Armed Services  
U.S. House of Representatives  
Washington, DC 20515  

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[Signature]

Stephanie Barna  
Performing the Duties of the Under Secretary of Defense for Personnel and Readiness

Enclosure:  
As stated

cc:  
The Honorable Adam Smith  
Ranking Member
The Honorable John McCain  
Chairman  
Committee on Armed Services  
United States Senate  
Washington, DC 20510

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Stephanie Barna  
Performing the Duties of the Under Secretary of Defense for Personnel and Readiness

Enclosure:  
As stated

cc:  
The Honorable Jack Reed  
Ranking Member
REPORT TO CONGRESSIONAL DEFENSE COMMITTEES

Report on the Metastatic Cancer Task Force

SUBMITTED BY THE ASSISTANT SECRETARY OF DEFENSE FOR HEALTH AFFAIRS

April 2018

The estimated cost of this report or study for the Department of Defense (DoD) is approximately $400 for the 2018 Fiscal Year. This includes $0 in expenses and $400 in DoD labor.
Generated on 12 JAN 2018   RefID: 1-43AAB16
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I. Executive Summary

This report fulfills the reporting requests of the House Report 115-219, page 282, to accompany H.R. 3219, the Department of Defense (DoD) Appropriations Bill, 2018; it presents the findings of a task force established to explore clinical and translational research efforts on extending the lives of patients with advanced state and recurrent metastatic cancer. This report defines metastatic cancer as one that has spread beyond the primary organ of origin and regional lymph nodes into other major organ sites.

In 2017, the 16-member Metastatic Cancer Task Force planned and conducted a two-day operational meeting to inform this report to Congress. 27 internationally-recognized experts in metastatic cancer were invited to speak on the state of research and treatment in their areas of expertise; each focused on the state of the science, research gaps, major barriers, and recommended collaborations and initiatives. By analyzing these testimonies, the Task Force identified seven areas around which the lives of patients with metastatic and recurrent cancer could be extended: Clinical Trials, Diagnostics, Biology of Disease, Therapies, System Infrastructure, Patient-related Factors, and Survivorship and Palliative Care. This report details the specifics of the testimony in those areas; it also provides 29 conclusions and 27 recommendations from the Task Force.

II. Purpose of Report

This report responds House Report 115-219, Page 282, to accompany 3219, the DoD Appropriations Bill, 2018, Metastatic Cancer Research:

The Committee continues to support the establishment of a task force to research metastasized cancer with a focus on clinical and translational research aimed at extending the lives of advanced state and recurrent patients. The Committee directs the Assistant Secretary of Defense (Health Affairs) to submit an updated report to the congressional defense committees not later than 60 days after the enactment of this Act on the status of the establishment of a task force under the Congressionally Directed Medical Research Program to focus on research for metastatic cancer of all types.2

This report fulfills the Committee’s requirement; it describes the establishment of and presents the findings of a task force focused on clinical and translational research aimed at extending the lives of advanced state and recurrent metastatic cancer patients.
Introduction

Cancer remains the second leading cause of death in the United States (U.S.) and a leading cause of death worldwide, despite advances in preventative care and research initiatives that have improved patient outcomes in recent decades. In the U.S. alone, it is estimated that there will be approximately 1,688,780 new cases diagnosed and 600,920 deaths from cancer in 2017. Cancer-related death rates have decreased by 23 percent over the last 25 years, which can be attributed to a decrease in the overall incidence of cancer, as well as improvements in both the early detection and treatment of certain cancers, including breast and colon cancer. However, significant advancements are still needed with regards to the prevention and treatment of metastatic disease, which is associated with 90 percent of cancer-related mortality. Notably, the prevention of cancer and the subsequent prevention of metastatic cancer is more cost-effective and may save more lives than treating metastatic disease. While further prevention, early detection, and treatment efforts are likely to continue to improve cancer-related mortality rates in the context of early stage disease, the effect on patient outcomes and associated economic cost is most significant for patients with metastatic cancer.

In recent decades, the five-year survival rate of certain cancers has improved dramatically. Specifically, metastatic cancers such as testicular cancer and Hodgkin’s lymphoma have seen high cure rates due to effectiveness of combination chemotherapy treatments. Prior to the early 1970s, the long-term survival rate among patients with metastatic testicular cancer was a mere 5 percent. However, with the introduction of combination chemotherapy regimens, those numbers have improved to between 80 and 90 percent. Furthermore, the introduction of targeted cancer therapies, such as those that are used in the treatment of human epidermal growth factor receptor 2 positive breast cancer or V-Raf murine sarcoma viral oncogene homolog B inhibitors for the treatment of some melanomas, have significantly extended the lives of patients with these metastatic cancers. Recently, the introduction of immune checkpoint inhibitors, which prime the immune system to attack tumor cells based on molecular targets such as the receptors cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) and programmed cell death protein 1 (PD-1), has also extended the period of progression-free survival and improved overall survival in some patients with metastatic cancers, including metastatic melanoma, non-small cell lung cancer, and renal cell carcinoma. While these advancements highlight some progress in the field, most patients with metastatic cancer still succumb to their disease. This necessitates improvements in metastasis prevention and treatment to focus on curing the disease and reducing overall cancer-related morbidity and mortality.

Methodology

The DoD, through Health Affairs, directed the John P. Murtha Cancer Center (MCC) of the Uniformed Services University/Walter Reed National Military Medical Center (WRNMMC) to lead its response. The MCC formed the Task Force from 16 invited federal employees who are recognized experts in the field of cancer and were drawn from four federal agencies (the DoD, National Cancer Institute [NCI], Congressionally Directed Medical Research Programs [CDMRP], and U.S. Department of Veterans Affairs [VA]) (Appendix A). Two Task Force members are also cancer survivors themselves. From March 2016 to December 2016, the Task Force held bi-weekly meetings by teleconference to strategize, organize, and develop the means
of informing the report. To do this, it was determined that outside (i.e., non-federal) national and international experts in the specific field of metastatic cancer research and treatment would be invited to testify to the Task Force at a two-day Operational Meeting, which was held on December 12-13, 2016 in McLean, VA. This meeting brought together the Task Force, metastatic cancer experts from around the world, and representatives from patient advocacy organizations to hear testimony presented by the select group of 27 speakers (Appendix C). Furthermore, this testimony was intended to drive the development of recommendations regarding the measures needed to accelerate clinical and translational research on metastatic cancer aimed at extending the lives of advanced state and recurrent patients. As such, each expert was directed by the Task Force to focus their testimony on the following questions:

1. **State of the Science**—Summarize up to five of the most important/seminal findings in your specific area of research over the past 5–10 years as it pertains to extending the lives of patients with metastatic cancer.

2. **Research Gaps**—Describe up to three major gaps in the field of metastatic cancer research that, if addressed, could potentially accelerate progress towards extending the lives of affected patients.

3. **Major Barriers**—Other than funding, describe up to four major barriers (i.e., scientific barriers, programmatic barriers, other barriers), in your field that are inhibiting progress towards extending the lives of metastatic cancer patients. Suggest ways to overcome these barriers.

4. **Recommended Collaborations and Initiatives**—Describe the top three initiatives that must occur in this field to accelerate clinical and translational research to extend lives of advanced stage and recurrent patients with metastatic disease (e.g., emerging trends or developments that can be exploited). What collaborations will be required to meet these gaps?

Following this Operational Meeting, a detailed Proceedings Report (Appendix H) was developed transcribing each speaker’s testimony, question and answer sessions, and panel discussions. Subsequently, the responses to the above questions from each speaker’s testimony were categorized into seven topic areas: (A) Clinical Trials, (B) Diagnostics, (C) Biology of Disease, (D) Therapies, (E) System Infrastructure, (F) Patient-related Factors, and (G) Survivorship and Palliative Care. Each topic area summarizes the state of the science, research gaps, major barriers, and recommended collaborations and initiatives. These seven topic areas, each with four major subcomponents, were then analyzed and utilized to make recommendations to further progress in the field of metastatic cancer.

**Report Organization**

The scientific testimonies gathered from the Metastatic Cancer Task Force Operational Meeting were categorized into the following seven topic areas:

A. **Clinical Trials** includes aspects of clinical trials such as innovation, administrative and regulatory burden, representative populations of enrolled patients, and issues regarding study design and outcomes.

B. **Diagnostics** includes topics related to technology (e.g., imaging, biomarkers) necessary for the rapid and accurate diagnosis and monitoring of metastatic cancer.
C. **Biology of Disease** includes topics related to research aimed at a greater basic understanding of cancer metastasis.

D. **Therapies** includes topics involving the treatment of metastatic cancer, such as “failed” or “off-label” drugs and the development of new drugs and drug targets.

E. **System Infrastructure** includes topics such as big data, bioinformatics, promotion and tenure of researchers, high-risk/high reward research, collaborations between researchers, and the consortia needed to progress the field of metastatic cancer.

F. **Patient-related Factors** includes topics such as healthcare disparities, modifiable factors (e.g., smoking, obesity, alcohol use, etc.), patient compliance with treatment, and the effect of social networks on patient outcomes.

G. **Survivorship and Palliative Care** includes topics related to the longer term care of metastatic cancer patients, such as via survivorship care plans or adequate access to palliative care.

**Highlighted Findings**
The 27 testimonies resulted in the realization of relevant, recurring findings across all cancer types. The detailed findings from this report are summarized in the Proceedings Report (Appendix H). In addition, speaker testimonies were analyzed, consolidated, and presented below, with each of the seven topic areas discussing the four major subcomponents: state-of-the-science, research gaps, major barriers, and recommended collaborations and initiatives.

V. **Expert Testimony and Task Force Summary**

A. **Clinical Trials**

1. **State of the Science**

Clinical trials evaluate whether an intervention improves outcomes for patients with cancer. Of the 1.7 million patients diagnosed with cancer every year in the U.S., 3 percent of adults and 60 percent of children enroll in a clinical trial. However, only 40 percent of all clinical trials and 60 percent of Phase III clinical trials meet their accrual goals. The data gained from prospective studies investigating metastatic cancer are often not directly comparable due to varying diseases, study assessments, and endpoints. Improvements in the survival of patients with metastatic cancer may be advanced as researchers and clinicians streamline the design and implementation of clinical trials.

A key element in the successful implementation of clinical trials is collaboration between researchers and clinicians. Since the 1960s, the NCI has played a key role in fostering collaboration in cancer research through the establishment of the Clinical Trials Cooperative Group Program. In 2014, the NCI restructured these groups to form the National Clinical Trials Network (NCTN), which included five adult Network groups in the U.S. and the Canadian Clinical Trials Group. The NCTN was developed to address new research challenges, including tumor biology and its implications for targeted therapy, as well as to streamline and centralize critical functions such as tissue banks, imaging support, and ethics reviews. Additional cancer research groups have been established to improve coordination and streamline the conduct of clinical trials. For instance, the Prostate Cancer Clinical Trials Consortium (PCCTC), a clinical research group sponsored by the Prostate Cancer Foundation and the DoD Prostate Cancer
Research Program, was formed to facilitate the use and dissemination of information between the scientific and medical communities.

Another element that plays a role in the success of clinical trials is recruitment and study design. Patient recruitment into clinical trials can be hindered by many factors, including the availability of information about the clinical trial, inconvenience, time commitment, and restrictive eligibility criteria. To help with clinical trial recruitment, patient navigators have been introduced at some study sites. The patient navigator functions as a clinical trials coordinator, who is available to answer patients’ questions and follow up with them once they have been evaluated by a treatment team. The navigator also provides a personalized approach to clinical trials by becoming a link between the patient and the researcher or clinician, and assisting with patient education.

Regulatory and administrative requirements can be a challenge to meet. The American Society of Clinical Oncology-American Association of Cancer Institutes (ASCO-AACI) Best Practices in Cancer Clinical Trials Initiative was established to promote practical solutions for existing regulatory and administrative research requirements. A working group convened and conducted a survey of research sites to identify the most burdensome administrative and regulatory aspects of conducting clinical trials. Subsequently, a workshop was held to identify tangible solutions to address these burdens. The findings from this workshop have been disseminated, and ASCO-AACI is now working to actively implement the recommendations of the working group.16

2. Research Gaps

There are relatively few trials and initiatives specifically focused on the science of metastasis. Notably, many clinical trials are designed based on data from primary tumors or patients without metastatic disease. A greater number of clinical trials focused on the study of metastatic cancer is needed to improve treatment and adequately assess risk and outcomes within representative populations. In particular, more randomized controlled trials with extensive follow-up protocols are necessary to advance the field of metastatic cancer research. Moreover, research in this field is not evenly distributed across patient cohorts and population groups, necessitating greater attempts to provide clinical trials outreach to patients with metastatic cancer across all demographics. In addition, research is needed to better understand the role of modifiable behaviors (e.g., exercise, smoking, diet, alcohol use) in the development and progression of metastatic cancer. Furthermore, studies involving epigenetic targeted therapies, proliferative and dormant cancer cells, predictors of risk and remission, the role of social interventions, mixed responses to treatment (e.g., new disease despite responsive metastases), and patients who are unresponsive to immunotherapy are needed.

3. Major Barriers

The complexity of study design, difficulty in recruiting trial participants, and burdensome administrative/regulatory requirements all pose barriers to the conduct of successful clinical trials for metastatic cancer.

Clinical trial study design is a major barrier within the field of metastatic cancer, as it is complex and the drug development process is costly. Current clinical trial study design is outdated and has not adapted to the changing landscape of cancer research. Greater connection between the laboratory and the clinic will advance the study and understanding of disease-
specific processes involved in metastasis. Preclinical and clinical research is often difficult to translate into clinical practice. Clinical trials use different assessments and endpoints, limiting their comparability. Information that can be learned from failed trials is less likely to be published in peer-reviewed literature. These challenges limit the interpretation of clinical trials and the development of new therapies.

Insufficient recruitment of patients can impact the success of clinical trials. Patients at high-risk for metastatic disease may not be aware of clinical trials and resources that are available to them. This limits the sample size and diversity of study cohorts, which then limits the generalizability of study results to the wider population. Lack of recruitment is a significant barrier for clinical trials investigating rare diseases, which would include many metastatic diseases and most pediatric cancers. Even if patients with rare diseases are identified, access barriers may prevent them from participating in clinical trials. Additional barriers to recruitment include patient and physician knowledge (clinical trials are not only for patients without other treatment options), diversity issues, insurance, and financial burden (e.g., travel, time off from work). Furthermore, the poor physical condition of patients with advanced cancer, which may limit their eligibility to enroll in studies, can negatively impact the success of clinical trials for metastatic cancer.

Healthcare disparities also hinder the success of clinical studies and can limit the generalizability of trial findings to the wider population. According to the NCI, healthcare disparities are “differences in cancer incidence, cancer prevalence, cancer survivorship, and burden of cancer or related health conditions that exist among specific population groups in the U.S.” These population groups may be characterized by age, disability, education, race and ethnicity, gender, geographic location, and/or income. To enhance generalizability, clinical trial design should focus on being inclusive of underserved populations.

There are many administrative requirements involved in conducting a clinical trial, including extensive regulatory requirements designed to protect patients. Such regulations include U.S. Department of Health and Human Services (HHS) regulations, the Common Rule, U.S. Food and Drug Administration (FDA) requirements, local institutional review board (IRB) interpretations of regulations, etc. The complexity of regulatory compliance results in delays in initiating and conducting clinical trials. For example, adverse events unrelated to the clinical study are often over-reported and might be lessened by highlighting the definitions of reportable adverse events and increased investigator and study-monitor education. Multi-center trials often incur parallel, duplicative contracting systems that result in multiple negotiations and renegotiations between each center, further delaying the start of complex clinical trials in metastatic cancer. Attempts should be made to balance important patient safety concerns with over-regulation and onerous administrative requirements.

4. Recommended Collaborations and Initiatives

Addressing the challenges associated with clinical trial design, patient recruitment, administrative/regulatory barriers, and results reporting is imperative to drive metastatic cancer research forward.

Clinical trial design for patients with metastatic cancer may require endpoints that can be different from standard non-metastatic cancer clinical trials. These novel endpoints will need to be designed into future metastatic cancer clinical trials and can include biomarker endpoints, surrogate endpoints, and novel imaging endpoints, as well as length of survival standard
endpoints.

Metastatic cancer clinical trials have certain challenges in terms of recruitment, which can involve inclusion criteria that are too restrictive for patients with metastatic disease. These may also include metastatic cancer patients with a poor or lower performance status who have undergone multiple treatment regimens and consequently enter trials with less functional reserve than patients beginning de novo cancer treatments. Therefore, recruiting metastatic cancer patients into clinical trials requires a consideration of modification of endpoints and inclusion criteria, and outreach, particularly at community cancer centers since patients prefer to be treated and receive access to clinical trials within their communities as opposed to large cancer centers in urban areas.

Like clinical trials for non-metastatic cancer, metastatic cancer clinical trials disproportionately underrepresent the diversity of the nation in terms of multiple patient characteristics. This makes the outcomes of the studies less representative of the nation as a whole. Efforts should be made to address healthcare disparities as they apply to clinical trials for metastatic cancer patients in terms of diversity, community outreach, and inclusion of all patient subgroups and ethnicities to more adequately represent the overall population with metastatic cancer.

There are multiple regulatory burdens on metastatic cancer clinical trials, including variations in the interpretation of federal regulations as they apply to the local IRB approval level and the need for a significant number of administrative support staff to run complex metastatic cancer clinical trials. Easing this regulatory burden will open more opportunities for involvement of all types of patients in metastatic cancer clinical trials. A proposed mechanism by which this could occur is through the encouragement of individual organizations or hospitals to have centralized IRB reviews of protocols across various organizations in order to minimize regulatory burden and/or to enter into reliance agreements between institutions to accept the results of one organization’s IRB as sufficient to meet the regulatory requirements of other IRBs. This would help minimize the redundant administrative impact on multi-center protocols involving metastatic cancer patients.

Another barrier to clinical trial efficiencies is linked to reporting and/or publishing of negative results. Properly disseminating negative trial results reduces the chances of redundant studies in the future. Furthermore, re-examination of the results against alternate endpoints or using different cohorts of the trial population can lead to new discoveries. However, access to data from outcomes that were originally labeled as "negative results" has been difficult. Publishing negative results is generally considered a low-priority activity within scientific circles and is often passed over by scientific journal editors. Recent updates to Title VIII of the FDA Amendments Act of 2007 are welcome improvements to this issue, including the “final rule” issued by the U.S. Department of HHS and a complementary policy by the National Institutes of Health in the fall 2016, that requires publishing summarized clinical trial results to clinicltrials.gov, not later than one year after the primary trial completion date. Further expansion of the rules, which do not yet cover early phase trial results for non-NIH funded efforts, and encouragement to publish negative results with complete datasets will also drive clinical trial efficiencies. Finally, encouraging industry to share early-phase trial results from non-federally funded studies would provide enormous benefit.
B. Diagnostics

1. State of the Science

For the purpose of this report, diagnostics refers to the tools used to identify new or progressive cancer and to monitor the effects of ongoing therapy. Over the last decade, significant growth in cancer imaging has aided in the diagnosis of metastatic cancer.

Advancements in magnetic resonance imaging (MRI), computed tomography (CT), ultrasound, and positron emission tomography (PET)/single-photon emission CT technologies have improved the field of cancer imaging, and the cost of the imaging has decreased over time. The recent development of novel and highly specific PET agents continues to improve imaging for certain tumor types.

Molecular profiling continues to facilitate the identification of biomarkers in certain tumor types. These can be used for the prediction and blood-based monitoring of disease progression and metastasis. Tremendous efforts have been made to discover novel cancer biomarkers to monitor metastasis; however, there is a striking discrepancy between the effort directed towards metastasis-relevant biomarker discovery and the number of biomarkers that are incorporated into clinical practice.

2. Research Gaps

Early detection of metastatic disease is currently not possible for many types of cancers. While much of this may be due to an insufficiency of adequate biomarkers or other detection modalities (e.g., imaging), it may also be due to an inability to recognize the disease early on, therefore necessitating increased patient and provider education, or advancing the science to understand and detect early disease.

As mentioned, there are too few biomarkers and other diagnostic/prognostic tools to monitor both the presence and status of metastasis. Examples can include the inability to reliably detect micrometastases, circulating tumor cells, cancer progression (e.g., dormancy versus regrowth), and the development of treatment resistance. Furthermore, there are insufficient methods of assaying predictive biomarkers.

Clinical predictors of metastasis to inform risk stratification are, in many cases, insufficient. Better clinical and molecular predictors are needed to define populations most at risk of disease progression to advanced cancer states, allowing for earlier and more targeted intervention to improve patient outcomes.

3. Major Barriers

Additional biomarkers are needed to monitor cancer progression, as well as to guide the selection of effective therapies. Reasons for the relative lack of biomarkers include the high cost of biomarker identification and development, challenges in the identification of true predictive biomarkers, challenges or difficulties in validating assays for predictive biomarkers, and an insufficient understanding of the biomarker development process from discovery to clinical deployment (e.g., what a biomarker has to be or how an assay has to be performed).

Technical barriers also impede the development of metastatic cancer diagnostics. Few facilities have the capabilities to develop novel imaging compounds. Of those that do, technical limitations and variable monitoring standards impede the ability to monitor tumor progression, metastasis, and the effect of therapies. Improvements are needed to effectively separate cells
from solid tissues, maintain cell viability, and perform single cell sequencing. Imaging technologies have valuable utility, but imaging agents can be taken up by many different processes, resulting in non-specificity. Additionally, there are a limited number of imaging tracers and standards for imaging results, as well as a lack of sufficiently sensitive and specific imaging and detection methods for many cancers.

4. Recommended Collaborations and Initiatives

Advancing diagnostics for the detection and monitoring of metastatic cancer requires technological advancements, the identification of biomarkers, and the development of novel diagnostic tests.

An initial recommendation is that disease burden be tracked with state-of-the-art technologies. For example, blood-based monitoring (i.e., liquid biopsy) may prove to be an efficient, useful, and information-rich disease detection technique. Blood samples should be collected throughout disease progression to better understand metastasis and treatment response over time. Furthermore, imaging technologies should be improved to detect minimal residual disease and dormant tumor cells.

Another recommendation is to invest additional research efforts into the development and validation of biomarkers for the monitoring of tumor cell changes, migration, and the tracking of outcomes. It would also be beneficial to pursue the identification and validation of surrogate biomarkers of metastasis and dormant tumor cells. Greater understanding of the full rigor of the biomarker development process needs to be made available to the wider scientific community. Early engagement with regulatory agencies (e.g., Oncology Center of Excellence at FDA, the FDA Center for Devices and Radiological Health) in the biomarker development process by scientists (i.e., clinicians and researchers) is encouraged. For example, the American Association of Cancer Research (AACR)-FDA-NCI Cancer Biomarkers Collaborative was established to accelerate the translation of cancer therapies for use in the clinic. The Collaborative does this by facilitating the processes needed for the development of validated biomarkers as well as their use in clinical trials to maximize patient benefit. This involves determining the context of use for the biomarker (e.g., diagnostic, therapeutic) and then demonstrating analytical validity, clinical validity, and clinical utility. Finally, addressing the ability to get prompt reimbursement decisions for FDA-approved biomarker panels is needed to decrease barriers to implementation of developed biomarker panels based on lack of reimbursement by payers.

Additionally, as biomarkers are being developed, it is recommended that sampling be focused at the treatment decision point instead of using samples of convenience (e.g., frozen samples of the primary tumor) to inform the choice of therapy. Imaging and/or biomarkers are needed to predict the likelihood that a biopsy will result in the positive detection of cancer, which can thus provide sufficient evidence that a biopsy should be performed in a particular patient.

Finally, immune diagnostic tests are recommended to assess immune status in individual patients, as this can affect their treatment response (e.g., state of tolerance, need for amplifying tumor-specific T cells, predictors of responses). Similar to the standardized Response Evaluation Criteria in Solid Tumors (RECIST), standardized criteria for the evaluation of responses to immunotherapy should be developed.
C. Biology of Disease

1. State of the Science

Until recently, most of the emphasis in cancer research has focused on the biology of primary tumors rather than metastatic tumors. Although most cancer deaths are the result of metastatic disease, some deaths are due to other factors, such as overwhelming cytokine responses. These factors contributing to cancer-related mortality could be further explored to develop novel targeted treatments.

Metastasis progression can occur in parallel with the primary tumor, and researchers are beginning to understand how cancer cells disseminate from their original location, travel through the body, and adapt to a new niche to form metastatic tumors. Metastases can be found in various distant organs, as well as in different regions within a single organ. Certain cancers tend to form metastases in specific organs. For example, breast cancers tend to form metastatic tumors in the bone, brain, liver and lung, whereas colon cancers typically tend to form metastases in the liver. Factors that contribute to and support the invasion of tumors and metastasis include blood flow, tumor microenvironment, signaling cascades, genomic instability of the primary tumor, metastatic suppressor genes, exosomes, chronic inflammation, and the microbiome. Metastatic potential is inheritable and there is significant value to identifying patient-specific metastatic vulnerability early in disease progression.

Recent evidence by Janni et al. suggests that the number of circulating tumor cells present in the blood correlates with a higher risk of developing metastasis. Dormant cancer cells can persist in patients both with and without overt metastasis. Furthermore, these dormant cells tend to be resistant to treatment and are associated with a poor prognosis. Notably, dormant and proliferative cells can co-exist in patients with metastatic cancer. Control of dormancy and reactivation of dormant cells is driven by cross-communication between the cancer cells and the microenvironment, and involves factors such as adhesion signaling, stress-signaling, and epigenetics.

The major obstacle for the eradication of metastases is the biologic heterogeneity of both tumor cells and the microenvironment that constitute primary cancers and metastases. By the time of diagnosis, primary tumors contain multiple cell populations with heterogeneity in growth rate, karyotype, cell surface receptors, antigenicity, immunogenicity, marker enzymes, gene expression, sensitivity to various cytotoxic drugs, invasion, and metastatic potential. This biologic diversity is not restricted to primary tumors. The cellular composition of metastases in the same organ or within different organs can be heterogeneous, both within a single metastasis (i.e., intrallesional heterogeneity) and among different metastases (i.e., interlesional heterogeneity). The degree of heterogeneity allows the cancer cells to evolve in response to treatment, which drives treatment resistance and metastatic relapse.

2. Research Gaps

While it is known that metastasis is a leading cause of cancer-related mortality, the direct mechanisms by which this occurs are not yet well understood. One of the largest research gaps in the field of metastasis research is understanding the biological processes that underlie cancer metastasis, residual disease, and death in advanced state patients. These mechanisms of metastasis require further study. In addition, the mechanisms that underlie inherited susceptibility to metastasis also require additional research. Furthermore, a better
understanding of cancer metastasis requires further investigation of the biology of dormant tumor cells. Understanding the mechanisms underlying the activation of dormant tumor cells is critical to understanding cancer recurrence and metastasis, and may elucidate targets for intervention that can prevent the progression of cancer or allow patients to live with chronic dormant tumor cells (i.e., they never develop into overt progressive metastases).

Similarly, there is inadequate knowledge regarding the role and composition of the tumor microenvironment or variations in specific organ environments on cancer metastasis, including the effect of the microenvironment on dormant tumor cells and tumor-stroma interactions. Much is still unknown regarding the effect of exogenous factors, such as obesity, on the tumor microenvironment and how it can impact factors such as hypoxia, pH, and interstitial fluid pressure to influence metastasis. Thus, studies to determine how the microenvironment can be targeted to prevent tumor metastasis are warranted. In addition, understanding how organ-specific biology affects response to treatment may advance the development of better therapies that can access metastatic sites that are currently challenging to treat (e.g., the brain).

Understanding drug resistance is also a significant research gap in the field. Cancers can become resistant to treatment, allowing the disease to progress to an advanced state. The mechanisms of drug resistance and altered patterns of recurrence following treatment with targeted therapies require further study to understand both the underlying biology and the methods by which resistance and recurrence can be overcome. Understanding the diversity and biologic variability of metastatic cancer may have implications for the mechanisms underlying drug resistance and recurrence. Thus, further study on the biological heterogeneity of cancer is needed as well.

The role of the host immune response in cancer metastasis is not yet well understood. Variations in immunity within and between individual cancer patients may contribute to differences in metastasis risk and overall patient outcomes. A greater understanding of how tumor cells and metastatic stem-like cancer cells evade immune surveillance is imperative and may provide a mechanism by which metastasis can be prevented or halted.

In addition, the role of genetic variation in cancer metastasis is not well understood. Identification of genetic risk factors and genetic susceptibility to metastasis may provide an opportunity to target the populations most at risk—via screening, education, targeted interventions, etc.—to minimize the risk of disease spread.

Another area requiring further study is the effect of emotional support. It is unknown how social networks, specifically emotional support, impact outcomes for patients with metastatic cancer or how emotional support may be maximized to best benefit these patients.

Finally, better experimental models are needed to further study both primary and metastatic cancer. Current experimental models of metastasis, including genetically engineered mouse models and patient-derived xenografts, are costly, time-consuming, and may not recapitulate the human host effectively enough to fully understand the disease. Models that incorporate immune responses and that reproducibly and efficiently develop metastasis are needed.

3. Major Barriers

Major barriers to improving the current understanding of metastatic cancer biology include the heterogeneous nature of metastatic cancer, the lack of adequate models, and an overall lack of understanding of the biological characteristics of metastasis.
Metastatic cancer is a highly heterogeneous disease; there is a wide variety of clinical subtypes among cancers, between patients, within an individual patient, and even within a single lesion. This biological heterogeneity exacerbates the challenges of developing experimental models and the selection of effective therapies. Moreover, tumor heterogeneity and the ability of cancer cells to evolve in response to therapy are the primary causes of metastatic progression and resistance to treatment. Successive rounds of therapy select for adaptive, therapy-resistant cells may drive cell evolution into an aggressive and fully resistant population.

In addition, there are a limited number of effective in vivo and in vitro models to study the biological characteristics of metastasis, even for the most common tumor types. Human disease patterns are not fully recapitulated in animal models for a range of reasons, such as the absence of intact immunity. Furthermore, genetically engineered mouse models do not reflect the heterogeneity of human cancers. There is wide variability in mouse models, and preclinical models are limited. Current studies are attempting to humanize mouse models via hematopoietic stem cell transplantation; however, these studies are still in their infancy. Patient-derived xenografts provide alternative models of spontaneous metastasis and can faithfully represent main driver mutations and epigenetic alterations seen in patients. However, those xenograft recipients lack a complete immune microenvironment and are difficult to use in the laboratory since they may require months for metastases to develop following tumor implantation. Insufficient numbers of multi-dimensional models of cancer cell-microenvironment interactions have been tested and the use of metastatic cancer cells for computational analysis and modeling has just begun. Overall, the existing preclinical models have resulted in limited translational information for clinical trials.

Finally, there are key biological characteristics of metastasis that have not yet been extensively studied. There is a lack of research on the biology of treatment-naïve micrometastases, minimal residual disease, dormant tumor cells, replacing or reactivating molecules that are inactivated in patients with cancer, and the role of circulating tumor cells in metastasis. Generally, cancer research and clinical decisions have predominantly focused on primary tumor cells instead of metastatic cells. However, metastatic cells may differ from primary tumor cells in genotype and phenotype, and hence, the knowledge gained from primary tumor-centric research may not be directly applicable to metastatic tumors.

### 4. Recommended Collaborations and Initiatives

Greater initiatives in four primary areas would advance the current understanding of the biology of metastatic cancer: improved metastatic research models, investigating the host microenvironment, improved strategies for studying the metastatic process, and better characterization of the factors involved in metastasis and treatment-related responses.

The development of new experimental models of metastasis would significantly advance the field of metastasis research. Faithful, accurate, and reproducible models are needed to rapidly and effectively study the progression of metastasis and the effects of treatment. Recommendations for new or improved models include experimental models for the 10 most common cancers, syngeneic murine models, immune competent models, and multidimensional models of cancer cell-microenvironment interactions. Better in vivo models that incorporate treatment of metastasis are also needed.

More studies investigating the host microenvironment are needed. Abnormalities within the host microenvironment contribute to cell migration, tumor proliferation, and treatment
resistance. Further studies are needed to understand the causes and consequences of these abnormalities, define the pre-metastatic window for modeling the metastatic microenvironments, and to further define tumor-stroma interactions. A better understanding of the metastatic microenvironment may help promote the development of effective strategies to normalize the microenvironment in both primary and metastatic lesions.

Another important initiative is the improvement of experimental methods and techniques. Affordable strategies for studying the metastatic process are needed. High-resolution molecular and imaging analyses on tissue samples pre- and post-therapy would provide additional information on the biology of residual disease. Increased availability of methods to monitor and analyze biomarkers prior to, during, and post-therapy and palliative treatments would improve the understanding of the cellular and molecular factors involved in metastasis and how these factors are affected by therapeutic interventions.

Finally, it is critical to characterize the influence of risk factors and the effects of treatment on cancer metastasis and relapse rates. For example, more studies are needed on polymorphisms, molecular variation, and the challenges posed by exogenous factors (e.g., modifiable risk factors). It may be useful to characterize organs not targeted by metastases to learn why metastases do not emerge in certain tissues. Studies on the effects of treatment may also help to improve outcomes by identifying how to best use available agents to maximize patient benefit. Additional methods to assess the impact of treatment include, but are not limited to, deep sequencing of metastatic tumors (such as tumor, immune, stromal, and endothelial cells) and the analysis of exosomal and growth factors before and after treatment.

D. Therapies

1. State of the Science

There is no standard treatment for advanced metastatic disease, given the heterogeneous nature of primary tumors and metastases. There are limited therapeutic targets (e.g., micrometastases, organ site of metastasis) and, as a result, limited treatment strategies. In addition, drugs that specifically target dormant tumor cells are needed. The limited research on therapies indicates that each metastasis could be considered a separate entity with regards to treatment.

Chemotherapeutic agents can be used as single agents or in combination for the treatment of metastatic cancer. In some diseases, such as metastatic testicular cancer or aggressive lymphoma, combination chemotherapy can be curative. In most tumor types; however, chemotherapy remains palliative and is used to extend quality and quantity of life.

While novel treatments have shown encouraging results against certain tumor types (e.g., targeted therapies like imatinib for chronic myelogenous leukemia and gastrointestinal stromal tumors, immune checkpoint blockers for melanoma, and monoclonal antibodies like trastuzumab for some cases of breast cancer), this success is not universal for all tumor types. For some tumor types like pancreatic adenocarcinoma, next-generation treatments such as nanotherapeutics, anti-vascular endothelial growth factor agents, immune therapies, and targeted cancer therapies used as monotherapies or in combination with chemotherapy, have only provided survival benefits on the order of weeks. Despite such disappointing results, combination therapy approaches remain an active area of clinical investigation.

Checkpoint inhibitors may be better than standard cytotoxic chemotherapy for metastatic lung
cancer, melanoma, head and neck cancer, bladder cancer, and kidney cancer.\textsuperscript{22–25} Checkpoint inhibitors break immune tolerance and induce an immune response in and around the tumor. There are many checkpoint inhibitors that can reverse immune tolerance in humans such as the monoclonal antibodies anti-CTLA-4 (e.g., ipilimumab), anti-PD-1 (e.g., nivolumab or pembrolizumab), and anti-programmed death-ligand 1 (e.g., atezolizumab). Checkpoint inhibitor activity has been demonstrated for several different cancers and the role of these immune therapies in other tumor types is under active investigation.

There is a need for additional novel therapies with less severe side effects for metastatic tumors. Fewer than half of all patients respond to agents commonly used in the metastatic setting, and for those who respond, tumors generally will develop resistance. It will be important to continue to study each tumor type and perhaps each site of metastasis to identify distinct treatment targets. This will aid in the optimization of personalized, targeted treatments and surgical care essential to treat existing disease and prevent future metastatic tumors.

2. Research Gaps

There is a limited understanding of treatments for metastatic cancer. Those that are currently available are derived from knowledge of primary tumors, are not organ or target specific, and are selected using ill-defined decision criteria with little understanding of potential impacts on metastatic risk.

Therapies used in clinical practice are often developed in preclinical studies using primary tumors, not metastatic tumors, as the experimental model. The nuances associated with metastatic disease and the effect of treatment on this cancer state may not be captured accurately and completely, necessitating the need for studies using appropriate metastatic models. Observed variations in therapeutic response rates at different metastatic sites are not yet well understood. A greater understanding of the effectiveness of combination therapies (such as immune, targeted, endocrine, radiation, surgery, etc.) is needed. Better predictors of the efficacy of certain treatments, such as checkpoint inhibitors, are needed.

Therapies that target metastases based on organ site may be novel and are likely to be highly valuable, in addition to treatments that target tumor colonization, micrometastases, and dormant tumor cells. New therapies are needed that maintain effectiveness against advanced cancer, but that also have tolerable, less severe side effects than currently available interventions. More research is needed to aid in the development of such novel therapeutics, as well as to better understand and optimize current treatments (e.g., adoptive cell therapies) for metastatic disease.

Further research is needed to identify novel targets to treat cancer, and identification of targets in cancers with epigenetic alterations is needed. Also, while most current therapies are antagonists, treatments that reactivate or replace molecules that have been lost or inactivated by the metastatic process need to be further explored.

Moreover, the methods by which the best treatment is selected for a specific patient are not well defined in most cases and are often not driven by biomarkers or other disease-related indicators because those indicators do not yet exist. Further research is needed to further optimize the treatment decision-making process.

Finally, it is unknown whether certain treatments can impact the risk of metastasis. A greater understanding of the mechanisms by which treatments affect cancer cells and tumor
metastasis, as well as developing improved methods of disease monitoring, would provide important knowledge regarding treatment effectiveness and potential strategies for mitigating metastatic risk.

3. Major Barriers

The intrinsic heterogeneity of metastatic cancer is a significant barrier to developing therapies. This heterogeneity contributes to the resistance to all forms of systemic therapy, including chemotherapy, hormonal therapy, targeted therapy, and immunotherapy. Immunotherapies, such as adoptive cell transfer, are highly personalized and are therefore difficult to make available to patients on a large scale.

In addition to the need for the development of novel therapeutics, there is also a need for improved optimization of existing treatments. Many compounds with clinical potential are dismissed as “failed drugs” following early studies, which has resulted in undeveloped therapies. Furthermore, for rare cancers such as neuroblastoma and Ewing sarcoma, the development of novel or improved therapies is hampered by the lack of incentive for pharmaceutical companies. Pharmaceutical companies are not incentivized to conduct clinical trials on such rare diseases because of the challenges involved with obtaining samples, enrolling patients, and eventually developing a marketable indication with sufficient profit margin to justify cost. In 2013, the Center for Cancer Research of the NCI launched the Rare Tumor Initiative to promote translational research on these less common cancers; however, similar initiatives are needed in this area as these diseases account for approximately 25 percent of cancer-related deaths.

Finally, drug development is primarily focused on antagonizing or inhibiting processes that are activated or upregulated in cancer patients. There needs to be more effort invested in trying to replace or reactivate molecules that have been lost, deleted, or inactivated throughout the metastatic process.

4. Recommended Collaborations and Initiatives

Repurposing of current drugs, further developing immunotherapies, and investigating novel drug targets is needed to advance therapies for the treatment of metastatic cancer.

Within the armamentarium of approved therapies, there may be drugs used in other diseases that may be repurposed to treat metastatic cancer. As an example, the Targeted Agent and Profiling Utilization Registry (TAPUR) is a prospective study investigating the anti-tumorigenic activity and toxicity of commercially available drugs for off-label uses. Seven pharmaceutical companies have contributed a combined 17 agents for study. Standard of care drugs, off-label drugs, and “failed” drugs should be re-evaluated so they can be repurposed or further optimized. The information gained from studying drugs that are currently available will be valuable in informing the development of novel therapies. Furthermore, the cancers that would most benefit from improved radiographic imaging and radionuclide therapy need to be defined.

Additional research is needed to further develop immunotherapies and to better identify subsets of patients most likely to benefit. Further investment should be directed toward developing commercially available vectors (e.g., viral vectors) for immune modulators. Novel combination approaches are needed, particularly for oligo-metastases and for patients not responding to standard care therapies. New treatment strategies are needed to reprogram proliferative cancer cells into dormant tumor cells. There is a need to create platforms that
facilitate the rapid preclinical testing of therapeutic combinations and to determine the mechanisms of drug synergy. Lastly, adjuvant therapy for micrometastatic cancer should be further explored, including studies on the effectiveness of traditionally non-cancer drugs such as aspirin, statins, and metformin.

Lastly, targets within the metastatic pathway should be further explored for drug development. These include immune-evasive metastatic stem cells, pathways of tumor cell dissemination and survival, mechanisms of tumor cell plasticity, dormant tumor cells, and molecules that are inactivated or lost.

E. System Infrastructure

1. State of the Science

Funding for current research in metastatic cancer is focused on the most common cancers (e.g., lung, breast). Studies on less common cancers often with higher mortality rates (e.g., esophageal, kidney, pancreatic) lack sufficient funding, which slows the progress of research and treatment development.

Grant funding mechanisms align with the traditional peer-review study section paradigm, which is a long process. Investigators often wait several months to receive a funding decision and award negotiations before beginning a project.

Collaborative research efforts, including data sharing, could significantly benefit metastatic cancer research. Interdisciplinary collaborations and the integration of basic and clinical research would help bridge translational research gaps. Electronic medical records (EMRs), which electronically capture a patient’s medical history, facilitate data sharing and can inform medical decisions that improve healthcare. EMRs increase health information availability, reduce duplication of medical tests, limit delays in treatment, and allow clinicians and patients to become better informed to make healthcare decisions. The electronic health record system supports other care-related activities directly or indirectly through various interfaces, including evidence-based decision support, quality management, and outcomes reporting. Further, EMRs support metastatic cancer research because they can be placed in a centralized portal for research sites.

2. Research Gaps

The field of metastatic cancer research needs to grow. Cancer metastasis research is costly and time consuming, making it challenging to encourage scientists to pursue this field of study. Notably, the research that is performed focuses primarily on the most common cancer types, necessitating the need for more research on less common, but often more deadly cancers.

3. Major Barriers

Significant barriers within various aspects of system infrastructure exist; including a lack of collaboration within the field, a lack of support for high-risk research, a lack of metastatic tissue samples, as well as the retaining, recruiting, and training of scientists needed to perform metastatic cancer research.

Within the field of metastatic cancer research, there is a need for interdisciplinary collaboration and integration between basic and clinical scientists. The lack of collaboration is likely a consequence of the competition for grants and first-authored publications, which are prerequisites for career advancement in the current system. Thus, much research is performed
by individuals or small groups, there is minimal data sharing, and there is a need for increased understanding of the clinical relevance of experimental data.

The current climate of research funding supports low-risk, “safe” science; study sections perceivably favor projects from laboratories that have demonstrated a long track record of expertise (i.e., publications) using traditional experimental models. This inclination towards established research ideas and models discourages innovation and limits research to incremental progress or a steady state. Another challenge is the variable and subjective definition of “innovative” and “high-risk” research throughout the field. Furthermore, competition for decreased research funds has led some researchers to revert to safe science and eschew potentially transformative ideas to obtain funding.

One of the most pervasive problems in metastatic cancer research is the lack of metastatic tissue samples, especially matched samples of primary tumors and metastases. This can be attributed to the limited clinical accessibility of metastatic lesions, the technical and logistical challenges of collecting pre- and post-treatment specimens, the limited use of warm autopsy (i.e., rapid autopsy), and limited access to annotated clinical samples and cohorts.

Furthermore, many laboratories are faced with the difficulty of recruiting and retaining bioinformaticians. Most laboratories lack dedicated personnel who are trained to analyze large data sets, and such individuals are in high demand. Without the support of bioinformaticians, researchers have limited ability to analyze and interpret big data (e.g., genomic and proteomic data), which is a significant need for advancing the understanding of metastasis.

The regulatory aspects for animal research present challenges in metastatic cancer research. Animal studies directed at metastatic research may require added justifications for animal protocol approval, since standard experimental endpoints as applied by many Institutional Animal Care and Use Committees (IACUCs) are not appropriate for metastatic research. Local IACUC interpretation of animal welfare regulations and guidelines may prevent and/or hinder longitudinal studies of metastasis and the tumor environment using experimental animal models. Furthermore, compliance with IACUC regulations requires a significant level of administrative effort and cost to maintain IACUC approvals.

The current grant review process and the need for more funding are also significant barriers to advancing metastatic cancer research. Metastasis studies are inherently complex, time-consuming, and costly. The length of time required to produce preliminary data and submit a grant proposal is incongruous with the current funding model. Currently, funding mechanisms are structured to support short-term projects (e.g., 5-year grants) because federal funding has limited flexibility with regard to use, and will expire after a given time. The grant review process is protracted and inefficient at executing a funding cycle to jumpstart new research ideas. Furthermore, grant reviewers may not necessarily have the expertise or understand the field enough to thoroughly evaluate a grant in the traditional peer review study section structure. These obstacles have made it difficult for researchers to attain grants, and thus, may have contributed to the slowed therapeutic advancement in fields such as microenvironment research, pediatric tumor metastasis, and the study of less common cancers (e.g., esophageal, kidney, pancreatic). If funding levels continue to decline, the field faces the threat of losing its leadership in conducting clinical research for cancer therapy and diagnosis.

Within the scientific community, there is no consensus on how or where to drive research on metastatic cancer. The majority of metastasis research is aimed at determining clinical
relevance, but biological studies are rarely driven by observations from population science. Training is another issue, as research training on metastasis-related experimental methods is inadequate. The knowledge and tools used to investigate primary tumors is being applied to metastasis, but the science of metastasis should be developed as its own entity. Finally, the propagation of metastasis research is endangered by the diminishing number of trainees in research laboratories. Requests for application announcements for early career investigators and collaborative projects have been met with small numbers of responses.

4. Recommended Collaborations and Initiatives

Greater collaboration and data sharing are needed throughout the field of metastatic research. One recommendation is to create policies that facilitate and incentivize data sharing. Multidisciplinary consortium grants and career advancements, such as promotion or tenure, would also be effective incentives for collaborative research. Interdisciplinary and international collaboration, such as through the establishment of a metastatic cancer working group, would bring together experts from disparate fields and institutions and enhance the collective efforts to accelerate clinical and translational research. Basic and clinical research should be integrated to improve research outcomes and translatability. Integrating cancer survivors into the research process should also be pursued as valuable collaborations to advance research projects, particularly clinical research. Collaborations between academia and industry should also be heavily encouraged. The creation of such networks would promote a collaborative infrastructure within the community and facilitate other joint efforts such as shared tissue banks and data sharing. Partnerships may also be achieved by creating centralized data portals and by mandating or incentivizing data sharing. For example, CancerLinQ™ is an electronic system that pools data from EMR systems for observational research. It currently has 1.6 million records that can be analyzed to improve quality of care.

Funding mechanisms should be designed to support innovative studies. Investing in high-risk, high-reward studies may lead to breakthroughs and weaken the conceptual biases that perpetuate “safe” and incremental science. Research should be broadened to study a wide range of cancers, especially those that are the most lethal.

Another important initiative would be to improve sample collection and banking. Implementation of warm autopsy programs or the provision of resources to biopsy tumors would provide investigators with valuable samples for study. There is a significant need for samples of metastatic tumors, “normal” tissue, and samples from metastatic cancers that have been successfully treated. Also, new tissue banking programs and repositories of annotated clinical samples should be created and made widely accessible to the research community. This would allow for the matching of primary and metastatic tumor samples as well as the preservation of tissues for future studies.

There should be increased focus on the recruitment and retention of researchers. Investment in early career researchers, postdoctoral fellows, and staff scientists would bolster capabilities within the field of cancer research. Recruitment, promotion, and tenure processes must take into consideration the length of experiments necessary in metastasis research to ensure that the next generation of researchers can continue to advance the field. Early career scientists should be recruited into metastatic cancer research, and research leadership should be balanced between senior and junior staff to promote the discussion and inclusion of different ideas.

There is a need to define clear regulatory standards to enable metastasis research using animal
models. The cost of complying with regulations should be included in the budget for consideration by funding agencies. The infrastructure needs to be maintained with sufficient resources to support the type of animal studies required for metastatic research.

An additional recommendation is to restructure the grant review and management system. The length of grant proposals should be the minimum necessary to conduct a thorough evaluation by peer reviewers. Grant review should be incentivized in order to bolster the reviewer pool and attract the strongest, most qualified reviewers. Study sections or panels that focus on common mechanisms of cancer metastasis, rather than a single cancer type, may also improve the peer review process. Expanding grant support beyond five years would facilitate advancements because it accommodates the lengthy experimental demands of metastatic cancer research.

Finally, a national bioinformatics approach to big data is needed to maximize the analytic power of studies. Investigators should be provided with educational opportunities to learn bioinformatics and to access a validation submission portal for bioinformatics discovery. A team or collaborative approach is most conducive to bioinformatics analysis, so training or recruiting efforts to support this approach are recommended. Furthermore, improving the interoperability of health information technology would reduce the cost of big data projects, and this is partially addressed by the 21st Century Cures Act.

F. Patient-related Factors

1. State of the Science

Lack of uniform access to care, racial, ethnic, socioeconomic, and insurance disparities remain an issue in the treatment of patients with cancer. For example, Hershman et al. found that African-Americans were much less likely to have access to treatment for ovarian cancer. This may result in poorer outcomes for these patients. Moreover, minority and underserved populations are frequently underrepresented in clinical trials.

Furthermore, there are many modifiable risk factors for developing metastasis, including environmental and lifestyle-related factors. One example is obesity, which may increase tumor microenvironment abnormalities that can induce treatment resistance and subsequent metastasis, including hypoxia, low pH, and high interstitial fluid pressure. Notably, the U.S. Centers for Disease Control and Prevention reports that more than one-third (36.5 percent) of U.S. adults are currently obese and may therefore be at a higher risk of developing cancer. There are sparse data on which modifiable behaviors (such as diet, exercise, smoking, and alcohol) may improve outcomes and help to identify potential interventions.

Compliance with healthcare recommendations remains a significant problem. It is a multidimensional phenomenon and, per the World Health Organization, is influenced by patient-related factors, therapy-related factors, condition-related factors, health system factors, and socioeconomic factors. For instance, older patients with cancer tend to suffer from multiple comorbidities, increasing the number of chronic conditions being treated simultaneously. Multiple comorbidities and the number of prescribed medications in the older population further increase treatment complexity and correlates with a decrease in medical compliance. Without compliance with recommended therapy, patients do not receive the full benefit of that therapy, thereby affecting healthcare costs, recurrence rate, and risk of mortality.

There are data that support the effects of social networks on improving survival outcomes in
cancer patients. However, this phenomenon and the role of social interventions on improving patient outcomes is not yet well understood. Interventions that address support, primarily via support groups, have yielded mixed results. A study by Spiegel et al. indicated that support group therapy did not improve survival in patients with metastatic breast cancer.\textsuperscript{37} The Life After Cancer Epidemiology Study by Kroenke et al. investigated the effects of social networks on mortality risk in women with invasive breast cancer between 1997 and 2000, and found that while the size of a patient’s social network was not associated with lower mortality, the quality of the social network improved mortality in these patients.\textsuperscript{36} Another study by Kroenke et al. assessed more than 2,800 women with breast cancer at various stages to determine the effect of social networks on this particular study population.\textsuperscript{38} The results of this study indicated that social isolation, defined as the absence of close relatives, living children, or friends, significantly increased the risk of mortality in women with breast cancer, independent of marriage status, involvement in religious/community activities, or the presence of a confidant.\textsuperscript{38}

2. Research Gaps

A gap in the field of metastatic cancer research is the underrepresentation of minority and underserved populations in clinical trials. Understanding the challenges in providing access to care would help facilitate enrollment in clinical trials. Additionally, more research is needed to determine how modifiable risk factors (such as diet, exercise, smoking, etc.) may impact patient outcomes such as survival. Better defining these modifiable risk factors and their effect on cancer progression may allow for the identification of targeted interventions. Further research is also needed to determine the effect of support networks on patient outcomes, as well as the mechanism by which emotional support can impact these outcomes. Better understanding both the effects and the mechanism by which these effects occur may allow for these support modalities to be maximized to improve patient outcomes.

3. Major Barriers

Access to healthcare remains a significant barrier in advancing metastatic cancer research. Patients with metastatic cancer may have limited access to care for financial, logistical, or socioeconomic reasons. In addition, many patients do not understand that by modifying risk factors such as diet, exercise, and smoking, they may reduce their risk of developing metastatic cancer. Finally, social support has demonstrated some benefit to patients, but the data in this field are inconclusive. Social support is defined in a variety of ways in clinical studies, and clinical trials do not currently assess the effect of social networks on patient outcomes.

4. Recommended Collaborations and Initiatives

Efforts should be taken to minimize geographic and racial inequalities in access to care and enrollment in clinical trials in metastatic cancer. National trials should be strongly encouraged to reflect the diversity of the U.S. population. Also, efforts should be directed towards developing programs that provide awareness of healthcare resources, encouraging adherence to treatment, and educating patients about risk factors for metastasis (e.g., smoking, obesity, compliance), especially in high-risk populations. Finally, the use of social media and the creation of support groups have the potential to increase compliance with treatment regimens and further studies are needed on the role of social networks in outcomes for patients with metastatic cancer.
Survivorship and Palliative Care

1. State of the Science

Survivorship focuses on the health and life of a person with cancer post-treatment, and includes physical, psychosocial and economic issues. The National Academy of Medicine (formerly the Institute of Medicine), recommends that all patients receive Survivorship Care Plans (SCP) upon completion of cancer treatment. However, this is not currently the case. Nationally, SCPs are not standardized and there is significant variability between the contents and quality of SCPs given to patients upon completion of cancer therapy. As cancer patients may live for years with chronic metastatic disease, it may be important to provide survivorship care plans that address their unique needs.

The goal of palliative care is to improve quality of life for both the patient and family. Furthermore, palliative care may increase survival times in patients with metastatic cancer and improve patient understanding of prognosis over time. The earlier palliative care is received, the higher degree of patient benefit. A study published in the New England Journal of Medicine evaluated early and extensive palliative care (such as illness-related education, symptom management, decision-making support, coping assistance for patients with non-small cell lung cancer and their family/caregivers, referrals to relevant care providers, and prescriptions). This study found that patients who received palliative care had longer survival times than patients receiving standard treatment without palliative care. A recent meta-analysis published by Kavalieratos et al. assessed the role of palliative care in outcomes of patients with life-limiting illness and found that, while there was no improvement in overall survival, quality of life was improved.

2. Research Gaps

Additional research is needed to address survivorship as an increasing number of patients may live long-term with chronic metastatic cancer. SCPs need to be studied, validated, and optimized to ensure the included elements maximize outcomes for patients with metastatic cancer.

Another major research gap in clinical trials is the lack of focus on palliative and long-term supportive care. More often, clinical trials are focused on patient response rates and outcomes, including survival. Quality of life measures are rarely studied as part of clinical trials.

3. Major Barriers

Patients with metastatic cancer are not currently receiving adequate survivorship support and palliative care.

SCP are becoming the standard of care for patients with cancer treated with curative intent. The American College of Surgeons’ Commission on Cancer (CoC) is requiring SCPs in CoC-accredited facilities for non-metastatic cancer patients treated with curative intent. However, for metastatic cancer patients, there is a need to define the role of SCPs. They need to be tailored depending on disease trajectory, as various metastatic cancers behave differently both between patients and metastatic sites. Some patients may live for years with advanced metastatic disease whereas others may only live for weeks or months. Consequently, there are groups of patients with metastatic cancer who, while they may ultimately succumb to their disease, will live for an extended period of time, necessitating the need for a SCP to inform both
them and their healthcare providers of appropriate care during this time.

There is also limited access to palliative care. Many patients receiving care for metastatic cancer do not have adequate access to palliative care resources and specialists.

4. Recommended Collaborations and Initiatives

An additional emphasis is needed on research regarding survivorship and palliative care for patients with metastatic cancer. Notably, there is a need to improve survivorship care for these patients. Specific care plans that coordinate treatment regimens, follow-up care, and behavioral recommendations need to be developed. Several Cancer Treatment Organizations (e.g., ASCO and Children’s Oncology Group) are creating standard SCP templates. SCPs should become standard of care for all patients treated for cancer, and should be further developed and refined specifically for patients with metastatic cancer.

As therapies continue to evolve, patients are surviving longer, and an increasing number of patients are living with chronic metastatic cancer. Further studies on survivorship and the psychosocial effects of metastatic cancer are needed.

There is also a need to improve palliative care by increasing palliative and long-term supportive care resources. This need can be met by increasing the inclusion of palliative care with standard and experimental therapies for metastatic cancer care. However, additional studies are needed to better define the role of palliative care for metastatic cancer patients and the populations that would most benefit from such interventions.

VI. Conclusions

Among other initiatives, extending the lives of patients with advanced or recurrent cancer will require improvements in the detection and monitoring of metastatic cancer, as well as novel therapies to treat these cancers.

There are numerous barriers that have inhibited progress in the treatment of metastatic cancer. For instance, unlike other areas of focus within the cancer field, there is no consensus group within this field. Further, incommensurate to the significance of cancer metastasis, this field is still generally small, limiting collaborations and conferences on this critical topic to further improve patient outcomes. Increased focus on research and development initiatives are needed to better understand both the biology of metastasis and to develop novel therapies that target these mechanisms to prevent and treat metastatic cancer. Following are the main conclusions for each of the seven topic areas addressed in this report.

A. Clinical Trials

1. Current clinical trial designs are not optimized for the study of patients with metastatic disease and the metastatic state.

2. Enrolling appropriate patient cohorts for clinical trials in metastatic cancer remains a barrier.

3. Regulatory and logistical requirements delay the timely initiation and completion of clinical trials.

4. New agents for the treatment of metastatic disease are frequently tested in nonmetastatic (i.e., primary tumor) preclinical models prior to their use in
patients with metastatic disease.

B. Diagnostics

1. The discovery and validation pipeline for novel biomarkers needs continued refinement in the research community to optimize efforts as there remains a significant discrepancy between the effort directed towards biomarker discovery and the number that make it to clinical practice.

2. The development and validation of molecular biomarkers is costly, time consuming, and often hampered by an insufficient understanding of the development process.

3. There are insufficient biomarkers and other modalities to monitor both the presence and status of small volume and microscopic metastasis.

4. In many disease sites, clinical predictors of metastasis have been insufficient and may be enhanced by combining with molecular predictors.

5. There remains a limited number of imaging tracers and a lack of sufficiently sensitive and specific imaging and detection methods to detect early metastatic disease for many cancers.

6. There is a lack of metastatic disease tissue sampling during the continuum of disease progression.

C. Biology of Disease

1. Knowledge of biology of metastatic disease is insufficient for the development of informed therapeutic strategies.

2. Additional, more accurate experimental animal models are needed to better understand the biology of the metastatic process.

3. The effects of local and distant microenvironments on metastatic disease development and progression are not clearly understood.

4. Better understanding of tumor heterogeneity between tumor types and also between sites of metastases is needed.

D. Therapies

1. The incomplete understanding of the metastatic process limits identification of potential therapeutic targets.

2. Current experimental models are not appropriately utilized for the development of anti-metastatic therapeutic strategies.

3. Better understanding of therapy resistance due to tumor heterogeneity between tumor types and between sites of metastases is needed.

4. There is inadequate optimization of existing therapies and study of their use in rare metastatic cancers.

5. Additional investigations of mechanisms of resistance to therapies are needed.
E. System Infrastructure
1. There is inadequate funding invested in metastatic research on less common cancers that are as deadly as more common cancers.
2. More interdisciplinary collaborations are needed in the research community, including basic researchers, clinical researchers, and disease survivors.
3. The grant review process can be improved by streamlining proposal requirements to expedite the review and funding process and incentivizing expert reviewers to participate.
4. There is a lack of availability of high-quality, clinically annotated human metastatic cancer samples to thoroughly study metastatic cancer.
5. Metastatic cancer research in animal models requires long-term studies that are challenging within the current funding and regulatory infrastructure.

F. Patient-related Factors
1. There are racial, socioeconomic, and geographic disparities in healthcare access, delivery, and subsequent enrollment in clinical trials for metastatic cancer.
2. Opportunities exist to provide more education and programs to patients with cancer about modifiable risk factors (e.g., compliance, obesity, smoking, and alcohol use) for preventing the development and progression of metastatic disease.
3. Robust social interaction and social networking may extend the lives of patients with metastatic disease.

G. Survivorship and Palliative Care
1. Receiving palliative care in conjunction with standard cancer treatments improves quality of life and may extend the lives of patients with metastatic cancer.
2. Survivorship Care Plans are not routinely provided to patients with metastatic cancer.

VII. Recommendations from Task Force
A. Clinical Trials
1. Expand the interdisciplinary approach to research, to include clinicians, translational and basic researchers, data scientists, and experts in fields other than medicine (e.g., engineers, chemists, mathematicians).
2. Develop standardized criteria for evaluating patient responses to immune therapies.
3. Develop uniform outcomes criteria beyond those presently utilized to allow better comparison of clinical trials of patients with metastatic cancer.
4. Consider trial designs that add strata for patients with metastatic cancer who are frequently ineligible for clinical trials (such as worse performance status, abnormal laboratory values, location of metastases, rare tumor types, comorbidities, and other conditions).

5. Develop strategies to ease the regulatory burden of the clinical trials process (e.g., increase utilization of centralized IRBs; refine adverse event reporting; provide additional guidance for the consistent application of regulations across IRBs).

B. Diagnostics

1. Invest in novel diagnostic imaging tracers and techniques that are more sensitive and specific for the detection of early metastatic disease states.

2. Streamline and facilitate biomarker development for the diagnosis and monitoring of metastatic disease.

3. Encourage tissue acquisition, when appropriate, and liquid biopsies throughout the duration of metastatic disease for clinical decision making, laboratory research, and molecularly-driven clinical trials.

C. Biology of Disease

1. Increase research investigating the etiology, progression, and treatment of metastatic disease.

2. Encourage and support studies to develop more accurate and representative models of metastatic disease.

3. Explore novel funding mechanisms to support longer-term basic and translational studies of metastatic disease.

D. Therapies

1. Study the metastatic process to identify therapeutics that will treat existing metastases, prevent the development of metastases, and/or target dormant cancer cells. Optimize use of existing therapies (e.g., chemotherapy, hormonal, targeted and immunotherapy).

2. Evaluate medications that are currently FDA-approved for other indications, as well as underdeveloped investigational agents for the treatment or prevention of metastasis.

3. Identify the determinants of efficacy for immunotherapy.

E. System Infrastructure

1. Increase research on less widely studied cancers.

2. Promote interdisciplinary collaborations by developing specific funding mechanisms, incentives, and resources for data sharing.

3. Incentivize investigator career development in metastatic cancer research
through recognition of group and collaborative science by academic promotion and tenure committees.

4. Streamline the proposal requirements and timelines for federal funding agencies.

5. Recruit and incentivize senior scientists to serve on review panels to ensure that the most qualified reviewers are providing scientific evaluations of research proposals.

6. Implement warm/rapid autopsy programs and establish metastatic tissue repositories of annotated clinical samples (with primary and metastatic tumor specimens) to be widely accessible to the research community.

F. Patient-related Factors

1. Improve access to care and clinical trial participation for patients with metastatic cancer particularly for underrepresented groups.

2. Ensure enrollment in clinical trials reflects the demographics of the U.S. population.

3. Increase cancer patient awareness of healthcare resources, encourage adherence to treatment, and inform patients about risk factors for metastasis (e.g., compliance, obesity, smoking, alcohol use).

4. Evaluate the role of social networks as they relate to outcomes for patients with metastatic cancer.

G. Survivorship and Palliative Care

1. Study whether inclusion of palliative care for patients with metastatic cancer extends life and determine which patients and families would most benefit from these resources.

2. Create standardized survivorship care plans for patients with metastatic cancer and validate whether their use improves outcomes for these patients.

This report, presenting in detail the conclusions and recommendations of the Metastatic Cancer Task Force, charged with exploring clinical and translational research aimed at extending the lives of advanced state and recurrent metastatic cancer patients, fulfills the request of the House Report 115-219, Page 280, to accompany the DoD Appropriations Bill, 2018, Metastatic Cancer Research.
We the undersigned members of the federal Metastatic Cancer Task Force do hereby submit this report to the congressional defense committees and concur with its statements, findings, and recommendations. The content of this report does not necessarily represent the official positions of DoD, NCI, VA, and CDMRP. Responsibility for the final content of this report rests entirely with the authoring committee.
VIII. Signature Page

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Chair, Metastatic Cancer Task Force
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Kent Hunter, PhD
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## Appendices

### Appendix A. Task Force Members

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Appendix B. Biographies of Task Force Members

Mary Lou Cutler, PhD

Department of Defense

Dr. Cutler is a Professor in the Department of Pathology and the Director of the Molecular and Cellular Biology Graduate Program at the Uniformed Services University of the Health Sciences (USUHS) in Bethesda, Maryland. Dr. Cutler serves as a representative of USUHS to the Murtha Cancer Center (MCC) at Walter Reed National Military Medical Center (WRNMMC). She received her PhD in microbiology from Hahnemann Medical College, now a part of Drexel University in Philadelphia, Pennsylvania. She completed postdoctoral studies in the laboratory of Dr. George Vande Woude at the National Cancer Institute (NCI) and worked in the biotechnology industry and as an investigator in the Laboratory of Tumor Immunology and Biology at the NCI prior to joining the faculty of USUHS.

Her research focuses on the role of cell adhesion molecules in signaling and migration of breast cancer. Dr. Cutler identified molecules that control adhesion and migration and determined the mechanisms by which they regulate cell stress and susceptibility to oncogenic transformation. Her laboratory identified novel adhesion molecule contributions to lactogenesis as well. Dr. Cutler has investigated these basic research questions in the context of cancer development and progression with funding from the National Institutes of Health (NIH), the Congressionally Directed Medical Research Programs (CDMRP) Breast Cancer Research Program (BCRP), and through collaborative research with the Clinical Breast Care Program Center of Excellence at the MCC.

Thomas Darling, MD, PhD

Department of Defense

Dr. Darling is a Professor and Chair of Dermatology at USUHS in Bethesda, Maryland. Dr. Darling received his MD and PhD degrees from Duke University. He completed his internal medicine internship at the University of North Carolina Hospitals and his dermatology residency at Duke University. In addition, he completed a research fellowship in the laboratory of Dr. Kim Yancey at the Dermatology Branch of the NCI.

Dr. Darling’s laboratory investigates the mechanisms of skin tumor formation in inherited tumor syndromes. A major area of focus has been on the tumor microenvironment and mechanistic target of rapamycin (mTOR; a member of the phosphatidylinositol 3-kinase-related kinase family of protein kinases), activation in tumor fibroblasts from patients with tuberous sclerosis, and its effects on tumor growth, angiogenesis, and tumor associated macrophages. Dr. Darling’s experience in xenograft mouse models using normal and mTOR-activated fibroblasts is being applied to the study of cancer-associated fibroblasts in melanoma.

Preston Gable, CAPT, MC, USN/RET

Department of Defense

CAPT Gable earned a BS summa cum Laude in Biochemistry from the University of Minnesota, College of Biological Sciences and earned his MD degree at the University of Minnesota, School of Medicine. He
completed his internship and residency in internal medicine, and completed his fellowship in hematology and oncology at the Naval Medical Center, San Diego (NMCSD). In 1995, CAPT Gable joined the Navy Medical Center as a staff physician in the division of Hematology/Oncology. Three years later, he was advanced to Fellowship in the American College of Physicians. He served as head of the Hematology/Oncology Department from 2001 until 2012, when he retired from active duty and was rehired as a civilian physician. CAPT Gable was awarded “Master Teacher of the Year” in 2013 by the Navy Chapter of the American College of Physicians, and is a Master Clinician at the NMCSD. He is an Assistant Professor at USUHS and the University of California, San Diego, and an associate member of the MCC.

Chad Hamilton, Col, USAF, MC

Department of Defense

Col Hamilton is a Principal Investigator of the DoD Gynecologic Cancer Center of Excellence and the Gynecologic Oncology Service Chief at WRNMMC, Bethesda, Maryland. Col Hamilton also serves as Program Director of the National Capital Consortium Fellowship in Gynecologic Oncology based at WRNMMC, co-chairs the NCI/Walter Reed Gynecologic Cancer Working Group, and is an Associate Professor in the Department of Obstetrics and Gynecology at the USUHS School of Medicine.

Col Hamilton received his undergraduate degree with academic distinction in Biology at the United States Air Force (USAF) Academy and his MD with honors from Tulane University School of Medicine. He completed his residency in obstetrics and gynecology at Wilford Hall USAF and Brooke Army Medical Centers in San Antonio, Texas and his fellowship in gynecologic oncology at Stanford University and the University of California at San Francisco.

Col Hamilton completed a deployment as a surgeon and obstetrician/gynecologist at Craig Joint Theater Hospital, Bagram Air Base, Afghanistan in 2008, and was subsequently awarded the Army Commendation Medal for meritorious service. As the former Chief of Gynecologic Oncology at Keesler USAF Medical Center, Keesler Air Force Base Mississippi, he was awarded the Meritorious Service Medal for his service in Mississippi in 2010 and again in 2011 during the integration of the Walter Reed Army Medical Center and the National Naval Medical Center into the new WRNMMC. He has been twice awarded a Special Experience Identifier from the Air Force Medical Service in recognition of excellence in clinical and academic teaching and for exceptional professional abilities. He was a 2015 Master Clinician Award Recipient at WRNMMC. He has published over 40 scientific articles, reviews, and book chapters and is the current Membership Chair for the Society of Gynecologic Oncology, a subspecialty board examiner for Gynecologic Oncology, and is a Programmatic Panel member for the CDMRP.

Kent Hunter, PhD

National Cancer Institute

Dr. Hunter is the Deputy Lab Chief of the Laboratory of Cancer Biology and Genetics at the NCI. He received a BS in biochemistry with Highest Honors from the Pennsylvania State University in 1985 and a PhD in Biology from the Massachusetts Institute of Technology in 1991. He was an associate member at the Fox Chase Cancer Center from 1996 to 1999. In 1999, he joined the Laboratory of Population Genetics at the NCI as an Investigator and became a Senior Investigator in 2007. In 2015, he became the Deputy Lab Chief of the Laboratory of Cancer Biology and Genetics. His research interests are the role of inherited factors in susceptibility for breast cancer progression and the use of genomic tools and strategies to understand the etiology of metastatic disease.

Michael Kelley, MD
Department of Veterans Affairs

Dr. Kelley is a Professor of Medicine at Duke University, Chief of Hematology and Oncology at the Durham VA Medical Center, and National Program Director for Oncology for the Veterans Health Administration. He received his undergraduate and MD degrees from the University of Michigan. He completed his residency in internal medicine at Duke University and his fellowship in medical oncology at the NCI where he was also a Senior Clinical Investigator and Research Fellow. Dr. Kelley returned to Duke University to join the faculty in the Department of Medicine in 1998.

Dr. Kelley’s academic interests are in molecular genetics, experimental therapeutics of targeted therapies, and outcomes research. His laboratory studied pathogenesis-directed therapeutics of lung cancer and genetics of rare oncological and hematological conditions. His translational work has included studies in chemoprevention and treatment of lung cancer.

As the VA’s National Program Director for Oncology, Dr. Kelley directs policy and program development that affects more than 50,000 veterans diagnosed with cancer each year in the nation’s largest integrated healthcare system. He is among the VA’s leaders contributing to the White House Cancer Moonshot Initiative and has provided testimony to the President’s Cancer Panel.

Dr. Kelley is an author of more than 85 peer-reviewed primary research articles as well as reviews, book chapters, and numerous meeting abstracts. He is a recipient of the U.S. Public Health Service’s Achievement Award, is the inventor for one patent, and is an ex officio member of the NCI’s National Cancer Advisory Board and the Clinical Trials and Translational Research Advisory Committee.

Elise Kohn, MD

National Cancer Institute

Dr. Kohn is the Head of the Gynecologic Cancer Therapeutics branch of the NCI Cancer Therapy Evaluation Program, where she coordinates development and execution of the advanced Phase II and the Phase III gynecologic cancer clinical trials portfolio. Dr. Kohn also oversees and guides studies in gastroesophagopancreatic neuroendocrine cancers, and developed and leads the NCI’s National Clinical Trials Network Core Correlative Science Committee. In this role, she provides oversight of scientific use of biospecimens obtained in the context of NCI-sponsored Network/Legacy Cooperative Group clinical trials.

Dr. Kohn trained at the University of Michigan and received Medical Oncology training at the NCI. Dr. Kohn spent over two decades overseeing a laboratory and clinical program in the NCI intramural program focused on signal transduction molecular targets in invasion, metastasis, angiogenesis, and proteomic applications applied toward ovarian cancer. Her clinical program focused on application of novel agents and translational opportunities to women’s cancers, especially ovarian cancer, via Phase I and Phase II studies.

Dr. Kohn serves on the Society of Gynecologic Oncologist and the American Society of Clinical Oncology Education Committees. She completed a tour on the integration panel of the Department of Defense Ovarian Cancer Research Program, on which she also served as panel chair for two years. She is a recently retired career officer in the U.S. Public Health Service. Dr. Kohn has received the Ovarian Cancer National Alliance’s Rosalind Franklin Excellence in Ovarian Cancer Research Award, NIH Director’s Merit Awards, and Diversity, and Mentoring Awards. Dr. Kohn was elected a Fellow of the American Association for the Advancement of Science in 2002.

Stanley Lipkowitz, MD, PhD

National Cancer Institute

Dr. Lipkowitz is the Chief of the Women’s Malignancies Branch in the Center for Cancer Research at
the NCI. He is an attending clinician on the NCI Intramural Oncology Service and in the Breast Cancer Clinic at the MCC at WRNMMC. Dr. Lipkowitz is an adjunct Professor of Medicine, an adjunct faculty member of the Molecular and Cell Biology Graduate Program at USUHS, and an adjunct Associate Clinical Professor in the Institute for Biomedical Sciences at the George Washington University, Washington, District of Columbia.

Dr. Lipkowitz received an A.B. from the College of Arts and Sciences at Cornell University and an MD and PhD from the Weill Cornell Medical College. He trained in internal medicine at the New York Hospital and came to the NCI as a medical oncology fellow. Dr. Lipkowitz’s laboratory studies the molecular and cell biology of breast cancer cells with the goal of translating basic findings into clinical trials.

Thomas Newton, Col, USAF, MC

Department of Defense

Col Newton has served as the Chief of the Department of Pediatrics at WRNMMC since June 2016. From March 2012 until May 2016, he served as the Chief of the Pediatric Hematology/Oncology Service at WRNMMC. Prior to his assignment at WRNMMC, Col Newton served as the Pediatrics Flight Commander and Pediatrics Subspecialty Service Chief at Keesler Medical Center in Biloxi, Mississippi and the Pediatrics Flight Commander at Malcolm Grow Medical Center at Joint Base Andrews, Maryland. Col Newton is board certified in Pediatrics and Pediatric Hematology/Oncology. He sits on the executive council of the MCC at WRNMMC and is a Clinical Associate Professor of Pediatrics at the USUHS School of Medicine. Col Newton has been involved in the American Academy of Pediatrics and has held several leadership positions within the Academy over the past decade. In 2012 Col Newton was awarded the Relentless for a Cure Award by the Leukemia Lymphoma Society for his work with school integration programs for childhood cancer survivors. His research interests include healthcare transitions and survivorship.

Jeremy Perkins, COL, MC, USA

Department of Defense

COL Perkins is the Chief of the Hematology-Oncology Service at WRNMMC/MCC, serves as Chair of the Walter Reed Institutional Review Board, and is the Army Hematology/Oncology Consultant to the Surgeon General. He graduated from the United States Military Academy at West Point, New York in 1993 and obtained his MD from USUHS in 1997. He completed his internship and residency in internal
medicine and fellowship in hematology and oncology at Walter Reed Army Medical Center. He is Board Certified in internal medicine, hematology, and oncology.

COL Perkins is a graduate of the Medical Services Officer Basic Course, Fort Sam Houston, Texas; Medical Services Officer Advanced Course, Fort Sam Houston, Texas; and Intermediate Level Education, Fort Belvoir, Virginia. He deployed twice in support of Operation Iraqi Freedom: in 2004 with the 31st Combat Support Hospital, and in 2007 with the 28th Combat Support Hospital as Director of the Deployed Combat Casualty Research Team. He also deployed in support of Operation Enduring Freedom as the Battalion Surgeon for the 2-505th Parachute Infantry Regiment with the 82nd Airborne to RC-East Afghanistan in 2012. COL Perkins conducted research to improve standards of battlefield care – chiefly focused on transfusion medicine for the critically wounded. From 2008 to 2009, he served as the Deputy Director of Military Casualty Research and the Department Chief of Blood Research at the Walter Reed Army Institute of Research.

He has authored numerous peer-reviewed articles which have been published in leading journals such as Transfusion, Critical Care Medicine, and the Journal of Trauma. His work has helped to define and shape current practices of battlefield transfusion medicine. At WRNMMC, he has focused on breast cancer and sarcoma. He is the Principal Investigator for a number of clinical trials for treatment of early stage and advanced breast cancer.

Louis Rivera, CDR, MC, USN

Department of Defense

CDR Rivera is Assistant Professor of Surgery at USUHS in Bethesda, Maryland and the Associate Program Director for the General Surgery Residency at the NMCSD. CDR Rivera received his MD from the University of Pittsburgh. He completed a 1-year research fellowship in trauma research. He completed his general surgery internship at the NMCSD. He was a General Medical Officer at the Branch Medical Clinic in San Diego from 2001 to 2003. He completed his General Surgery Training at the Naval Medical Center in 2007. He served for 1 year as the Ship's Surgeon aboard the USS Nimitz. In 2008, he began his Surgical Oncology Fellowship at the Roswell Park Cancer Institute.

During CDR Rivera’s tenure at Roswell Park Cancer Institute, he conducted preclinical and clinical research. In his clinical studies, he evaluated the role of biomarkers in predicting the risk of metastatic disease from breast cancer and studied the contribution of mastectomy to outcomes for breast cancer patients with metastatic disease. Through preclinical studies, he helped to develop models for testing response to intraperitoneal chemotherapy for peritoneal malignancies. In 2010, CDR Rivera returned to San Diego where he practices as a Surgical Oncologist.

CDR Rivera has served his country abroad in Afghanistan and Djibouti. In 2014, he assumed leadership as Chief of the Surgical Oncology and Colorectal Service and Associate Program Director at the NMCSD. CDR Rivera is a survivor of Stage IV, recurrent Hodgkin's lymphoma which developed in the early part of his medical training. He values the patient perspective this experience has afforded him.

Inger Rosner, COL, MC, USA

Department of Defense

COL Rosner is the Director of the Center for Prostate Disease Research (CPDR) at WRNMMC; the Director of Urologic Oncology, Urology Service; and Assistant Professor of Surgery at USUHS in
Bethesda, Maryland. As the CPDR Clinical Director, COL Rosner oversees the CPDR Clinic at WRNMMC which is part of the MCC “Center for Excellence.”

COL Rosner graduated from medical school at USUHS in 1997 and attended residency at WRNMMC from 2002 to 2007. COL Rosner completed a fellowship in Urologic Oncology at the NCI in 2008.

COL Rosner is the Principal Investigator for several research protocols and has published dozens of papers based on her research in the field of urologic oncology. Her clinical interests include multidisciplinary care to prostate cancer patients from the newly diagnosed to the castrate-resistant metastatic. She specializes in minimally invasive and robotic-assisted surgery.

COL Rosner is involved in several projects to evaluate decision making, patient health disparities and quality of life outcomes in patients diagnosed and treated for prostate cancer along their continuum of cancer care. She is also a mentor to WRNMMC urology residents and USUHS medical students. Dr. Rosner is a member of numerous professional societies, including the Society of Urologic Oncology and the American Urologic Association.

Wanda Salzer, Col, USAF, MC

**Congressionally Directed Medical Research Programs, U.S. Army Medical Research and Materiel Command**

Col Salzer is the Director of the CDMRP at Fort Detrick, Maryland. She served in the military medical research community as Chair of the Neurotrauma Steering Committee, and participated in five Joint Programmatic Review Panels, providing program oversight for funding new research in diverse diseases, conditions, and injuries effecting military personnel, their families, veterans, and the American public.

Col Salzer graduated from Our Lady of Holy Cross College, New Orleans, Louisiana in 1989 with a BS in Biology, followed by an MD from Tulane University Medical School. She completed her pediatric residency at Keesler Air Force Medical Center, Biloxi, Mississippi, and pediatric hematology/oncology fellowship at the Walter Reed Army Medical Center, Washington, District of Columbia. Her graduate education also included the Air Command and Staff College, and Air War College, Maxwell Air Force Base, Alabama, followed by a Masters of Health Science Degree from Duke University School of Medicine, Durham, North Carolina. She is Board Certified in general pediatrics, and pediatric hematology/oncology.

Col Salzer has published research in pediatric rare diseases such as neurofibromatosis 1 and pediatric lymphoblastic leukemia. She is a leader in research, currently serving as Chair, Phase III Randomized Trial for Newly Diagnosed High Risk B-precursor Acute Lymphoblastic Leukemia for the Children’s Oncology Group and as Vice Chair, Pediatric Central Institutional Review Board, for the NCI. Over her career, Col Salzer has received many awards for her outstanding research, concern for patients in clinical practice, and efforts to improve medical practice through innovative research and technology. Among her awards she has received the Bailey K. Ashford Award from Walter Reed Army Medical Center; the Andrew M. Margileth Award from the American Academy of Pediatrics, Section of Uniformed Services; and the Golden Apple Award from Keesler Pediatric Residency Program.

Craig Shriver, COL, MC, USA

**Department of Defense**

COL Shriver is the Professor of Surgery and the Director of the MCC at the USUHS in Bethesda and WRNMMC. He is also Director of the congressionally-mandated Clinical Breast Cancer Project, a military- civilian coalition providing excellent clinical care, cutting-edge breast cancer research, and an extensive biorepository of human breast cancers and tissue that can be used by researchers around the world.
COL Shriver earned a Bachelor's Degree in Biochemistry (Cum Laude) from the Albright College in Reading, Pennsylvania and an MD (Alpha Omega Alpha) from Temple University School of Medicine. COL Shriver was commissioned in the U.S. Army Medical Corps in 1984. His postgraduate training included his surgical internship and residency at the Walter Reed Army Medical Center. Dr. Shriver was selected for advanced fellowship training in surgical oncology at the Memorial Sloan-Kettering Cancer Center in New York.

COL Shriver’s military education includes completion of the Advanced Officer Course, and graduating with honors (top 10 percent of his class) from the Command and General Staff College in June 2000. His operational assignments include a 2-year tour at Fort Bragg, North Carolina, and direct surgical support of four overseas combat military operations. He deployed in support of Operation Just Cause (the liberation of Panama) in 1989, serving as Chief Triage Officer and Surgeon for the Forward Surgical Team of the 5th MASH. He then went on to become Surgeon of the 307th Medical Battalion of the 82nd Airborne Division, providing far-forward surgical support during Operation Desert Shield and Desert Storm (1990–1991), and earning the coveted Combat Medical Badge. He was decorated by his command for his direct surgical support of the medical response to the terrorist attack against the Pentagon on 11 September 2001. Since the terrorist attacks of 11 September 2001, as chief of General Surgery at the nation’s largest military hospital, he has led his surgeons in the treatment of over 7,500 patients from Operations Iraqi Freedom and Enduring Freedom. In 2007, COL Shriver served in Afghanistan with the 1-91 Cavalry, 173rd Airborne, winning the coveted “Order of the Spur” award from his cavalry unit, for gallant and intrepid service under fire on the front lines of combat in Afghanistan. COL Shriver also was decorated with the Combat Action Badge during that tour, for service under fire in direct engagement with enemy forces. COL Shriver completed his fourth combat tour, second in Afghanistan, returning on 20 February 2011.

Other military awards include the Legion of Merit (2 awards), Meritorious Service Medal, Joint Services Commendation Medal, Army Commendation Medal with two oak leaf clusters, and the Civilian Outstanding Service Medal. He was awarded the prestigious “A” Designator Award from the Surgeon General, given to only a select few military physicians who are the leaders of healthcare in the Army. He was awarded the Order of Military Medical Merit, given to “civilian or military physicians who meet the highest standard of “citizen-soldier-physician.” In 2008, COL Shriver was promoted to the rank of Professor of Surgery at the USUHS in Bethesda, Maryland. COL Shriver in 2010 was elected into the prestigious American Surgical Association, the oldest and most premier of all surgical societies in the world. COL Shriver has been an author on three separate articles published in the prestigious New England Journal of Medicine, and has also been an author on an article in the world’s most premier research publication, Nature, in October 2012. A nationally-known Surgical Oncologist and as Director of the MCC, COL Shriver in July 2014 served on a FDA Panel as an Advisor to the FDA, evaluating the controversial surgical technique known as laparoscopic power morcellation. COL Shriver was selected by the USUHS as the first Oliver Beahrs Professor of Surgery in April 2015.

Gayle Vaday, PhD

Congressionally Directed Medical Research Programs, U.S. Army Medical Research and Materiel Command

Dr. Vaday serves as a program officer at the CDMRP and program manager of the DoD BCRP. She is responsible for strategic program planning, execution, and management, overseeing all aspects of the acquisition program cycle for the BCRP, including funding opportunities and scientific reviews. She also oversees investment of the Breast Cancer Research Stamp funds allocated to the BCRP. In addition to managing the BCRP, Dr. Vaday is a Program Management Lead, serving in a supervisory and senior leadership role for the CDMRP’s programs and processes. She is also an Army Managers’ Internal Control evaluator of the CDMRP’s scientific review process.
Dr. Vaday graduated from Whittier College with a BA degree in Biology. She received her PhD in Microbiology and Immunology from the University of Rochester School of Medicine and Dentistry, where she received several awards, including the Melville Hare Award for Distinguished Research. She completed postdoctoral training as a Feinberg Fellow at the Weizmann Institute of Science in Israel.

Prior to joining the CDMRP, Dr. Vaday was a Research Assistant Professor at Stony Brook University and a Research Biologist at the Northport Veterans Affairs Medical Center (NVAMC). At the NVAMC, she served as Chair of the Institutional Animal Care and Use Committee. Her research on breast and prostate cancer was funded by grants from the Carol M. Baldwin Breast Cancer Research Fund and the VA.

At the CDMRP, Dr. Vaday served as a Contracting/Grants Officer’s Representative (COR/GOR), as well as task order lead for support contracts, research contracts, and assistance agreements. She authored Small Business Innovation Research (SBIR) topic solicitations and served as the COR for several SBIR research contracts. She previously represented the DoD as a member of the Interagency Breast Cancer and Environmental Research Coordinating Committee co-led by the National Institute of Environmental Health Sciences and the NCI. She is currently an ex officio member of the Advisory Committee for Breast Cancer in Young Women, an interagency committee led by the U.S. Centers for Disease Control and Prevention.

Harvey Wilds, CAPT, MC, USN

Department of Defense

CAPT Wilds is a specialty lead at the Naval Medical Center Radiation Oncology at the NMCSD and Principal Investigator of numerous clinical trials. CAPT Wilds obtained a BS in Biology from the University of Detroit. He was commissioned as an Ensign in 1991 and served aboard the USS EMORY S LAND (AS-39) as the medical department division officer and radiation health officer until 1993. He completed his MD at USUHS in 1997 and completed a transitional internship at Naval Medical Center Portsmouth (NMCP). He completed flight surgeon training and was assigned to Air Test and Evaluation Squadron ONE in Patuxent River, Maryland from 1999 to 2001. After his flight surgery tour, he completed training in radiation oncology at The Johns Hopkins Hospital in 2005. CAPT Wilds was assigned to NMCP and served as medical director, project manager for prostate brachytherapy and director of clinical research in radiation oncology. During his time at NMCP he was also given the opportunity to serve as the senior medical officer on Provincial Reconstruction Team Farah in Farah, Afghanistan from 2009 to 2010.
Appendix C. Biographies of Presenters

Julio Aguirre-Ghiso, PhD

Mount Sinai School of Medicine

Dr. Aguirre-Ghiso is the Director of Head and Neck Cancer Basic Research and the Director of Solid Tumor and Metastasis Research at the Mount Sinai School of Medicine, as well as the Assistant Director of Basic Science Shared Resources at the Tisch Cancer Institute at Mount Sinai. He received his PhD from the University of Buenos Aires in 1997 and completed a postdoctoral fellowship at Mount Sinai. Since 2008, he has been a professor at Mount Sinai in the Division of Hematology and Oncology, the Department of Medicine, and the Department of Otolaryngology.

Dr. Aguirre-Ghiso’s research has focused on non-proliferating dormant disseminated tumor cells (DTC), leading to a paradigm shift in the understanding of cancer dormancy biology. His laboratory identified a molecular “dormancy signature” that predicts prolonged metastasis-free periods in different cancers. Dr. Aguirre-Ghiso’s work has illuminated new avenues for cancer research, such as the finding that dormant tumor cells can originate very early during cancer evolution, even during pre-malignant stages of cancer. His team has also designed an epigenetic reprogramming therapy to induce dormancy in DTCs and worked with Eli Lilly to develop a translational program targeting dormant disease. Another current project is the role of endoplasmic reticulum stress signaling in tissue morphogenesis and DTC biology. Dr. Aguirre-Ghiso was recently a co-recipient of the Falk Foundation Award from the Dr. Ralph and Marian Falk Medical Research Trust.

Charles M. Balch, MD

University of Texas MD Anderson Cancer Center

Dr. Balch has led a distinguished career as a clinical and academic surgical oncologist for the past 40 years, and is a leading authority in both melanoma and breast cancer. He has published extensively on the conduct and methodology of clinical research, and has authored of 760 publications, which have been cited over 24,000 times in the biomedical literature. He is the Founding Editor-in-Chief of the Annals of Surgical Oncology, and co-Editor-in-Chief of Chinese Clinical Oncology.

Dr. Balch has served in leadership roles with the Society of Surgical Oncology (as President in 1992), the American Board of Surgery (Board of Directors), the Association of Academic Surgeons (President), the Commission on Cancer (Chair, Board of Directors), and the American Joint Committee on Cancer (Executive Committee). He has had held major leadership roles involving clinical research in four comprehensive cancer centers. He has also held leadership roles involving clinical research in cancer cooperative groups, National Institutes of Health (NIH) study sections, and in professional organizations. In past years, Dr. Balch has served as Executive Vice President and Chief Executive Officer (CEO) of the American Society of Clinical Oncology (ASCO), and as President and CEO of the City of Hope National Medical Center. At the University of Texas, MD Anderson Cancer Center, Dr. Balch has served as Executive Vice President for Health Affairs, Vice President of Hospital and Clinics, Head of the Division of Surgery, Chair of the Department of Surgical Oncology, among other positions.

Jonathan Brody, PhD

Thomas Jefferson University

Dr. Brody is the Director of Surgical Research and Co-director of the Jefferson Pancreatic, Biliary, and Related Cancer Center at Thomas Jefferson University. He is also a Professor within the departments of Surgery and Pathology at Thomas Jefferson University, the Chair of the DoD council’s Cancer Research Program, and a member of the Kimmel Cancer Center. Dr. Brody received his PhD from The Johns Hopkins University School of Medicine. During his training, Dr. Brody won the prestigious
Experimental Pathologist-in-Training Award from the American Society of Investigative Pathology. His laboratory focuses on many molecular aspects of pancreatic cancer, including developing ways to target a novel pro-survival network in pancreatic cancer cells and optimizing current therapies used in the clinic.

Dr. Brody is the lead primary investigator on the prestigious American Association for Cancer Research (AACR) Pancreatic Cancer Action Network Research Acceleration Network grant. He also sits on the Scientific Advisory Board for the Molecular Diagnostic Panel of the Pancreatic Cancer Action Network. Previously, Dr. Brody developed and patented novel buffers for DNA identification and conducted pivotal studies on a common chemotherapeutic agent, 5-fluorouracil. He has published over 100 peer-reviewed publications in top tier scientific and cancer journals, and has co-authored multiple book chapters and review articles on pancreatic cancer, including the chapter on pancreatic cancer in Rosenberg’s and DeVita’s Principles and Practice of Oncology. He serves on many international study sections as Vice Chair of the Tumor Biology and Genomics study section for the American Cancer Society, Chair of the DoD Peer Reviewed Cancer Research Program, and also serves on NCI panels. He won the AACR Pancreatic Cancer Career Development Award in 2010 and was awarded American Cancer Society Research Scholar grant for his work on the role of HuR protein in pancreatic cancer.

Peter Choyke, MD

National Cancer Institute, National Institutes of Health

Dr. Choyke is the Chief of the NCI’s Molecular Imaging Program, which he founded in 2004. He received his MD from Jefferson Medical College, completed his residency in Diagnostic Radiology at Yale, and completed his fellowship at the University of Pennsylvania. He subsequently joined the faculty of Georgetown University and soon thereafter the Diagnostic Radiology Department at the NIH Clinical Center. In his early career, he helped discover the genes responsible for hereditary renal cancers, including von Hippel Lindau, Birt Hogg Dube, Hereditary papillary type 1, and Hereditary leiomyosarcoma renal cell carcinoma.

Dr. Choyke’s research interests and areas of expertise include prostate cancer, cell tracking, radiopharmaceutical development, and lymphatic imaging. His more recent work focuses on translating molecular imaging methods, including MRI and PET, into clinical usage. He has pioneered the use of advanced medical imaging in oncology, including the development of MRI-Ultrasound Fusion biopsy of the prostate, a technique that has revolutionized the way prostate cancer is diagnosed. Currently, his team is focusing on new theranostic and molecular imaging approaches in oncology including photomunotherapy, a promising new method of treating cancers with light, and cell tracking studies for cell-based therapies.

Lisa M. Coussens, PhD

Knight Cancer Institute, Oregon Health and Sciences University

Dr. Coussens is the Chair of the Department of Cell, Developmental and Cancer Biology and Associate Director for Basic Research in the Knight Cancer Institute at Oregon Health and Sciences University. She also holds the Hildegard Lamfrom Chair in Basic Science. She received her PhD in Biological Chemistry from the University of California, Los Angeles in 1993, followed by a postdoctoral fellowship in Cancer Biology at the University of California at San Francisco.

Dr. Coussens’ research focuses on elucidating the roles of immune cells and their mediators as critical regulators of solid tumor development. Her laboratory reported that lymphocytes selectively regulate myeloid cell functions in mouse models of squamous and mammary carcinoma, mesothelioma, and pancreatic adenocarcinoma, and that selective inhibition of key factors regulating either myeloid
recruitment or function significantly enhances efficacy of chemo- and radiation therapy, and thereby extends long term survival of tumor-bearing mice. These discoveries are currently being translated into the clinical realm: Dr. Coussens is the lead primary investigator on a KOMEN Promise grant conducting an investigator-initiated multi-center Phase Ib/II clinical trial evaluating a novel macrophage-antagonist in combination with chemotherapy in women with metastatic triple negative breast cancer. More recently, Dr. Coussens was awarded a Stand Up To Cancer – Lustgarten Foundation Pancreatic Cancer Convergence Dream Team Translational Research grant focused on clinical evaluation of immune-based therapies in pancreatic cancer. Dr. Coussens also received the prestigious Gertrude B. Elion Award from the AACR, the Mallinckrodt Award for Medical Science, a V Foundation Scholar Award, and two sequential Era of Hope Scholar Awards.

Nigel Crawford, M.B.ChB, PhD
National Human Genome Research Institute, National Institutes of Health

Dr. Crawford has been a tenure-track investigator at the National Human Genome Research Institute since September 2009. He obtained his M.B.Ch.B. degree (MD equivalent) from the University of Liverpool, and his PhD from the University of Louisville. He then served as the Price Fellow for Surgical Research in the Department of Surgery at the University of Louisville and completed postdoctoral fellowship in the laboratory of Kent Hunter at NCI.

Dr. Crawford has a longstanding research interest in the influence of germline variation on human disease. While at the University of Louisville, he used molecular epidemiological techniques to characterize the influence of the germline on the development of inflammatory bowel disease. His studies at NCI concentrated on the influence of germline variation on breast cancer metastasis, where he identified germline regulators of metastasis-associated extracellular matrix (ECM) genes, which are frequently dysregulated in both mouse mammary tumors and human breast carcinomas prone to metastasis. He identified seven candidate genes with expression highly correlated to that of metastasis-predictive ECM genes. His more recent work continues his focus on germline variation and its modulation of tumor progression and metastasis, particularly in prostate and breast cancers. Dr. Crawford received a number of awards and honors, including an American Association for Cancer Research Scholar-in-Training award in 2007.

Don S. Dizon, MD
Harvard Medical School and Massachusetts General Hospital Cancer Center

Dr. Dizon is the founder and current Director of the new Oncology Sexual Health Clinic at the Massachusetts General Hospital Cancer Center (MGHCC). He is the Clinical Co-Director of Gynecologic Oncology at MGHCC and an Associate Professor of Medicine at Harvard Medical School. He received his MD from the University of Rochester, School of Medicine and Dentistry, completed his residency in Internal Medicine at Yale-New Haven Hospital, and did his fellowship in medical oncology at the Memorial Sloan Kettering Cancer Center (MSKCC). Previously, he was the Director of Medical Oncology at the Program in Women's Oncology at Women and Infants Hospital of Rhode Island and an Associate Professor of Obstetrics and Gynecology and Medicine at the Warren Alpert School of Medicine at Brown University. While at Brown, he founded the Center for Sexuality, Intimacy, and Fertility for women with cancer, the first and only program of its kind in Rhode Island.

Dr. Dizon’s clinical research interests include novel therapies, including chemotherapy and immunotherapy, for women’s cancers, particularly ovarian and breast cancers. In addition to his clinical duties, he is a co-chair of the Cervical Cancer Task Force for the NCI Gynecologic Cancer Steering Committee. He is also prolific on social media and maintains online columns for the ASCO and for the journal The Oncologist. His ASCO column received APEX awards for publication excellence in 2013 and 2014. He is the chair of the social media working group for ASCO and was named the inaugural
chair of the Digital Engagement Committee for the Southwest Oncology Group.

**Bettina Drake, MPH, PhD**

**Siteman Cancer Center, Washington University School of Medicine**

Dr. Drake is an Associate Professor in the Division of Public Health Sciences at the Washington University School of Medicine. She received her MPH from the University of North Texas Health Science Center, her PhD in Epidemiology from the Arnold School of Public Health at the University of South Carolina, and completed a postdoctoral fellowship at the Harvard School of Public Health.

Dr. Drake’s research focuses on identifying preventive strategies to reduce disparities in cancer patients. The objectives of her research program are: (1) to identify the modifiable and non-modifiable risk factors for cancer as well as the at-risk groups for these factors; (2) to utilize community-based approaches to design, implement, and disseminate research information; and (3) to promote education and awareness of research and research participation in minority communities. Currently, she works with the Program for the Elimination of Cancer Disparities (PECaD) conducting community-based research on minority recruitment in biorepository studies. She also co-leads the Prostate Cancer Community Partnership, a community partnership of PECaD that is working to reduce local disparities in patients with prostate cancer. Dr. Drake was an Association of Schools for Public Health/Centers for Disease Control and Prevention, Prevention Research Center Research Fellow from 2004 to 2006. While at the University of North Texas Health Science Center she received the Leon Brachman Community Service Award.

**David E. Fisher, MD, PhD**

**Harvard Medical School and Massachusetts General Hospital**

Dr. Fisher is the Chair of the Dermatology department, Director of the Melanoma Program, and Director of the Cutaneous Biology Research Center at Massachusetts General Hospital (MGH). He received his PhD from Rockefeller University and his MD from Cornell University. He completed his internal medicine residency at MGH and his fellowships in adult and pediatric oncology at Dana-Farber Cancer Institute and Boston Children’s Hospital. After his fellowships, he conducted postdoctoral research in the lab of Nobel Laureate Phillip Sharp at the Massachusetts Institute of Technology.

Dr. Fisher is an expert in molecular oncology with particular emphasis on the biology of melanocytes and their involvement in malignant melanoma. His laboratory has carried out seminal research on melanocyte development, signaling, and transcription. He has discovered several human oncogenes, generated a reagent used worldwide for melanoma diagnosis, and serves as principal investigator for a Harvard-wide Program Project Grant on melanoma. He also studied novel skin cancer prevention strategies based on models of redhead/fair-skinned high-risk susceptibility and non-mutagenic tanning. Dr. Fisher has published over 250 scholarly articles, many in high profile journals, and is former President of the Society for Melanoma Research and Chair of the Scientific Advisory Committee of the Melanoma Research Foundation.

**Peter Friedl, MD, PhD**

**Radboud University Nijmegen Medical Centre and University of Texas MD Anderson Cancer Center**

Dr. Friedl is the Director of the Microscopical Imaging Centre at the Radboud University Nijmegen Medical Centre in the Netherlands and a faculty member at the University of Texas, MD Anderson Cancer Center. He is also the head of the imaging section at the David H. Koch Center, Department of Genitourinary Oncology, at the MD Anderson Cancer Center. He received his MD from the University of Bochum in 1992 and his PhD from McGill University. He completed his postdoctoral
training at the University of Witten/Herdecke and clinical residency at the University of Würzburg, both in Germany.

Dr. Friedl’s research focuses on the mechanisms and plasticity of cell migration in immune regulation and cancer metastasis, with emphasis on cell-matrix adhesion, pericellular proteolysis, and cell-cell communication during migration. His laboratory has identified pathways determining diversity and plasticity of cell migration, collective cancer cell invasion, and the contribution of migration pathways to immune defense and cancer resistance. His current work addresses the microenvironmental regulation of cancer cell cooperation and collective behavior and their relevance for the metastatic cascade. Dr. Friedl has received numerous awards and honors. Most recently, he received the Award of the European Society for Molecular Imaging, the Prize for the Advancement of Molecular Science from the City of Florence, and a Consolidator Grant from the European Research Council.

Cyrus Ghajar, PhD
Fred Hutchinson Cancer Research Center

Dr. Ghajar is the Director of the Laboratory for the Study of Metastatic Microenvironments in the Fred Hutchinson Cancer Research Center’s Translational Research Program. He is also an Assistant Member of both the Public Health Sciences and Human Biology Divisions.

Dr. Ghajar’s primary research interest is the tissue microenvironment and its influence on the behavior of DTCs. Specifically, his laboratory is working to understand how tissues regulate survival, growth, and therapeutic resistance of DTCs, and how local and systemic changes awaken DTCs. His ultimate interests lie in targeting dormant DTCs to prevent metastasis. In 2015, he was the recipient of a $4.1 million DoD Breast Cancer Research Program (BCRP) “Era of Hope” Scholar Award.

Sarah Goldberg, MD
Yale School of Medicine and Yale Cancer Center

Dr. Goldberg is an Assistant Professor of Medicine in the division of Medical Oncology at the Yale School of Medicine and Yale Cancer Center. She received her MD from Mount Sinai School of Medicine and her MPH from Harvard University. She completed her internal medicine residency at MGH and a fellowship in Medical Oncology at Dana-Farber Cancer Institute and MGH.

In her clinical practice, Dr. Goldberg specializes in the treatment of patients with thoracic malignancies. Her research interests include personalized medicine and immunotherapy for non-small cell lung cancer and identification of biomarkers, with a particular focus on brain metastases. She developed and led multiple clinical trials for patients with lung cancer using targeted and immunotherapies and also led translational research projects to identify biomarkers predictive of treatment response using both tumor and blood samples from patients with lung cancer. In 2015, she was the recipient of the Charles A. Coltman, Jr. Fellowship from the Southwest Oncology Group (SWOG)/Hope Foundation. In the same year, she also received the first SWOG Trial Support award.

Clifford Hudis, MD
American Society of Clinical Oncology

Dr. Hudis is the CEO of the ASCO, the largest professional society in the world dedicated to education, research, and quality of care for patients with cancer. He received his MD from the Medical College of Pennsylvania, did his residencies at the Hospital of the Medical College of Pennsylvania and the Philadelphia Veterans Administration Hospital followed by a fellowship at MSKCC. Prior to joining ASCO, he served for nearly two decades as the Chief of the Breast Medicine Service and Attending Physician at MSKCC where he was also a Professor of Medicine at the Weill Medical College of
Cornell University. He was co-Chair of the Breast Committee of the Alliance for Clinical Trials in Oncology (formerly Cancer and Leukemia Group), Chair of the Scientific Advisory Committee of the Breast Cancer Research Foundation, a former Associate Editor of the Journal of Clinical Oncology, and the President of ASCO (2013–2014).

For almost 30 years, Dr. Hudis has worked to develop more effective treatments and preventive measures for breast cancer. His early work focused on translating the kinetic predictions of the Norton-Simon model into more effective dose-dense adjuvant chemotherapy programs. For the past decade, he has focused on the interplay of inflammation, obesity, and cancer in the clinic. His team’s recent work on low grade, chronic white adipose inflammation in most overweight and obese women is informing intervention studies and public policy initiatives at an international level.

Rakesh K. Jain, PhD

Harvard Medical School and Massachusetts General Hospital

Dr. Jain is the A.W. Cook Professor of Radiation Oncology (Tumor Biology) at Harvard Medical School and Director of the Steele Laboratories of Tumor Biology at MGH. He has held both positions since 1991. He is also an affiliated faculty member at the Harvard-Massachusetts Institute of Technology Division of Health Sciences and Technology and a member of the Biological and Biomedical Sciences Program at Harvard Medical School. He received his PhD in Chemical Engineering from the University of Delaware - Newark.

Dr. Jain is a pioneer of research at the interface of engineering and oncology, and has made seminal contributions to fields of research, including in tumor microenvironment, drug delivery, in vivo imaging and bioengineering. These include uncovering barriers to the delivery and efficacy of molecular-, nano- and immuno-therapeutics; developing new strategies to overcome these barriers; and then translating these strategies from bench to bedside. He has proposed fundamental principles guiding the development and novel use of drugs for treatment of cancer and non-cancerous diseases characterized by abnormal vessels and matrix. He has mentored more than 200 doctoral and postdoctoral students from over a dozen different disciplines. As an author of more than 650 publications, he is among the top 1 percent of cited researchers. Dr. Jain has the rare distinction of being a member of all three U.S. National Academies: the National Academy of Sciences, the National Academy of Engineering, and the National Academy of Medicine. He has received more than 75 awards, including the ASCO Science of Oncology Award (2012) the AACR-Princess Takamatsu Memorial Lectureship (2014), the DoD Breast Cancer Research Innovator Award (2010–2015), and the NCI Outstanding Investigator Award twice (1993–2000 and in 2015–2022). He was also chosen as one of 50 Oncology Luminaries on the 50th anniversary of ASCO in 2014, and received the U.S. National Medal of Science from President Obama in 2016.

Rosandra Kaplan, MD

National Cancer Institute, National Institutes of Health

Dr. Kaplan is a pediatric oncologist and translational researcher who is an investigator in the Pediatric Oncology Branch at NCI. Dr. Kaplan received her MD from Dartmouth Medical School, and completed a pediatric residency at the combined residency program at Children’s Hospital Boston and Boston Medical Center. She completed her hematology/oncology fellowship at MSKCC and Weill Cornell Medical Center and a postdoctoral research fellowship with Dr. David Lyden and Dr. Shahin Rafii, studying bone marrow derived stem and progenitor cells in vaculogenesis and metastasis. Before coming to the NIH in 2010, she was an assistant Professor of Pediatrics at Weill Cornell Medical Center and MSKCC.

Dr. Kaplan was the first to describe the pre-metastatic niche by demonstrating that tumor-secreted factors establish a hospitable microenvironment in distant tissue sites composed of activated stromal
cells, recruited hematopoietic cells, and extracellular matrix that promote DTC growth. Her current research program focuses on the key stromal and hematopoietic cells and alterations in the extracellular matrix that are important for the creation of a niche environment that promotes metastatic progression. Her laboratory has recently determined that hematopoietic stem cell activation and hematopoietic stem and progenitor cell mobilization is important for promoting metastatic progression, and the overall goal of her laboratory is to discover new targets to inhibit the crosstalk between tumor cells and the microenvironment. She is the recipient of several awards, including the Charles, Lillian and Betty Neuwirth Clinical Scholar in Pediatric Oncology, Doris Duke Charitable Career Development Award, a co-investigator in the Komen Foundation Investigator-Initiated Award, Hope Street Kids grant award, and the ASCO Young Investigator Award.

Joanna Kitlinska, PhD
Georgetown University Medical Center

Dr. Kitlinska is an Associate Professor in the Department of Biochemistry and Molecular and Cellular Biology at the Georgetown University Medical Center. She received her PhD in Medical Biology and Human Genetics from the Medical School in Lublin, Poland.

Her research focuses on the role of neuropeptide Y in the development, growth and progression of pediatric tumors, specifically neuroblastoma and Ewing sarcoma. Currently, her laboratory is investigating the role of neuropeptide Y in metastasis and its interactions with tumor microenvironment, as well as the impact of hypoxia on these processes. Dr. Kitlinska is also interested in the effect of prenatal and adulthood stress on cancer development and progression. She has received grants from the Children’s Cancer Foundation and an Investigator Initiated Pilot Project award from Georgetown-Howard Universities Center for Clinical and Translational Studies.

Joan Massagué, PhD
Memorial Sloan Kettering Cancer Center

Dr. Massagué is the Director of the Sloan Kettering Institute and a member of the Cancer Biology and Genetics Program. He is also a professor at Weill-Cornell Graduate School of Medical Sciences. He received his PhD from the University of Barcelona, followed by a postdoctoral fellowship at Brown University. In 1989, he was appointed Investigator at the Howard Hughes Medical Institute, and from 1990 to 2013, Dr. Massagué was the Chairman of the Cancer Biology and Genetics Program and the Cell Biology Program at MSKCC.

Dr. Massagué’s research is focused on investigating the mechanisms by which growth factors, signaling pathways, and gene expression programs regulate normal cell proliferation and cancer metastasis. His work has revolutionized the field’s understanding of transforming growth factor-beta (TGF-β) signaling. Most recently, his team detected some of the genes and mechanisms responsible for cancer metastasis in the bones, lungs, and brain, opening new avenues for clinical treatment. He is a member of the National Academy of Sciences and the National Academy of Medicine as well as many other prestigious organizations, including the American Academy of Arts and Sciences, the Spanish Royal Academies of Medicine and Pharmacy, and the European Molecular Biology Organization, and is a Fellow of the American Association for Cancer Research Academy. He has received numerous awards for his research, including the Prince of Asturias Award in Science and Technology, the Vilcek Prize in Biomedical Science, the Passano Prize, the Frontiers of Knowledge Award in Biomedicine from the BBVA Foundation, the Clowes Memorial Award from the American Association for Cancer Research, the Feodor Lynen Medal, the National Prize for Research in Biology, the Charles Rodolphe Brupbacher Prize for Cancer Research, and the Pezcoller Foundation-AACR International Award for Cancer Research.
Andy Minn, MD, PhD

University of Pennsylvania Perelman School of Medicine

Dr. Minn is an Assistant Professor in the Department of Radiation Oncology and an Assistant Investigator in the Abramson Family Cancer Research Institute at the University Of Pennsylvania Perelman School Of Medicine. He received his MD and PhD in immunology from the University of Chicago. He completed his residency training in radiation oncology at MSKCC and postdoctoral training with Dr. Joan Massagué, studying gene programs that drive organ-specific breast cancer metastasis. His laboratory focuses on the interaction between cancer cells and the tumor and immune microenvironment to influence cancer therapy resistance to both conventional and immune therapies. In particular, he is interested in how anti-viral and innate immune signaling pathways underlie these interactions to impact therapy response. Recently, he has applied these interests to understand mechanisms of response and resistance to combination therapies using immune checkpoint blockade. In 2015, he was awarded a Scientific Research Award by the American Cancer Society’s Pennsylvania Division, Southeast Region, and the Michael S. Brown New Investigator Research Award by the Perelman School of Medicine.

Alfred Neugut, MD, PhD

Columbia University and Herbert Irving Comprehensive Cancer Center

Dr. Neugut is a Myron M. Studner Professor of Cancer Research and Professor of Medicine and Epidemiology at Columbia University, and Associate Director for Population Sciences for the Herbert Irving Comprehensive Cancer Center, also at Columbia. He is also the Director of Junior Faculty Development for the Department of Epidemiology at the Mailman School of Public Health. He received his MPH, MD, and PhD in Pathobiology from Columbia University, completed his residency at the Albert Einstein College of Medicine, and then completed his fellowship in Medical Oncology at MSKCC.

Dr. Neugut is a medical oncologist with a particular interest in gastrointestinal tract cancers, especially colorectal and gastric cancers, and in cancer epidemiology and prevention. He initiated a series of important studies focused on risk factors for the occurrence and recurrence of colorectal adenomatous polyps; these studies extended into the use and yield of colonoscopy and fecal occult blood testing for routine screening and diagnosis. An editorial by Dr. Neugut in 1988 was the first to suggest the use of colonoscopy for routine screening of asymptomatic adults, a common practice now. His second major research focus was the occurrence of second malignancies, especially the impact of radiation therapy. At the present time, a significant amount of Dr. Neugut's research is centered on studying quality of care in the use of chemotherapy and radiotherapy for cancer in the elderly and others. His group has found significant effects of age, race/ethnicity, as well as financial status and the level of co-payments in leading to lower quality care and decreased adherence to prescribed chemotherapy and hormonal therapy. Dr. Neugut has published over 500 peer-reviewed chapters and papers and has led two NCI-funded training grants for predoctoral and postdoctoral trainees for over 25 years. He is a recent recipient of the Distinguished Achievement Award of the American Society of Preventive Oncology.

Klaus Pantel, MD, PhD

University Medical Center Hamburg-Eppendorf Center of Experimental Medicine

Dr. Pantel is the Chair of the Institute of Tumor Biology at the University Medical Center Hamburg-Eppendorf. The institute, which he founded in 2002, is part of the Centre of Experimental Medicine and the University Cancer Center Hamburg. He received his MD from the University of Cologne, School of Medicine, and completed a postdoctoral fellowship in the Department of Internal Medicine’s Division of Hematology and Oncology at the Wayne State University School of Medicine. Previously, he has served as the Deputy Director of the Centre of Experimental Medicine, and as Professor of Molecular
Genetics and Head of the Molecular Oncology in the Department of Gynecology and Obstetrics at the University Medical Center Hamburg-Eppendorf. The pioneering work of Dr. Pantel in the field of cancer micrometastasis, circulating tumor cells, and circulating nucleic acids is reflected by more than 400 publications in prestigious, high-ranking biomedical and scientific journals. He received the AACR Outstanding Investigator Award in 2010, the German Cancer Award in 2010, and the European Research Council Advanced Investigator Grant in 2011. Dr. Pantel also coordinates the European TRANSCAN group “CTC-SCAN”, the European Innovative Medicine Initiative consortium CANCER-ID on blood-based “Liquid Biopsies” and serves on the editorial boards of several international cancer journals.

Steven A. Rosenberg, MD, PhD

National Cancer Institute

Dr. Rosenberg is the Chief of Surgery at NCI and a Professor at USUHS and at the George Washington University School of Medicine and Health Sciences. He is also a professor in the Department of Laboratory Medicine at the Karolinska Institute in Stockholm, Sweden. Dr. Rosenberg received his MD degree from The Johns Hopkins University and PhD in Biophysics from Harvard University. Following the completion of his residency training in surgery in 1974 at Brigham Hospital, Dr. Rosenberg became the Chief of Surgery at the NCI, a position he maintains today.

Dr. Rosenberg has been a pioneer throughout his four decade career. His immunotherapy research resulted in the first effective immunotherapies for patients with advanced cancer. His basic and clinical studies of interleukin-2 directly resulted in the approval of this immunotherapy by the FDA for the treatment of patients with metastatic melanoma and renal cancer, many of whom remain disease-free over 25 years after treatment. His studies of cell transfer immunotherapy resulted in durable complete remissions in patients with metastatic melanoma and directly demonstrated the role of T lymphocytes in human cancer immunotherapy. He pioneered the development of gene therapy and was the first to successfully insert foreign genes into humans. His studies of the adoptive transfer of genetically modified lymphocytes were the first to result in the regression of metastatic cancer including patients with melanoma, sarcomas and lymphomas. In recent work, Dr. Rosenberg established new approaches for the application of immunotherapy to patients with a variety of common solid cancers by targeting the unique mutations present in the patient’s cancer. Dr. Rosenberg has been the recipient of numerous awards. Among them are the Meritorious Service Medal for the U.S. Public Health Service, the Friedrich Sasse Prize from the University of West Berlin, the Nils Alwell Prize, the Distinguished Alumnus Award from The Johns Hopkins University, the Griffuel Prize for Research from the French Association for Research on Cancer, and the Milken Family Foundation Cancer Award. Dr. Rosenberg was awarded the Ellis Island Medal of Honor and twice received the Armand Hammer Cancer Prize for pioneering work in cancer research. He has received many of the highest honors from professional societies, including the Karnofsky Prize from the ASCO, the John Wayne Award for Clinical Research from the Society of Clinical Oncology, the Flance-Karl Award from the American Surgical Association, the prize for scientific excellence in medicine from the American-Italian Cancer Foundation, the Richard V. Smalley Memorial Award from the International Society for Biological Therapy of Cancer, the Medal of Honor for Basic Research from the American Cancer Society, the Lifetime Achievement Award of Distinction from the Susan B. Komen Foundation, and the Samuel J. Hetman Service to America Medal as the Federal Employee of the Year from the Partnership for Public Service.

Howard I. Scher, MD

Memorial Sloan Kettering Cancer Center

Dr. Scher is the Chief of the Genitourinary Oncology Service at MSKCC, a professor of Medicine at the Weill Cornell Medical College, and the D. Wayne Calloway Chair in Urologic Oncology. He received his MD from New York University School of Medicine, and completed his residency at
Bellevue Hospital Center in New York and fellowships at MSKCC and the Weill Cornell Medical College.

Dr. Scher’s research is focused on the development of targeted therapies and biomarkers to guide individual patients’ treatment selection, improve the way drugs are evaluated in the clinic, and accelerate regulatory approvals. He has led international efforts to standardize the design and analysis of Phase II prostate cancer trials (PCWG2, PCWG3) and helped elucidate key molecular and genetic features of prostate cancer, translating these insights into the clinic by leading early Phase and Phase III registration trials of abiraterone acetate and enzalutamide, which are now FDA approved. Dr. Scher also serves as the principal investigator of the NIH Specialized Program of Research Excellence in Prostate Cancer at MSKCC and the DoD-sponsored Prostate Cancer Clinical Trials Consortium, and has received the 2015 AACR Team Science Award for his multidisciplinary work developing AR inhibitors.

Anil K. Sood, MD

University of Texas MD Anderson Cancer Center

Dr. Sood is the Professor and Vice Chair for Translational Research in the Departments of Gynecologic Oncology and Cancer Biology, and co-director of the Center for RNA Interference and Non-Coding RNA at the MD Anderson Cancer Center. He is also Director of the Blanton-Davis Ovarian Cancer Research Program and co-leads the Women’s Cancer Moonshot Program, which focuses on ovarian and breast cancers. Dr. Sood received his MD from the University of North Carolina-Chapel Hill School of Medicine.

His research focuses on three main areas: (1) mechanisms of angiogenesis and metastasis in ovarian cancer; (2) effects of neuroendocrine stress hormones on ovarian cancer growth and progression, and (3) development of new strategies for systemic in vivo siRNA delivery. Dr. Sood has received major recognition for his research accomplishments, including the Hunter Award, the Margaret Greenfield/Carmel Cohen Excellence in Ovarian Cancer Research Prize, and the GCF/Clauudia Cohen Research Foundation Prize for Outstanding Gynecologic Cancer Researcher. Dr. Sood has published over 460 peer-reviewed articles and holds 15 patents related to novel drugs and technologies. He is an elected member of the American Society for Clinical Investigation and an elected fellow of the American Association for the Advancement of Science.

Hensin Tsao, MD, PhD

Harvard Medical School and Massachusetts General Hospital Cancer Center

Dr. Tsao is a professor of Dermatology at Harvard Medical School and serves as the Director of both the MGH Melanoma and Pigmented Lesion Center and the MGH Melanoma Genetics Program. He is also the Head of the Skin Cancer Genetics Laboratory in the Wellman Center for Photomedicine at MGH, where he oversees a research program in melanoma genetics. He received his MD from the College of Physicians and Surgeons at Columbia University and his PhD in Biophysics/Biochemistry from the Columbia University Graduate School of Arts of Sciences. Dr. Tsao completed his internship, dermatology residency, and melanoma fellowship, in the Harvard University-affiliated hospitals. He concluded his training with a postdoctoral fellowship in the Division of Oncology at MGH. In 2001, Dr. Tsao joined the Wellman Center for Photomedicine and Department of Dermatology at MGH, where he established the Skin Cancer Genetics Laboratory and the MGH Melanoma Genetics Program in order to better understand the molecular basis of melanoma predisposition, progression and therapeutic response.

Dr. Tsao is the author of 200 peer-reviewed research articles, reviews, abstracts, textbook chapters, and online media texts. He has also delivered over 250 presentations on melanoma, genetics, and skin disease throughout the world. He has received numerous awards including the Alfred Steiner Dean’s
Award and Titus Munson Coan Prize from Columbia University, the Deborah Shalita Marmour Clinical Career Development Award from the Dermatology Foundation, the Young Investigator Award and the Marion Sulzberger Award from the American Academy of Dermatology, the D.M. Carter Award and the Howard Milstein Innovation Award from the American Skin Association, the William Montagna Award and Lectureship from the Society for Investigative Dermatology, the MGH Partners-in-Excellence Award for Leadership and Innovation, and the MGH Cancer Center’s “100” Award. For his clinical and scientific contributions, Dr. Tsao was selected as one of Boston’s Top Doctors (2010–2015) and inducted into the American Dermatological Association and the American Society for Clinical Investigation in 2008 and 2009, respectively.

Danny R. Welch, PhD

University of Kansas Cancer Center

Dr. Welch is a professor at the NCI-designated University of Kansas Cancer Center in the Department of Cancer Biology, which he founded in 2011. He is also the Associate Director for Basic Sciences and Education at University of Kansas Cancer Center and has appointments as a professor in both Pathology and Laboratory Medicine and Molecular and Integrative Physiology. He received his PhD in Biomedical Sciences from the University of Texas at Houston, and joined Pennsylvania State University College of Medicine in 1990 as one of the original faculty in the Jake Gittlen Cancer Research Institute. While at Penn State, Dr. Welch was as a member of the American Cancer Society’s Pennsylvania Division Board of Directors and director of the National Foundation for Cancer Research Center for Metastasis Research. In 2002, Dr. Welch’s laboratory moved to the University of Alabama at Birmingham where he became the Leonard H Robinson Professor of Pathology.

Dr. Welch’s laboratory has discovered 8 of the 30 known metastasis suppressor genes. His laboratory has also recently discovered how some of those metastasis suppressors function and is designing therapies to take advantage of their mechanisms of action. Most recently, Dr. Welch and colleagues have uncovered evidence that the mitochondrial genome plays an unexpectedly large role in regulating breast cancer tumorigenicity and metastasis, as well as cardiovascular disease. Dr. Welch is the author of more than 194 peer-reviewed publications and more than 20 book chapters. He is also co-editor of the textbook Cancer Metastasis. In 2011, he was named the Hall Family Foundation Endowed Chair in Molecular Medicine and a Kansas Bioscience Authority Eminent Scholar. He is currently a Komen Scholar and President of the Cancer Biology Training Consortium.

Alana Welm, PhD

Huntsman Cancer Institute, University of Utah

Dr. Welm is an Associate Professor of Oncological Sciences at the University of Utah’s Huntsman Cancer Institute. She received her PhD in Cell and Molecular Biology at Baylor College of Medicine, and completed her postdoctoral training at the University of California, San Francisco, where her work focused on developing new models of breast cancer metastasis. Dr. Welm started her laboratory at the Huntsman Cancer Center in 2007, and was promoted to Associate Professor with tenure in 2013.

Dr. Welm’s research focuses on breast cancer metastasis using in vivo modeling of mouse and human breast cancers. Dr. Welm’s group discovered that the Ron kinase pathway is an important facilitator of breast cancer metastasis through its unique dual function in tumor cells and in resident macrophages. The laboratory’s current areas of research include (1) preclinical studies of various Ron inhibitors for treatment and prevention of metastatic breast cancer; (2) preclinical and early clinical studies of the Ron/Met inhibitor BMS777607/ASLAN002 in bone metastatic cancers; (3) discovering molecular mechanisms by which Ron kinases promote metastasis through cell-autonomous and non-cell-autonomous pathways; and (4) refining “precision medicine” for metastatic breast cancer using functional assays in patient-derived breast tumor grafts.
Bruce Zetter, MD
Boston Children’s Hospital and Harvard Medical School

Dr. Zetter is the Charles Nowiszewski Professor in the Departments of Cell Biology and Surgery at Harvard Medical School. He received his PhD from the University of Rhode Island, followed by fellowships at the Massachusetts Institute of Technology and the Salk Institute. After his fellowships, he became an Assistant Research Biochemist at the University of California in San Francisco. Dr. Zetter joined the faculty of Harvard Medical School in 1978. From 1993 to 2001, he directed the Physiology course for all first year medical students. From 2001 to 2004, he served as Vice President of Research and from 2004 to 2008 as Chief Scientific Officer at Boston Children’s Hospital.

Dr. Zetter is a leader in the research of tumor progression, cancer diagnosis, cancer metastasis, and tumor angiogenesis. His current research interests are tumor metastasis, novel cancer treatments, and tests that predict future outcomes for cancer patients. He is on the editorial board of eight peer-reviewed journals and serves on several grant review boards for public agencies such as the American Heart Association, NASA, and the American Cancer Society. He chaired the NIH review board on Tumor Progression and Metastasis, and chaired review panels on breast and prostate cancer for the NIH and the U.S. DoD.

Dr. Zetter has given over 300 lectures at universities, conferences, and businesses and has chaired many conferences on the topic of tumor metastasis. He has also served as an expert witness for the United States Senate Cancer Coalition hearings in Washington, District of Columbia. He has received numerous national and international awards, including a Faculty Research Award from the American Cancer Society, the prestigious MERIT award from the NCI, and a Creativity Award from the Prostate Cancer Foundation. He has also received three teaching awards from the students at Harvard Medical School.
Appendix D. References


Appendix E. Acronyms

AACR American Association of Cancer Research
ASCO American Society of Clinical Oncology
ASCO-AACI American Society of Clinical Oncology-American Association of Cancer Institute
BCRP Breast Cancer Research Program
CDMRP Congressionally Directed Medical Research Programs
CoC Commission on Cancer
CPDR Center for Prostate Disease Research
CT Computerized tomography
CTLA-4 Cytotoxic T-lymphocyte-associated protein
DoD Department of Defense
DTC Disseminated tumor cell
ECM Extracellular matrix
EMR Electronic medical record
FDA U.S. Food and Drug Administration
HER2 Human epidermal growth factor receptor 2
IACUC Institutional Animal Care and Use Committee
IRB Institutional Review Board
MCC John P. Murtha Cancer Center
MGH Massachusetts General Hospital
MGHCC Massachusetts General Hospital Cancer Center
MRI Magnetic resonance imaging
MSKCC Memorial Sloan Kettering Cancer Center
mTOR Mechanistic target of rapamycin
NCI National Cancer Institute
NCTN National Clinical Trials Network
NIH National Institutes of Health
NMCP Naval Medical Center Portsmouth
NMCSD Naval Medical Center San Diego
NVAMC Northport Veterans Affairs Medical Center
PCCTC Prostate Cancer Clinical Trials Consortium
PD-1 Programmed cell death protein 1
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<thead>
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<th>Acronym</th>
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<tr>
<td>PECaD</td>
<td>Program for the Elimination of Cancer Disparities PET Positron emission tomography</td>
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<tr>
<td>SBIR</td>
<td>Small Business Innovation Research</td>
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<tr>
<td>SCP</td>
<td>Survivorship Care Plan</td>
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<tr>
<td>SWOG</td>
<td>Southwest Oncology Group</td>
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<tr>
<td>TAPUR</td>
<td>Targeted Agent and Profiling Utilization Registry</td>
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<tr>
<td>TGFβ</td>
<td>Transforming Growth Factor-beta</td>
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<tr>
<td>U.S.</td>
<td>United States</td>
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<tr>
<td>USAF</td>
<td>United States Air Force</td>
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<tr>
<td>USUHS</td>
<td>Uniformed Services University of the Health Sciences VA United States Department of Veterans Affairs</td>
</tr>
<tr>
<td>VEGF</td>
<td>Vascular endothelial growth factor</td>
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<td>WRNMMC</td>
<td>Walter Reed National Military Medical Center</td>
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Appendix F. Glossary

**Adjuvant Therapy:** Additional cancer treatment given after primary treatment to lower the risk that the cancer will come back. May include chemotherapy, radiation therapy, hormone therapy, targeted therapy, or biological therapy. (National Cancer Institute)

**Antigenicity:** The capacity to act as an antigen. (Merriam-Webster)

**Anti-VEGF:** A substance that binds to receptors for a protein called vascular endothelial growth factor (VEGF), which may be found on some types of cancer cells. This may prevent the growth of new blood vessels that tumors need to grow. There are different types of anti-VEGF receptor monoclonal antibodies being studied in the treatment of cancer. These substances are a type of antiangiogenesis agent and a type of monoclonal antibody. (National Cancer Institute)

**Benign:** Not cancerous; benign tumors may grow larger, but do not spread to other parts of the body. (National Cancer Institute)

**Bioinformatics:** The science of using computers, databases, and math to organize and analyze large amounts of biological, medical, and health information. (National Cancer Institute)

**Biomarker:** A biological molecule found in blood, other body fluids, or tissues that is a sign of a normal or abnormal process, or of a condition or disease. A biomarker may be used to see how well the body responds to a treatment for a disease or condition. It can also be used as a diagnostic tool. (National Cancer Institute)

**Biopsy:** The removal of cells or tissue for examination by a pathologist. (National Cancer Institute)

**Cancer:** A term for diseases in which abnormal cells divide without control and can invade nearby tissues. Cancer cells can also spread to other parts of the body through the blood and lymph systems. There are several main types of cancer. Carcinoma is a cancer that begins in the skin or in tissues that line or cover internal organs. Sarcoma is a cancer that begins in bone, cartilage, fat, muscle, blood vessels, or other connective or supportive tissue. Leukemia is a cancer that starts in blood-forming tissue, such as the bone marrow, and causes large numbers of abnormal blood cells to be produced and enter the blood. Lymphoma and multiple myeloma are cancers that begin in the cells of the immune system. Central nervous system cancers are cancers that begin in the tissues of the brain and spinal cord. Also called malignancy. (National Cancer Institute)

**Cancer Vaccines:** A substance or group of substances meant to cause the immune system to respond to a tumor or to microorganisms, such as bacteria or viruses. A vaccine can help the body recognize and destroy cancer cells or microorganisms. (National Cancer Institute)

**Checkpoint Inhibitors:** A type of immunotherapy that disrupts signals that allow cancer cells to block an immune attack. (American Cancer Society)

**Chemotherapy:** Treatment that uses drugs to stop the growth of cancer cells, either by killing cells or by stopping them from dividing. (National Cancer Institute)

**Circulating Tumor Cell:** Tumor cells that have been shed into the vasculature and may be on their way to potential metastatic sites. (Plaks, V., Koopman, C. D., & Werb, Z., 2013)
Clinical Research: Research in which people, or data or samples of tissue from people, are studied to understand health and disease. Clinical research helps find new and better ways to detect, diagnose, treat, and prevent disease. Types of clinical research include clinical trials, which test new treatments for a disease, and natural history studies, which collect health information to understand how a disease develops and progresses over time. (National Cancer Institute)

Clinical Trial: A type of research study that tests how well new medical approaches work in people. These studies test new methods of screening, prevention, diagnosis, or treatment of a disease. Also called clinical study. (National Cancer Institute)

Common Rule: Also known as the Federal Policy for the Protection of Human Subjects, this policy was published in 1991 as subpart A of the U.S. Department of Health & Human Services regulation 45 CFR part 46. The Common Rule outlines the basic provisions for institutional review boards, informed consent, and assurances of compliance. Human subject research conducted or supported by each federal department/agency is governed by the regulations of that department/agency. (Department of Health & Human Services)

Comorbidity: The condition of having two or more diseases at the same time. (National Cancer Institute)

Cytokines: A type of protein that is made by certain immune and non-immune cells and has an effect on the immune system. Some cytokines stimulate the immune system and others slow it down. They can also be made in the laboratory and used to help the body fight cancer, infections, and other diseases. (National Cancer Institute)

Cytokinome: The whole universe of human cytokines; the totality of the proteins and their interactions in and around biologic cells. (Costantini, S., Castello, G., and Colonna, G., 2010)

Cytotoxic Agent: A substance that kills cells, including cancer cells. These agents may stop cancer cells from dividing and growing and may cause tumors to shrink in size. (National Cancer Institute)

Deoxyribonucleic Acid (DNA): The molecules inside cells that carry genetic information and pass it from one generation to the next. (National Cancer Institute)

DNA Sequencing: A laboratory process used to learn the exact sequence (order) of the four building blocks, or bases, that make up DNA. Information is stored in DNA in a code made by arranging the four bases (identified by the letters A, C, G, and T) in different orders. DNA sequencing can be used to find DNA mutations (changes) that may cause diseases, such as cancer. (National Cancer Institute)

Dormancy: Stage in cancer progression in which the cells cease dividing but survive in a quiescent state while waiting for appropriate environmental conditions to begin proliferation again. (Aguirre-Ghiso, 2007)

Dormant Tumor Cell: A tumor cell marked by a suspension of activity, temporarily devoid of external activity, or temporarily in abeyance yet capable of being activated. (Merriam-Webster)

Endpoint: In clinical trials, an event or outcome that can be measured objectively to determine whether the intervention being studied is beneficial. The endpoints of a clinical trial are usually
included in the study objectives. Some examples of endpoints are survival, improvements in quality of
life, relief of symptoms, and disappearance of the tumor (National Cancer Institute).

**Epidemiology:** The study of the patterns, causes, and control of disease in groups of people.
(National Cancer Institute).

**Epigenetics:** The study of how age and exposure to environmental factors, such as diet, exercise,
drugs, and chemicals, may cause changes in the way genes are switched on and off without changing
the actual DNA sequence. These changes can affect a person’s risk of disease and may be passed from
parents to their children. (National Cancer Institute)

**Ewing Sarcoma:** A type of cancer that forms in the bone or soft tissue. (National Cancer Institute)

**Exosome:** A tiny vesicle created and released from the plasma membrane of various types of cells,
especially immune cells, and capable of inducing antigen-specific immune responses; a cellular protein
complex containing enzymes that degrade nuclear and cytoplasmic RNA. (Medical Dictionary)

**Genomic Sequencing:** A laboratory method that is used to determine the entire genetic makeup of a
specific organism or cell type. This method can be used to find changes in areas of the genome that
may be important in the development of specific diseases, such as cancer. (National Cancer Institute)

**Genomics:** The study of the complete set of DNA (including all of its genes) in a person or other
organism. Almost every cell in a person’s body contains a complete copy of the genome. The genome
contains all the information needed for a person to develop and grow. Studying the genome may help
researchers understand how genes interact with each other and with the environment and how certain
diseases, such as cancer, diabetes, and heart disease, form. This may lead to new ways to diagnose,
treat, and prevent disease. (National Cancer Institute)

**Heterogeneous:** Made up of elements or ingredients that are not alike. (National Cancer Institute)

**Hormonal Therapy:** Treatment that adds, blocks, or removes hormones. For certain conditions
(such as diabetes or menopause), hormones are given to adjust low hormone levels. To slow or stop
the growth of certain cancers (such as prostate and breast cancer), synthetic hormones or other drugs
may be given to block the body’s natural hormones. Sometimes surgery is needed to remove the
gland that makes a certain hormone. Also called endocrine therapy, hormone therapy, and hormone
treatment. (National Cancer Institute)

**Hypoxia:** Diminished availability of oxygen to body tissues. (Medical Dictionary)

**Imaging:** In medicine, a process that makes pictures of areas inside the body. Imaging uses methods
such as x-rays (high-energy radiation), ultrasound (high-energy sound waves), and radio waves (e.g.,
PET, MRI). (National Cancer Institute)

**Immune Checkpoint Inhibitor:** A type of drug that blocks certain proteins made by some types of
immune system cells, such as T cells, and some cancer cells. These proteins help keep immune
responses in check and can keep T cells from killing cancer cells. When these proteins are blocked,
the “brakes” on the immune system are released and T cells are able to kill cancer cells better.
Examples of checkpoint proteins found on T cells or cancer cells include PD-1/PD-L1 and CTLA-4/B7-1/B7-2. Some immune checkpoint inhibitors are used to treat cancer. (National Cancer Institute)

**Immunotherapy:** A type of biological therapy that uses substances to stimulate or suppress the immune
system to help the body fight cancer, infection, and other diseases. Some types of immunotherapy only
target certain cells of the immune system. Others affect the immune system in a general way. Types of
immunotherapy include cytokines, vaccines, bacillus Calmette-Guerin (BCG), and some monoclonal antibodies. (National Cancer Institute)

**Laparoscopy:** Surgery done with the aid of a laparoscope. A laparoscope is a thin, tube-like instrument with a light and a lens for viewing. It may also have a tool to remove tissue to be checked under a microscope for signs of disease. Also called laparoscopic-assisted resection. (National Cancer Institute)

**Ligand:** A group, ion, or molecule coordinated to a central atom or molecule in a complex. (Merriam-Webster)

**Liquid Biopsy:** A test done on a sample of blood to look for cancer cells from a tumor that are circulating in the blood or for pieces of DNA from tumor cells that are in the blood. A liquid biopsy may be used to help find cancer at an early stage. It may also be used to help plan treatment or to find out how well treatment is working or if cancer has come back. Being able to take multiple samples of blood over time may also help doctors understand what kind of molecular changes are taking place in a tumor. (National Cancer Institute)

**Malignancy:** A term for diseases in which abnormal cells divide without control and can invade nearby tissues. Malignant cells can also spread to other parts of the body through the blood and lymph systems. There are several main types of malignancy. Carcinoma is a malignancy that begins in the skin or in tissues that line or cover internal organs. Sarcoma is a malignancy that begins in bone, cartilage, fat, muscle, blood vessels, or other connective or supportive tissue. Leukemia is a malignancy that starts in blood-forming tissue, such as the bone marrow, and causes large numbers of abnormal blood cells to be produced and enter the blood. Lymphoma and multiple myeloma are malignancies that begin in the cells of the immune system. Central nervous system cancers are malignancies that begin in the tissues of the brain and spinal cord. Also called cancer. (National Cancer Institute)

**Melanoma:** A form of cancer that begins in melanocytes (cells that make the pigment melanin). It may begin in a mole (skin melanoma), but can also begin in other pigmented tissues, such as in the eye or in the intestines. (National Cancer Institute)

**Meta-analysis:** A process that analyzes data from different studies done about the same subject. The results of a meta-analysis are usually stronger than the results of any study by itself. (National Cancer Institute)

**Metastasis:** The growth of cancer cells from the place where they first formed to another part of the body. In metastasis, cancer cells break away from the original (primary) tumor, travel through the blood or lymph system, and form a new tumor in other organs or tissues of the body. The new, metastatic tumor is the same type of cancer as the primary tumor. For example, if breast cancer spreads to the lung, the cancer cells in the lung are breast cancer cells, not lung cancer cells. The plural form of metastasis is metastases. (National Cancer Institute)

**Metastatic Cancer:** Having to do with metastasis, which is the spread of cancer from the primary site (place where it started) to other places in the body. Often referred to as recurrent cancer, advanced cancer, or stage IV cancer that spreads from origination to another body part. Not all advanced cancers and recurrent cancers are metastatic; in the case of recurrent cancers, the cancer can return to the original tumor site, but in this report, we use advanced cancer, recurrent cancer, and metastatic cancer interchangeably. (National Cancer Institute)

**Microbiome:** The collection of all the microorganisms and viruses that live in a given environment,
including the human body or part of the body, such as the digestive system. The human microbiome may play a role in a person’s health. Studying the human microbiome may help prevent and treat disease in the future. (National Cancer Institute)

**Microenvironment:** The environment at the microscopic or cellular level. (Medical Dictionary)

**Micrometastasis:** Small numbers of cancer cells that have spread from the primary tumor to other parts of the body and are too few to be picked up in a screening or diagnostic test. (National Cancer Institute)

**Morbidity:** Refers to having a disease or a symptom of disease, or to the amount of disease within a population. Morbidity also refers to medical problems caused by a treatment. (National Cancer Institute)

**Mortality:** Refers to the state of being mortal (destined to die). In medicine, a term also used for death rate, or the number of deaths in a certain group of people in a certain period of time. Mortality may be reported for people who have a certain disease, live in one area of the country, or who are of a certain gender, age, or ethnic group. (National Cancer Institute)

**Mouse Model:** The use of special strains of mice to study a human disease or condition, and how to prevent and treat it. (National Cancer Institute)

**Mutation:** Any change in the DNA sequence of a cell. Mutations may be caused by mistakes during cell division, or they may be caused by exposure to DNA-damaging agents in the environment. Mutations can be harmful, beneficial, or have no effect. If they occur in cells that make eggs or sperm, they can be inherited; if mutations occur in other types of cells, they are not inherited. Certain mutations may lead to cancer or other diseases. (National Cancer Institute)

**Nanotherapeutics:** The application of nanotechnology in areas of drug delivery and therapy. (Hafner, Lovrić, Lakoš, & Pepić, 2014)

**Neoadjuvant Therapy:** Treatment given as a first step to shrink a tumor before the main treatment, which is usually surgery. Examples of neoadjuvant therapy include chemotherapy, radiation therapy, and hormone therapy. It is a type of induction therapy. (National Cancer Institute)

**Neoantigen:** A newly expressed antigen on tumor cells or cells infected with oncoviruses. The antigen is produced in the tumor cells, and found usually on the cell surface where it acts as a signal that the cell has to be destroyed before the cell proliferates or metastasizes. (Biology Online)

**Neoplasm:** An abnormal mass of tissue that results when cells divide more than they should or do not die when they should. Tumors may be benign (not cancer), or malignant (cancer). Also called tumor. (National Cancer Institute)

**Neuroblastoma:** A type of cancer that forms from immature nerve cells. It usually begins in the adrenal glands but may also begin in the abdomen, chest, or in nerve tissue near the spine.
Neuroblastoma most often occurs in children younger than 5 years of age. It is thought to begin before birth. It is usually found when the tumor begins to grow and cause signs or symptoms. (National Cancer Institute)

**Oligometastasis:** A type of metastasis in which cancer cells from the original (primary) tumor travel through the body and form a small number of new tumors (metastatic tumors) in one or two other parts of the body. For example, cancer cells may spread from the breast to form one or two new tumors in the brain or spread from the colon to form new tumors in the liver. These types of tumors may be treatable. (National Cancer Institute)

**-omics:** A suffix of nouns that denote a body of facts, knowledge, principles, etc., usually corresponding to adjectives ending in -ic, or -ical: ethics. e.g., genomics, proteomics. (Dictionary.com)

**Palliative Care:** Care given to improve the quality of life of patients who have a serious or life-threatening disease. The goal of palliative care is to prevent or treat as early as possible the symptoms of a disease, side effects caused by treatment of a disease, and psychological, social, and spiritual problems related to a disease or its treatment. Also called comfort care, supportive care, and symptom management. (National Cancer Institute)

**Performance Status:** A measure of how well a patient is able to perform ordinary tasks and carry out daily activities. (National Cancer Institute)

**Polymorphism:** A common change in the genetic code in DNA. Polymorphisms can have a harmful effect, a good effect, or no effect. Some polymorphisms have been shown to increase the risk of certain types of cancer. (National Cancer Institute)

**Primary Cancer:** A term used to describe the original, or first, tumor in the body. Cancer cells from a primary cancer may spread to other parts of the body and form new, or secondary, tumors. This is called metastasis. These secondary tumors are the same type of cancer as the primary cancer. Also called primary tumor. (National Cancer Institute)

**Proteomics:** The study of the structure and function of proteins, including the way they work and interact with each other inside cells. (National Cancer Institute)

**Radionuclide:** An unstable form of a chemical element that releases radiation as it breaks down and becomes more stable. Radionuclides may occur in nature or be made in a laboratory. In medicine, they are used in imaging tests and in treatment. Also called radioisotope. (National Cancer Institute)

**RECIST:** A standard way to measure how well a cancer patient responds to treatment. It is based on whether tumors shrink, stay the same, or get bigger. To use RECIST, there must be at least one tumor that can be measured on x-rays, CT scans, or MRI scans. The types of response a patient can have are a complete response (CR), a partial response (PR), progressive disease (PD), and stable disease (SD). Also called Response Evaluation Criteria In Solid Tumors. (National Cancer Institute)

**Ribonucleic Acid (RNA):** One of two types of nucleic acid made by cells. RNA contains information that has been copied from DNA (the other type of nucleic acid). Cells make several different forms of RNA, and each form has a specific job in the cell. Many forms of RNA have functions related to making proteins. RNA is also the genetic material of some viruses instead of DNA. RNA can be made in the laboratory and used in research studies. (National Cancer Institute)
Sarcoma: A type of cancer that begins in bone or in the soft tissues of the body, including cartilage, fat, muscle, blood vessels, fibrous tissue, or other connective or supportive tissue. Different types of sarcoma are based on where the cancer forms. For example, osteosarcoma forms in bone, liposarcoma forms in fat, and rhabdomyosarcoma forms in muscle. Treatment and prognosis depend on the type and grade of the cancer (how abnormal the cancer cells look under a microscope and how quickly the cancer is likely to grow and spread). Sarcoma occurs in both adults and children. (National Cancer Institute)

Social Network: A network of individuals (such as friends, acquaintances, and coworkers) connected by interpersonal relationships. (Merriam-Webster)

Stem Cell: A cell from which other types of cells develop. For example, blood cells develop from blood-forming stem cells. (National Cancer Institute)

Stroma: The supportive tissue of an epithelial organ, tumor, gonad, etc. consisting of connective tissue and blood vessels. (Dictionary.com)

Survivorship: In cancer, survivorship focuses on the health and life of a person with cancer post-treatment until the end of life. It covers the physical, psychosocial, and economic issues of cancer beyond the diagnosis and treatment phases. (National Cancer Institute)

Survivorship Care Plans: In 2006, the Institute of Medicine (now the National Academy of Medicine) issued a report recommending that every cancer patient receive an individualized survivorship care plan that includes guidelines for monitoring and maintaining their health. In response to that report, many groups have now developed various types of “care plans” to help improve the quality of care of survivors as they move beyond their cancer treatment. (American Cancer Society)

Syngeneic: Having to do with individuals or tissues that have identical genes. For example, identical twins and cells and tissues from them are syngeneic. (National Cancer Institute)

T Cell: A type of white blood cell. T cells are part of the immune system and develop from stem cells in the bone marrow. They help protect the body from infection and may help fight cancer. Also called T lymphocyte. (National Cancer Institute)

Targeted Therapy: A type of treatment that uses drugs or other substances to identify and attack specific types of cancer cells with less harm to normal cells. Some targeted therapies block the action of certain enzymes, proteins, or other molecules involved in the growth and spread of cancer cells. Other types of targeted therapies help the immune system kill cancer cells or deliver toxic substances directly to cancer cells and kill them. Targeted therapy may have fewer side effects than other types of cancer treatment. Most targeted therapies are either small molecule drugs or monoclonal antibodies. (National Cancer Institute)

Translational Research: A term used to describe the process by which the results of research done in the laboratory are used to develop new ways to diagnose and treat disease. (National Cancer Institute)

Tumor: An abnormal mass of tissue that results when cells divide more than they should or do not die when they should. Tumors may be benign (not cancer), or malignant (cancer). Also called neoplasm. (National Cancer Institute)
**Tumor Microenvironment:** The normal cells, molecules, and blood vessels that surround and feed a tumor cell. A tumor can change its microenvironment, and the microenvironment can affect how a tumor grows and spreads. (National Cancer Institute)

**Xenograft:** The transplant of an organ, tissue, or cells to an individual of another species. (National Cancer Institute)
## Appendix G. List of Operational Meeting Attendees

<table>
<thead>
<tr>
<th>Name</th>
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<tr>
<td>Jay Bitkower</td>
<td>Action to Cure Kidney Cancer</td>
<td>Advocacy Group Attendee</td>
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<td>Stephanie Chisolm</td>
<td>Bladder Cancer Advocacy Network</td>
<td>Advocacy Group Attendee</td>
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<td>Dian Corneliussen-Liitke</td>
<td>METAvivor</td>
<td>Advocacy Group Attendee</td>
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<td>Meghan Fitzgibbons</td>
<td>Ulman Cancer Fund for Young Adults</td>
<td>Advocacy Group Attendee</td>
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<td>Mary Hesdorffer</td>
<td>Mesothelioma Applied Research Foundation</td>
<td>Advocacy Group Attendee</td>
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<td>Maimah Karmo</td>
<td>Tigerlily Foundation</td>
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<td>Chad Ramsey</td>
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<td>Prostate Health Education Network</td>
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<td>Department of Defense</td>
<td>Metastatic Cancer Research Task Force</td>
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<td>Thomas Darling</td>
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Appendix H. Proceedings Report

U.S. Department of Defense – Military Health System (MHS)

Metastatic Cancer Research Operational Meeting Proceedings Report

17 January 2017

Bethesda, MD
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Executive Summary

Cancer is a significant source of morbidity and mortality worldwide. While research advancements have led to improved patient outcomes, patients with metastatic cancer often succumb to their disease. Therefore, additional research is needed to better understand the biology of tumor metastasis and to develop interventions that prevent or treat metastasis.

To address gaps in metastatic cancer research, the Department of Defense (DoD) supported the establishment of a Task Force of cancer experts to comprehensively review the state-of-the-science of metastatic cancer, current gaps and barriers inhibiting progress in this field, and the initiatives needed to extend the lives of patients with advanced or recurrent cancer. This Federal Task Force was to oversee and lead the execution of the Metastatic Cancer Task Force Testimony and Operational Meeting held on 12–13 December 2016 in McLean, Virginia. The Operational Meeting brought together world renowned experts in the field of metastatic cancer to present testimony that will ultimately inform a Report to the Congressional Defense Committee highlighting the current state of metastatic cancer research and the Task Force recommendations aimed at promoting the acceleration of progress in this field to extend the lives of patients with metastatic cancer. Here, the proceedings of this meeting is summarized in detail, providing a framework for the Report to the Congressional Defense Committee to be completed and submitted in July of 2017.
Introduction

Cancer remains the second leading cause of death in the United States (U.S.) and a leading cause of death worldwide despite preventative and research initiatives that have improved patient outcomes in recent decades (Kochanek, Murphy, Xu, & Tejada-Vera, 2016; Stewart BW & Wild CP, 2016). In the U.S. alone, it is estimated that there will be approximately 1,688,780 new cases diagnosed and 600,920 deaths from cancer in 2017 (Siegel, Miller, & Jemal, 2016). Cancer-related death rates have decreased by 23 percent over the last 25 years, which has been attributed to a decrease in the overall incidence of cancer and improvements in both the early detection and treatment of certain cancers, including breast and colon cancer (Siegel et al., 2016). However, additional advancements are needed with regards to the prevention and treatment of metastatic disease, which is associated with significant cancer-related mortality.

In recent decades, cancers such as metastatic testicular cancer and Hodgkin’s lymphoma have had high cure rates as a result of effective combination chemotherapy treatments (Funt, Feldman, & Bosl, 2016; Vassilakopoulos & Johnson, 2016). Furthermore, the introduction of targeted cancer therapies such as those used in the treatment of human epidermal growth factor receptor 2 positive (HER2+) breast cancer or V-Raf murine sarcoma viral oncogene homolog B (BRAF) inhibitors for the treatment of some melanomas, have significantly extended the lives of patients with certain metastatic cancers (Lee, Thomas, & Ng, 2017; Swain et al., 2015). Recently, the introduction of immune checkpoint inhibitors, which prime the immune system to attack tumor cells based on molecular targets such as the receptors for cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) and programmed cell death protein 1 (PD-1), have also extended the period of progression-free survival and improved overall survival in some patients with metastatic cancers, including metastatic melanoma, non-small cell lung cancer, and renal cell carcinoma (Borghaei et al., 2015; Choueiri et al., 2016; Hodi et al., 2016). While these advancements highlight progress in the field of metastatic cancer, patients with late stage disease often succumb to their disease, necessitating improvements in metastasis prevention and treatment to reduce overall cancer-related morbidity and mortality.

Increased focus on research and development initiatives are needed to better understand both the biology of metastasis and to develop novel therapies that target these mechanisms to prevent and treat metastatic cancer. In pursuit of such advancements, Congress has emphasized the need for the establishment of a task force focused on research to extend the lives of patients with metastatic cancer (House of Representatives, 2016):

“The Committee continues to support the establishment of a task force on research for metastasized cancer with a focus on clinical and translational research aimed at extending the lives of advanced state and recurrent patients. The Committee directs the Assistant Secretary of Defense (Health Affairs) to submit a report to the congressional defense committees not later than 60 days after the enactment of the Act on the status of establishing such a task force.”
In response to the House Armed Services Committee Report 114–139 regarding the 2016 National Defense Appropriations Bill, a Federal Task Force of 16 cancer experts was established that led the planning and execution of the Metastatic Cancer Task Force Testimony and Operational Meeting on December 12–13, 2016 in McLean, Virginia. This meeting brought together the Task Force, metastatic cancer experts from around the world, and representatives from patient advocacy organizations to hear testimony presented by a select group of 27 world renowned metastatic cancer experts regarding the measures needed to “accelerate clinical and translational research on metastatic cancer aimed at extending the lives of advanced state and recurrent patients.” As a result, expert testimony was centered on the following questions:

1. Summarize up to five of the most important/seminal findings in your specific area of research over the past 5–10 years as it pertains to extending the lives of patients with metastatic cancer.

2. Describe up to three major gaps in the field of metastatic cancer research that if addressed could potentially accelerate progress towards extending the lives of affected patients. What collaborations will be required to meet these gaps?

3. Describe up to four major barriers (i.e., scientific barriers, programmatic barriers, other barriers) in your field that are inhibiting progress (other than funding) towards extending the lives of metastatic cancer patients. Suggest ways to overcome these barriers.

4. Describe the top three initiatives that need to occur in this field in order to accelerate clinical and translational research to extend lives of advanced stage and recurrent patients with metastatic disease (e.g., emerging trends or developments that can be exploited, etc.).

These expert speakers discussed a myriad of research topics within the metastatic cancer field, spanning topics that included tumor cell dormancy, innovative cancer treatments, novel imaging modalities, the role of the tumor microenvironment and the host immune response in metastasis, as well as the gaps, barriers to progress, and initiatives needed to advance the field of metastatic cancer research and extend the lives of patients. Here, a detailed summary of each speaker presentation and transcripts of both the question and answer sessions and panel discussions are presented. This report will ultimately inform a congressional report discussing the current state-of-the-science of clinical and translational research in metastatic cancer, gaps, and recommendations with regards to extending the lives of patients with advanced or recurrent cancer.
Speaker Presentations

Speakers from government and academia summarized major findings in the field of metastatic cancer research aimed at extending the lives of patients with metastatic cancer. These presentations sought to establish a shared understanding of the current state of scientific knowledge of cancer metastasis, describe major gaps in the field, highlight scientific and/or programmatic barriers that are inhibiting progress, and suggest ways to overcome these barriers. The final outcome was to provide recommendations on the initiatives that are needed to accelerate clinical and translational research that will extend lives of advanced stage and recurrent patients with metastatic disease.

Technology to Accelerate Clinical Research

Clifford Hudis, MD, FACP, FASCO
American Society of Clinical Oncology

Dr. Hudis discussed the state of clinical research on recurrent and metastatic cancer and ways to accelerate this research. He also described the work of the American Society of Clinical Oncology-Association of American Cancer Institutes (ASCO-AACI) Clinical Research Project, the Targeted Agent and Profiling Utilization Registry (TAPUR), and the CancerLinQ system. In his presentation, he highlighted the most important findings that can extend the lives of patients, major gaps in metastasis research, major barriers that inhibit progress, and recommended initiatives to accelerate clinical and translational research.

The most important research findings that extend the lives of patients with metastatic cancer:

1. There have been rapid increases in the amount of available routine care data as a result of the accessibility of electronic medical records (EMRs).

2. The ASCO-AACI Best Practices in Cancer Clinical Trials Initiative was established to promote practical solutions aimed to help meet existing regulatory and administrative requirements on research (Figure 1). A working group convened and conducted a survey of research sites to identify the most burdensome administrative and regulatory aspects of conducting clinical trials. They then held a workshop to identify tangible solutions to address these burdens. The findings from this workshop have been disseminated recently and ASCO-AACI is now working to actively implement the recommendations of the working group (Vose et al., 2016).
Major gaps in the field of metastatic cancer research:

1. There are no standard treatment options for patients with advanced metastatic disease. These patients may undergo genomic profile testing and subsequently may be presented with an actionable variant (e.g., a drug or a clinical trial for a drug). To better implement precision medicine capabilities, oncologists need to learn from the real world practice of prescribing targeted therapies to patients with advanced cancer whose tumor harbors a genomic variant known to be a drug target.

2. Of the 1.7 million patients diagnosed with cancer every year in the U.S., only about 3 percent of adults with a solid tumor enroll in a clinical trial. Patients enrolled in clinical trials tend to be younger, healthier, and less diverse than the 97 percent of patients who are not enrolled. Thus, much of the potential information that could be gained from this greater patient population is unavailable for use by the scientific and medical communities.

• Collaborations required to meet these gaps: The TAPUR is a prospective study designed to investigate the anti-tumor activity and toxicity of commercially available, targeted anticancer drugs prescribed for treatment of patients with advanced solid tumors, B cell non- Hodgkin’s lymphoma, or multiple myeloma with a genomic variant known to be a drug target or to predict sensitivity to a drug. This study aims to investigate participants that are better representative of the cancer patient population (Figure 2).
Seven participating drug companies have contributed 17 approved therapeutic agents; however, these drugs are used off label in the study.

TAPUR and NCI-Molecular Analysis for Therapy Choice (NCI-MATCH) are complements of each other. One distinction between TAPUR and NCI-MATCH is the timing of the testing. TAPUR only accepts patients who received commercial testing and were well enough and had resources to do so. Another distinction is that NCI-MATCH uses investigational agents whereas TAPUR studies drugs that are already commercially available. In addition, NCI-MATCH is matching patients at a 5 percent level whereas TAPUR is matching at 62 percent level.

CancerLinQ is an electronic system that pools data from different EMR systems to improve quality of care and conduct observational research. CancerLinQ currently involves 1.6 million records, 16 EMRs, 73 participating institutions, and more than 2,000 oncologists. Notably, CancerLinQ is onboarding one new health system per week and TAPUR is anticipated to be a rolled-up component of CancerLinQ.

Major barriers that inhibit progress towards extending the lives of metastatic cancer patients:

Scientific Barriers: (1) There is a need for more efficient treatment development, given the complexity and high cost of drug development. (2) Few patients are enrolled into prospective clinical research studies, especially adults with metastatic disease.

Programmatic Barriers: (1) The volume of severe adverse events reported is excessive. Only 14 percent of the required severe adverse event reports are legitimate and the rest are unnecessary by any industry or regulatory standard. (2) A parallel, duplicative contracting system results in the negotiation and renegotiation of agreements between Principal Investigators and each center in a multi-center trial. (3) The question of what is research non-billable versus what is the standard of care is often litigated at the local level in each study, each site, and on occasion each carrier.

Others: (1) Measures of quality, value, and outcomes are increasingly going to influence the way the physician workforce is paid. (2) There is an increasingly changing regulatory environment.

Suggested ways to overcome these barriers: (1) Identify and implement strategies to increase compliance with adverse events reporting requirements. (2) Develop a centralized portal for research sites to streamline routine requests from sponsors and contract research organizations. (3) Identify common language, clinical standards, and guidelines to determine routine-versus research-related services and costs.

Initiatives needed to accelerate clinical and translational research: (1) Streamlined and novel study designs are needed, including multi-stakeholder input regulators. The U.S. Food and Drug Administration (FDA) as well as payers all must participate in this discussion. (2) Interoperability of health information technology is needed, which is addressed in the 21st Century Cures Act and will reduce the cost of big data projects. (3) Additional support from data experts to process and analyze large amounts of data is also required.
**Additional comments:** It is necessary to consider survivorship when treating cancer patients as an increasing number of patients may live long-term with chronic metastatic cancer.

**Question and Answer Session Transcript:**

Right, perfect. So we're going to start that question and answer period from the task force members. Task force, as you answer-- as you ask your questions, please do click the button and pull that microphone towards you. We are capturing the event for audio in order to get a transcript started. So we'll start the five minute countdown for question and answers. Thank you.

This, by the way, is ASCO headquarters over in Alexandria. It's lonely over there, I'd love you to come visit me.

Thank you, Dr. Hudis. That was excellent. Craig Shriver. We hear this number about only 3 percent enroll in clinical trials of all cancer patients. What's the ideal number, especially when you consider that many patients are diagnosed early stage disease? We know what the standard of care is. We have level of one evidence that it's OK. Nobody is going to repeat the early NSABP trials. Probably a more important metric would be those patients who fail standard therapy. Do we know what percent of those are enrolled in clinical trials?

So actually I don't necessarily agree with the premise. The issue is, our view of clinical research as a black versus white distinction. That you're on a prospective study and therefore we can learn from you, that's the 3 percent, or you're not. That's the current world. I think there is a huge range of shades of gray in between there. And I think we need to take a page out of the broader economic activity of business and learn from all of our interactions. It's not the highest level, but it will answer questions. That was the precise plea that I'm making when I talk about CancerLinQ.

And that leads me to answer your question. What's the right number? I think we should be learning from every single patient. In the adjuvant setting, if somebody is getting conventional therapy for colon cancer or for breast cancer, we still have lots to learn from their experience. They have drug-drug interactions, they have toxicities that are unanticipated, they have nutritional and lifestyle factors that may play a role in their outcome. So I agree the underlying idea is that it's expensive to do research and we can't afford to spend money on every single question, obviously. But if it's cheap and easy to get it out of the record, we should. I would say more is better. And I'll end, it's again a little bit pat, but it's not lost on anybody that with conventional cytotoxic chemotherapy, our pediatrician colleagues made real advances, changed pediatric leukemia as one example. And it was a series of iterative modest steps that led to a big gain. So we can gain a lot even from older therapies if we study them with some rigor and we have the resources to do that now. Maybe I'm not answering your question because I'm not giving you a right answer. My answer is we should learn from everybody.
And it sounds like CancerLinQ could be the platform for that.

That's our goal, is that every experience is actually contributing. And I use again Amazon and Google as again somewhat glib examples of the fact that at least commercially, that's what goes on. Don't make a mistake about it. Each search you do at Amazon, each keystroke you enter at Google, is helping them get a little smarter. There are no wastes.

Sir, what are some distinctions between TAPUR and NCI-MATCH?

Yes, so I highlighted this without saying it. The clearest distinction is the timing of the testing. Because what--and we struggled with this. It is a huge burden, ambitious for them in the MATCH program, to get consent, send the specimen out for testing, have to deal with the field testing, have to wait for the results, and you know that a decent number of patients get lost even in that window. So I don't want to say that we're smarter in this, and we're not. We're cheating. We have a selection bias, a conditional probability problem. We're only taking patients who not only got testing done commercially, but were well enough and had resources to do that. And then were well enough four, six, eight weeks later, to present to a doctor's office and consent.

So we have lightened the burden at the ASCO side. We do not compete with them. In fact the two studies were rolled out at a joint press conference at ASCO in 2014, if I remember correctly, as complements. Because they really are. And for us it's just part of this theme of trying to learn from what's going on in the real world already.

Cliff, follow up to that. MATCH does use investigational agents, but--

Right. An important distinction too. Exactly right. We not only do we cheat on when we test, but we cheat by only taking drugs that are in the market already.

But I don't think it's a cheat. I think they're complementary. Exactly. However, MATCH--

Trying to be humble. MATCH is matching at a 5 percent level, you're matching at a 62 percent level. Right.

Actionable obviously is in the eyes of the beholder, and I think a lot of things we call actionable are just passengers. So how do you address the dramatic difference between the two, and the fact that there's actually a broader series of potential targets in MATCH because they have newer agents as well, compared to yours? I mean that's really a dramatic difference that's hard to explain. I can't explain it beyond the summary that you've given for it, except to say that our trial is set up to take advantage of what's going on in the world already. Maybe the flip side is, we will have zeroes. Our matches may not be as good, but they are what docs want to do right now off label. If that makes sense. Because they see the lesion reported from a standard test, they pick a drug that makes sense, and we are at least documenting that it does or doesn't have any
activity. I suspect we're going to have a lot of strikeouts.

So the difference is the lack of scientific proof of--

Of course.

So it's just, they're doing it because it's there, so--

Yeah. And I don't-- I'm not defensive about it. That's what everybody's arguing for at academic centers. They all have molecular tumor boards. They're all doing this. And unfortunately genomic alteration is, in some settings, only one aspect of the malignancy. Context matters. And where it does, we need to learn.
Metastatic Latency, Immune Evasion and Outbreak

Joan Massagué, PhD

Memorial Sloan Kettering Cancer Center

Dr. Massagué discussed the biology of metastatic stem-like cancer cells (MetSCs) and how they evade immunotherapy to develop metastases. In his presentation, he highlighted the most important findings that can extend the lives of cancer patients, major gaps in metastasis research, major barriers that inhibit progress in the field, and recommended initiatives to accelerate clinical and translational research.

The five most important research findings that extend the lives of patients with metastatic cancer:

1. At the time of diagnosis, many tumors have already seeded distant organs with pathogenic cells that may later emerge as metastases. However, pathogenicity and the existence of cells in distal sites on their own does not imply that metastasis will occur, as disseminated cancer cells must break through certain barriers to cause malignancy (Massagué & Obenauf, 2016).

2. The two primary causes of metastatic relapse and resistance to treatment are tumor heterogeneity and the capacity of cancerous cells to evolve in response to therapy. Additional rounds of therapy continue to enrich the heterogeneous population of immune-resistant cells to drive their evolution into a more aggressive and fully resistant population; however, immune cells in the stroma of cancer cells and the vessels that the tumor attacks are also heterogeneous.

3. MetSCs are unique cells with the ability to initiate tumor development, leading to metastatic relapse. Not all cells in a tumor have the same capability to resist immune responses and form metastases. The majority of cells that extravasate and infiltrate distant organs are eliminated by innate immune surveillance, but some MetSCs remain and have the ability to reinitiate a tumor (Figure 3). MetSCs may be rare in certain tumors and fairly abundant in other (i.e., more aggressive) tumors.
4. Although targeted drugs reduce tumors by stopping cell growth and immunotherapy eliminates what targeted therapies cannot, these treatments are currently insufficient; they do not completely eradicate the slow cycling and immune-evading MetSCs that can remain and subsequently trigger relapse.

5. MetSCs are chemoresistant in part because they can remain dormant in a slow cycling, immune-evasive state for months or even decades. Most MetSCs exist as single cells, or as small clusters, and are somehow evading detection and elimination by the immune system. The residual disease has molecular and genetic forms of drug resistance, including the secretion of factors that can elevate the resilience of the cell population and create fully resistant clones that have the ability to reconstitute the tumor.

**Major gaps in the field of metastatic cancer research:**

1. There is a lack of understanding of the specific characteristics of the MetSCs that remain after a primary or metastatic tumor is treated. Research on the biology of residual disease is lagging. Very little is known about the niches the cells inhabit within organs and the bottlenecks that separate the residual stage from overt progression.

2. It is unknown how cancer cells evade immune surveillance during both latent and active growth states. Cancer cells can be proactively immunosuppressive during active growth states by producing cytokines, chemokines, and other signals that make them tumor supportive; however, it is not known how these cells become immune evasive when they are not aggressively active tumors. There are very few models on latent metastasis. In 2016, Malladi et al. developed a model in which isolated cells are implanted into the bloodstream or orthotopically in a mouse, and organs are seeded with solitary latent MetSCs (Malladi et al., 2016). These cells have markers of metastasis (e.g., SOX2, SOX9) and become latent when receiving growth inhibitory signals from their environment and also by producing autoinhibitors of proliferation. However, when natural killer (NK) cells are depleted from these mice, metastases explosively develop in all organs. Thus, metastatic latency is implemented and retained by the immune system. Outbreaks must be based on the ability of cells to both proliferate and remain immune evasive as they are in the latent state. NK cells cannot detect these cells in the latent state; cell-surface markers on these cancer cells that are used by NK cells to detect them and kill them are down-regulated.

3. The mechanism behind MetSC dormancy and immune evasion has not yet been elucidated. In addition, the processes that cause them to be reactivated is not yet understood. An example of immunity preventing an outbreak can be seen in transplantation studies with kidney donors who had localized melanoma or glioblastoma multiforme. In this instance, immunosuppression in the organ recipient unleashed the metastatic capacity of disseminated pathogenic cells.

4. It is unknown whether treatments to debulk tumors reactivate dormant MetSCs.
5. It is has yet to be determined whether the immune microenvironment can be targeted to prevent or eliminate metastatic relapse.

- **Collaborations required to meet these gaps:** (1) Conduct high-resolution molecular and imaging analysis on tissue samples following treatment. Too little emphasis has been placed on investigating the biology of residual disease. (2) Collaborate with experts in immunology on metastatic cancer research. (3) Develop experimental models of clinical samples (e.g., patient-derived xenografts [PDXs] and patient-derived organoids [PDOs]) and combine them with computational/system biology analyses to determine the precise biology of these individual disseminated cells, not just collective tumors. (4) Target metastatic cells by utilizing additional research on immune evasion mechanisms. The inDrop™ single cell transcriptional profiling system provides single cell sequencing, a new technique that profiles individual cells in residual cancer cell populations, elucidating cell states and their phenotypic relatedness (A. M. Klein et al., 2015). Using the mouse model of latent metastasis, these cells can be tracked as they differentiate and evolve into metastatic cells.

**Major barriers that inhibit progress towards extending the lives of metastatic cancer patients:**

- **Scientific Barriers:** (1) There is a lack of research models on metastasis using patient-derived samples (e.g., PDXs, PDOs). (2) There is a lack of sufficient connection between experimental models and mathematical/computational analyses.

- **Programmatic Barriers:** (1) There is a paucity of interdisciplinary collaborations across relevant fields with new discoveries. (2) Funding agencies do not support the type of high-risk/high-reward projects that are necessary to make sufficient progress.

- **Suggested ways to overcome these barriers:** Funding agencies should consider the project concept and investigator’s track record with innovation and success, independent of years of experience. Funding agencies should also be open-minded and willing to place bets on high-risk research, and should have an idea of what emerging technologies are the most promising.

**Initiatives needed to accelerate clinical and translational research:** (1) Promote interdisciplinary research that combines experimental modeling and systems biology (e.g., patient tissue samples and mathematical treatment of high-resolution data imaging). (2) Invest in cost-effective methods to better track and predict the evolution of metastatic disease in patients undergoing treatment (e.g., through liquid biopsy). (3) Pursue innovative therapies that target the unique immune evasive properties of MetSCs.

**Additional comments:** Although some patients with aggressive cancers relapse while others do not, even those that do not may still have undetected MetSCs. The differences between these patients involves numerous processes that follow parallel but separate tracks. Time to metastasis is a function of innumerable individual steps that we are only beginning to enumerate and understand. Each one has its own biology and its own bottlenecks. Some organs are fairly permissive to hosting latent MetSCs, but not permissive to allowing them to break
through. In other organs, metastasis occurs immediately. The difference between these two bottlenecks and their response therapy requires additional research.

Question and Answer Session Transcript:

Well thank you, sir that was excellent. Your recommendation, insufficient willingness of funding agencies to support high risk, high reward projects. What does a perfect funding environment look like to do that type of research? In other words, who decides what resources go to these high risk, high reward projects? What's your recommendation for that?

It's a combination of-- it's a combination of looking at the project, the concept behind the project that is being proposed, the track record of the investigator-- is this somebody who has some track record of knowing to bet-- to place well his or her bets and research? Doesn't have to be somebody who has 20, 30 decades of research in their back. You can see that in any new independent investigator. These days new independent investigators have 10 years of research in their back, as students and as clinical or laboratory fellows. So track record, I would say is very important, because this is a lot based on instinct. Where, how to place your bets.

And then you have to be willing to run the risks with them. You can predict pretty well what the research needs and opportunities are going to be in the next year. But I can never predict what research was going to bring to me, 2 and 3 and 4 years from now. I've been fortunate to be funded by a blend of agencies, some of whom are more conservative, some of whom-- the Howard Hughes Medical Institute in particular-- are a good example of how to handle this, or how to place bets on research that is high risk, but is not a foolish risk. And you need experts, you need expert judges who, again, have an open mind and an instinct for what the problem is. What the new innovative ways of thinking about it must be. This is not what you can collect from looking at thousands of papers. That is the part-- that is the mass of data. So it's a big answer but it comes down to instinct, and taste, and counsel, and discerning what technologies really are strong as opposed to just being new and flashy. There’s a lot of that discerning to be done as well.

A question about the latent cells. There are some diseases that are incredibly aggressive, like testicular cancer, some leukemias, and lymphomas, and yet in particular those seem to be curable, at least operationally. Doesn't mean the cells are gone, it means that patient's never relapsed. And there are case reports of patients dying 40 years later, having an autopsy and for example still having Hodgkin's disease. Do you have any insight in to what fundamentally is the difference between the curable guys who probably have metastatic stem cells that we don't know about, and the ones like breast cancer and all the others that don't seem to be able to get there?

These are processes that follow parallel but separate tracks. The aggressiveness, the susceptibility to therapy of any kind. We have cured many people with just old fashioned conventional therapy. And then the newer ones, the susceptibility to that is one thing, and you can have it in fairly aggressive tumors. And the resistance also in those, and also with very late emerging metastasis. The emergence to meta-- the time to metastasis is a function of something else. It's a function of-- it's basically a mathematical equation, if you will. Metastasis is not just cells leave a tumor, sit there latent, and then they grow.
To get to this growth, there are innumerable individual steps that we are only beginning to enumerate and to imagine. But each one of them has all of its biology, and all of its bottlenecks. The example that I mentioned before about kidney. Kidney turns out, seems to be, preliminarily but also based on this transplantation evidence, a fairly permissive organ to host latent metastatic cells, pathogenic cells. It's just not very permissive at allowing them to take off. Renal metastasis, yes it happens when metastasis very overt, but it's not a front line. Adrenal is. Lung, you know, bone marrow, brain, liver, are the front lines. Yet it's kidney that has very more ample bottleneck for allowing it to be colonized by micrometastatic cells, but a very tight bottleneck. What makes it tight? Let's go there and get more of it. And so that's a separate set of parameters, biological and molecular, than those that make the cells, whether they grow or not, more or less susceptible to therapy.
Reengineering the Tumor Microenvironment to Improve Survival of Metastatic Cancer Patients

**Rakesh K. Jain, PhD**

**Edwin L. Steele Laboratory for Tumor Biology Massachusetts General Hospital Harvard Medical School**

Dr. Jain discussed the impact that the microenvironment of the primary tumor or metastatic site has on metastasis. Dr. Jain shared scientific evidence illustrating that metastasis is not a cell autonomous process and highlighted the role that the microenvironment plays in helping cancer cells migrate and shaping the response to treatment. In the sections below, the most important research findings that extend the lives of patients with metastatic cancer, major gaps in the field, major barriers that inhibit progress, and initiatives needed to accelerate clinical and translation research are summarized.

**The most important research findings that extend the lives of patients with metastatic cancer:**

1. Impaired blood supply results in a hypoxic and abnormal microenvironment that allows cancer cells to evade the immune system, increases their invasive and metastatic potential, and applies selective survival pressures to which cancer cell populations adapt (Figure 4) (R. K. Jain, 2014).

2. Table 1 summarizes novel treatments that extend the survival rate of metastatic cancer patients and the limitations that the microenvironment imposes on these treatments (R. K. Jain, 2014).

3. Nanotherapeutics, anti-vascular endothelial growth factor (VEGF) agents, immune checkpoint blockers, and targeted cancer therapies used as monotherapies or in combination with chemotherapy have only provided survival benefits on the order of weeks to months in some tumor types, and have not been efficacious at all in others (R. K. Jain, 2014).
Table 1. Recent Advances and Limitations in the Treatments for Metastatic Cancer Patients

<table>
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<tr>
<th>Treatment Type</th>
<th>Improvement to Rate of Survival</th>
<th>Limitation(s)</th>
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| Nanotherapeutics       | Survival benefits are limited between weeks to 2 months for most cancers (e.g., ovarian cancer responds to nanotherapeutics with a six month increase in survival rate). | • Challenges in the delivery of nanoparticles  
• Low tumor penetrance (30 percent) (V. Jain, Jain, & Mahajan, 2015) |
| Anti-VEGF agents       | Survival benefits are limited to weeks to 5 months for most cancers. | • Treatments can result in hypoxia and yield migratory cells |
| Immune checkpoint blockers | Four agents have had durable responses and cures depending on the type of malignancy. | • Unpredictable response of cancer types or patients with same cancer type  
• Low tumor penetrance  
• Toxicity, which is increased in obese patients |
| Targeted therapies     | Survival benefits are limited between weeks to 2 months for most cancers. | • Unpredictable response of different cancer types  
• Toxicity |

Major gaps in the field of metastatic cancer research:

1. There is a lack of understanding of how the microenvironment influences metastasis and shapes the treatment response (R. K. Jain, 2013).

2. A greater understanding is needed of the effect of obesity on increased microenvironment abnormalities such as hypoxia, low pH, and high interstitial fluid pressure that can induce treatment resistance. The U.S. Centers for Disease Control and Prevention predicts that in 10–20 years, 50 percent of Americans will be obese. In addition, studies indicate that obesity propagates cancer survival and migration; however, the precise mechanism is unknown.

• Collaborations required to meet these gaps: N/A.

Major barriers that inhibit progress towards extending the lives of metastatic cancer patients:

Scientific barriers: N/A.

Programmatic barriers: (1) More resources are needed, even a fraction of the resources devoted to gene therapy, to be used for microenvironment research that would provide the necessary research and treatments to improve the survival rate of patients suffering from metastatic cancer. If programs and funding agencies do not incentivize and support further research on the role of the microenvironment in cancer progression, then successful treatments will not only remain an enigma, but the U.S. will face major epidemics as higher proportion of Americans become obese.

• Suggested ways to overcome these barriers: N/A.
**Initiatives needed to accelerate clinical and translational research:** (1) Functional studies of tumor vasculature and density to determine ways to reduce blood flow to tumors. (2) Improve the understanding of the causes and consequences of abnormalities within the microenvironment of metastases. (3) Develop more effective strategies to normalize the microenvironment in both primary and metastatic lesions. (4) Address the challenges posed by obesity in tumor progression and treatment.

**Question and Answer Session Transcript:**

Dr. Jain, Don Dizon, Mass General.

Yes?

I think you're findings are very provocative. I wonder if you have any thoughts about how to sequence, say, losartan chemotherapy, immunotherapy, avastin, or bevacizumab, and chemotherapy. Any theories into the contribution of sequence of agents?

Yes. So we have tried to address that question. You're asking not only for anti-VEGF therapy, but also for matrix normalizing therapy. What we showed in our rectal carcinoma patient study, with Chris Willet many years ago, but it takes in rectal carcinoma patients about two weeks before the vessels get normalized. So that would be the time when you want to start. But obviously, it's going to vary from patient to patient, or from disease to disease. Currently, I think that imaging is the only way you can find out. Those methods are available.

And in the case of losartan, it takes about, in mice, about 10 days. In the clinical trial, which our colleagues at Mass General are doing, they have given it about a month in advance, and then the results would be presented at GI ASCO in the end of January or so. Yes?

Thank you Dr. Jain. I just wanted to respond, and comment, that indeed this is a great opportunity for yourself, and all speakers, to do exactly what you did, which is to make direct recommendations to the task force to inform Congress with targeted opportunities, which of course include funding. But in addition to that, I just wanted to bring to the attention, which I'm sure you know, as well as folks in the audience. In addition to the fact that we're recording this whole session, and that will be used for the report; that on the task force is the head of the congressionally directed medical research programs, Colonel Salzer, at the other end of the table here.

Yes. I had the fortune of getting Innovator Award from her. So In the audience are many senior leaders from the National Cancer Institute. So certainly many opportunities to get your message out. Thank you.
Liquid Biopsy as Diagnostic Tool to Unravel the Biology of Metastatic Cells in Cancer Patients

Klaus Pantel, MD, PhD
Chairman of the Institute of Tumor Biology at the University Medical Center Hamburg-Eppendorf in Germany

Dr. Pantel discussed the need for and importance of developing diagnostic tools, such as liquid biopsy, for the diagnosis and characterization of metastatic cancer cells. In the sections below, the most important research findings that extend the lives of patients with metastatic cancer, major gaps in the field, major barriers that inhibit progress, and initiatives needed to accelerate clinical and translation research are summarized.

The five most important research findings that extend the lives of patients with metastatic cancer:

1. Cancer cells disseminate early into the bone marrow and likely into other organs during tumor development. This dissemination is not a random process mediated by tumor shedding, but rather one that is regulated by specific sets of genes (Braun et al., 2005a; Köllermann et al., 2008; Werner et al., 2015).

2. The microenvironment, and in particular the presence of osteoclast cells in the bone marrow, strongly influences the process that starts from a single disseminated tumor cell and leads to bone metastases (Bednarz-Knoll et al., 2016; Ell et al., 2013; Lu et al., 2011).

3. Disseminated tumor cells survive by adapting to the new metabolic environment and the stress responses induced by being in a foreign niche (e.g., when a breast cancer cell adapts to the bone marrow environment) (Bartkowiak et al., 2015; LeBleu et al., 2014).

4. The genotype and phenotype of metastatic tumor cells may differ from that of the primary tumor within a single cancer patient. It is important to note that primary tumors are used to make clinical decisions with regard to the treatment of metastatic disease, which may not be effective when treating metastatic disease.

5. The number of circulating tumor cells (CTCs) found in the blood is associated with a higher risk of
developing metastasis (Janni et al., 2016). Important information (e.g., therapeutic targets, drug resistance, etc.) can be gained in real time from metastatic tumor cell products (e.g., cells, cell products such as cell-free deoxyribonucleic acid [DNA] and ribonucleic acid [RNA] fragments) that circulate in patients through liquid biopsy of blood samples (Figure 5) (Alix-Panabières & Pantel, 2014, 2016; Schwarzenbach, Hoon, & Pantel, 2011; Schwarzenbach, Nishida, Calin, & Pantel, 2014).

### Major gaps in the field of metastatic cancer research:

1. The ability to detect CTCs in the blood is critical.

2. A better understanding of the mechanisms behind cancer dormancy is needed. In addition, the development of interventions that can promote dormancy as a way of facilitating the long-term survival of patients with chronic disease is needed.

3. Earlier detection of cancer metastasis and disease progression based on the use of information regarding the molecular characteristics of an individual cancer patient’s metastatic tumor cells and not solely on primary tumor cells is needed.

4. A mechanism by which tumor cell resistance to systemic therapies can be monitored is needed to facilitate the appropriate and timely switch from interventions that are not effective to those that are.

- **Collaborations required to meet these gaps:** (1) International consortia are necessary to bridge the gap between published biomarker data and the biomarkers available for use in cancer patients (e.g., the European Union/Innovative Medicines Initiative network Cancer-ID, 37 partners from academia, non-profit organizations, and industry). (2) The cross-validation of experimental studies in cancer patients is needed to better understand how preclinical data translates into clinically-relevant information.

### Major barriers that inhibit progress towards extending the lives of metastatic cancer patients:

**Scientific Barriers:** (1) Tumor cell heterogeneity presents a significant barrier. (2) There is a need for real time information gathering from patients with metastatic cancer. Therefore, biomarkers to detect and characterize minimal residual disease in patients at risk for relapse is important for targeted interventions to prevent the spread of cancer.

**Programmatic Barriers:** (1) There is a need for transatlantic working groups to foster collaborations and decrease competition between researchers. (2) There is significant cost associated with the research and development needed to develop new biomarker tests for clinical use. Therefore, improved translational research programs are needed.

**Others:** N/A.

- **Suggested ways to overcome these barriers:** (1) Develop reliable diagnostic approaches to detect and restage metastatic disease early. (2) Establish international working groups that
facilitate and coordinate worldwide research efforts. (3) Change regulatory standards for new diagnostic tests.

**Initiatives needed to accelerate clinical and translational research:** (1) Develop reliable liquid biopsy diagnostics to facilitate the rapid and accurate re-staging and monitoring of metastatic disease. (2) Establish consortia that integrates both basic and clinical research to focus on minimal residual disease and metastatic cancer cell dormancy. (3) Coordinate international research efforts to establish large-scale biobanks for genomic, gene expression, and functional level analyses on metastatic tumors.

**Question and Answer Session Transcript:**

Well first, Dr. Pantel, thank you very much for your excellent presentation. Thank you for coming all the way from Europe to present to the task force. We very much appreciated your comment there towards the end about the ability to reproduce some of these tests of the dozens and dozens that people are looking at for liquid biopsy. And I had a saying once to one of the folks in my lab, if others can replicate your study that's called science, if they can't, it's called magic.

And that's the only thing that counts. Not the impact factor, right?

Right. I agree.

Yes. I think you touch upon an important point, which is collaborators need to work together. And you bring up your European initiative as well, and I think that certainly includes industry also. What do you feel, what are some recommendations from your collaboration that you have in Europe, when industry is involved, because clearly they have different motivations than scientists and folks advocating for patients? But this is an important part of it. Have you approached the role of industry in your collaboration, in terms of IP, and things like that?

Well, I think what we did was, really we said, OK this consortium is not made to promote your own test, or to develop your own test. We just invited companies that already had tests; that were already developed. And we were telling them that this group can really help, in a certain way, to show that your test is robust enough to really make it into the next step. And some of the companies were very keen about that. Some of the companies were very much afraid of that, as you can imagine. But then we said, OK, we can do it here with you, together, in our consortium, or, I mean, other people will do it, so to say. And then the news will spread around, and you have no control, you don't even know whether it has been done nice to these experiments. And I think to have a kind of, let's say, controlled environment to do this "nasty ring experiment test," you know, was a good argument for them to participate in that. But sometimes, in order to coordinate such a consortium, you need to be a good psychologist, because sometimes you have to tell bad news. Like you have to do it for a cancer patient about the test system. You're right. It can be tricky. Yeah?
Beautiful work. So, about 10 years ago we showed that when cancer cells travel alone, they don't metastasize efficiently. But if they travel in clumps, it goes up further. Dr. Fidler, and Lance Lerda showed that 30 years ago. But what we discovered is when cancer cells co-travel with fibroblast from where they, the original organ, they had the highest propensity of metastasis. And then we tested in patients, metastasis and brain. Brain isn't a fibroblast. If you look at metastasis in the brain from breast cancer, kidney cancer, pancreatic cancer, they're fibroblasts. Where are they coming from? They're coming from cancer cells. So they are co-travelers with it. And then last year a colleague at Mass General Hospital, Dan Habor and Shyamala Maheswaran, they showed had a very nice paper as to why the clumping of cancer cells is better for survival, and so one. So one of my concerns about CTCs is while it's very useful, it's much better than not knowing what's going on, but you're missing out on the whole stroma, which is playing a role in metastasis, and survival of cancer cells in it. Look, when I came to the United States, I brought two suitcases with me, right? Until I got established here. Well that's what cancer cells do. They bring fibroblast, or other host cells to the site until they get settled. That's a provisional stroma. And then they recruit new stroma. So shouldn't there be some effort on that, besides the single cell CTCs.

No, absolutely. I mean, we are also looking at aggregates. It's a bit more complicated because they are tumor cell aggregates, there are tumor fibroblast aggregates, tumor monocytes aggregates; there are tumor platelet aggregates. I think it will keep us a bit busy to figure out which are the most important. So we get a bit of the stroma information too. But overall, you're right. We don't get all the information. But my simple answer is it's better to be, let's say, to have one eye that works, than be completely blind. And so I prefer that.

But maybe we can ask Dr. Shriver to spend money on the second eye.

That would be fantastic.

That's why we're meeting today, because if we keep improving one eye I don't think we're going to be able to see three dimensionally.

No, no, but that's why I say--

You need two eyes to see--

Exactly. It could be also complimentary information. Absolutely. You're right.

There is something to think about.
Why Do Cancer Patients Die and How to Stop It

Bruce R. Zetter, PhD

Charles Nowiszewski Professor, Departments of Cell Biology and Surgery Harvard Medical School

Boston Children’s Hospital

Dr. Zetter discussed what is known regarding factors that lead to death in cancer patients. In the sections below, the most important research findings, major gaps in the field, major barriers that inhibit progress, and initiatives needed to accelerate clinical and translation research to better understand cancer-related death are summarized.

The most important research findings that extend the lives of patients with metastatic cancer:

1. Cancer deaths are not solely due to metastatic burden on essential organs. Other factors, including cytokines, play a role in patient death and provide additional targets to extend the lifespan of patients.

2. Systemic nanoparticle delivery of small interfering RNAs and messenger RNA (mRNA) represents a promising approach to restoring functionality of proteins that are down-regulated or inactivated in cancer cells. Nanoparticles have delivered phosphatase and tensin homolog (PTEN) mRNA to mice with PC-3 xenografts expressing solid tumors. The relative tumor size of mice with PTEN mRNA was significantly smaller than that of control mice expressing green fluorescent protein mRNA, providing direct evidence that PTEN nanoparticle delivery can restore tumor suppression (X. Zhu et al., 2015).

Three major gaps in the field of metastatic cancer research:

1. There is an incomplete understanding of how cancer patients die. It is well accepted and understood that some cancer patients die as a result of the local consequences of metastatic burden (i.e., organ failure due to the displacement of normal tissue by tumor). However, there is less information about how patients die from the release of cytokines that produce systemic effects in the presence of minimal metastatic burden to essential organs, direct response to treatment, or distal consequences of metastatic burden such as inflammation, coagulopathies, and cachexia.

2. Research should focus on the deadliest cancers as opposed to the most common cancers.

3. Most therapeutic approaches involve antagonizing, blocking, inhibiting, and silencing molecules that are upregulated or activated in cancer; however, many molecules are lost (i.e., deleted) or inactivated in stage IV cancers and we rarely try to replace or reactivate them. Are we missing a potentially effective strategy?
• Collaborations required to meet these gaps: N/A.

Major barriers that inhibit progress towards extending the lives of metastatic cancer patients:

Scientific barriers: (1) There is a lack of attention and effort invested in a large percentage of defects in cancer because the pharmaceutical industry primarily works on antagonizing agents. Many molecules are lost, deleted, or inactivated in stage IV cancers, and there is not enough research effort trying to replace or reactivate them.

Programmatic barriers: (1) It is difficult to translate preclinical and clinical research to clinicians, and it is unrealistic to expect to achieve therapeutic advancements and validation studies in less than 10 years. (2) There is inadequate funding and lack of philanthropic support for the less common, but deadly cancers such as esophageal, kidney, pancreatic, uterine, bladder, and stomach cancer (Bruce Zetter & Lara Maggs, 2016).

• Suggested ways to overcome these barriers: N/A.

Initiatives needed to accelerate clinical and translational research: (1) Work toward a better understanding of the mechanisms of patient death from stage IV cancer. Utilize liquid biopsies, such as through high throughput mass spectrometry, to identify the cytokinome that may cause death in patients and also utilize specific antagonists to treat patients and extend lives. (2) Incentivize researchers to embark on a broader range of cancer studies, in particular focusing on those cancers that are most lethal but have been historically understudied. (3) Invest in efforts that are designed to reactivate or replace the function of cytokines and other molecules that are lost in stage IV cancers. One such strategy is through the use of nanoparticles to deliver mRNA to tumors in vivo to restore functional tumor suppressor activity.

Question and Answer Session Transcript:

Hi. Louis Rivera, from San Diego. As a cancer survivor I can remember being admonished by friends and family that I was going to beat it. I was going to win the battle, and the idea that cancer is an adversary. I think what you're suggesting is healing the cancer, or maybe even living with it, which sounds like a little bit of a hard sell.

Yeah, absolutely. Neither of us would be the first to say that one of our goals is to make cancer a chronic disease. And even while Rakesh is talking about that C word, cure. I still don't use it. All right? In fact, we know now that virtually everyone past puberty has cancer. Have a cancer carcinoma in situ somewhere. We're all cancer patients. And the only difference between those who are going to die, and those who aren't going to die, is how fast the cancer progresses, how fast it goes from, if it spreads from-- which it always does-- from latency, to aggressiveness. We're all somewhere on the cancer spectrum. And so what we want to do is dial us all into a place on the cancer spectrum where we're living with it. Every person in that room is living with cancer. It might be three cells, it might be five cells. Somewhere in your body there's a cancer. All right? It's not us, and them. All right? We're all together in this. And so if we're at the stage where the cancer has gotten very aggressive, and it needs to be thwarted, we have to work to dial it back. Not necessarily to get rid of it all, but to make it a chronic disease. We all
I think you're 100 percent right. We don't cure any chronic diseases. We don't cure diabetes. We don't cure arthritis. We don't cure-- I don't know anything we cure aside from infectious disease. I think the idea of curing cancer is really not the right way to approach it, but to make it exactly a long term chronic disease, and just to deal with it. Have a drug that keeps you going for 20 or 30 years, and dealing with the side effects as you go along. Also on the idea of the 40 percent of the research dollars going toward breast cancer, I've thought about that many times in the past also, and I agree with you that it's largely because of the advocacy groups, and of the certain je ne sais quoi that breast cancer has in our society. But the other maldistribution is really a reflection, I think, of other factors. It is hard to study uncommon cancers simply because they're uncommon. You can't do a cohort study for a renal cell carcinoma, or bladder cancer, or cancers like that. So a large part of the funding is not simply arbitrary, or you can just snap your fingers, and say, let's spend more money on these things that really reflect realities.

I just wanted to add--

Who's speaking?

I'm right here. I just wanted to add that some people can live well with stage 4 cancer. I've been stage four for 10 years, and I'm doing well. So the fact that you are stage four doesn't necessarily stop everything. If you can induce dormancy, or something else, a lot of us do live quite well.

Absolutely the goal. Everyone living well.

We can't hear the mic.

OK. I work for the Mesothelioma Applied Research Foundation, which is an extremely rare disease that falls into that category of what you were discussing, and when I look also at-- it's not only the numbers that drive this, but it also has to do with the socioeconomic impact factor of these type of patients as well. They tend to be poorly educated. They tend not to have philanthropy in the family, so they don't fund their own disease. The disease is also more recognized as a legal disease, rather than a cancer that people suffer from. So that conversation needs to change as well. And one more point, not related to mesothelioma, I've noticed also in my practice over the years that there are many patients who develop multiple malignancies, and certainly out survive the forecast of their survivals, and I wonder who is studying these patients with three, four, and even five multiple cancers.

So, there are certainly people who are studying the genetics of the people with multiple cancers, and there are some genes that come up more often. I've been told apocryphally, and seen examples, where sometimes those patients actually do well. That they live for a long time, so maybe some of the cancers are keeping down some of the other cancers. We don't understand that phenomenon very well at all. I'm out of time. Colin is getting nervous, so we're going to move on.
Danny R. Welch, PhD

Professor & Chair, Department of Cancer Biology, Hall Family Endowed Professor of Molecular Medicine, Associate Director for Basic Sciences & Education, University of Kansas Cancer Center

Director, NFCR Center for Metastasis Research

Dr. Welch discussed the state-of-the-science of the mechanisms behind tumor metastasis, focusing primarily on tumor migration and colonization. Here, the most important research findings that extend the lives of patients with metastatic cancer, major gaps in the field, major barriers that inhibit progress, and initiatives needed to accelerate clinical and translation research are summarized.

The most important research findings that extend the lives of patients with metastatic cancer:

1. Tumors can communicate with other parts of the body and establish a premetastatic niche where new colonies can form. There are many mechanisms by which tumor cells can migrate and establish metastases (Figure 6) (Peter Friedl, Locker, Sahai, & Segall, 2012; Peter Friedl & Wolf, 2003; Overholtzer et al., 2007; Sabeh, Shimizu-Hirota, & Weiss, 2009; Te Boekhorst, Preziosi, & Friedl, 2016). Tumors recruit inflammatory cells that may be either pro-tumorigenic or anti-tumorigenic. As the tumor cells migrate, they can form “conga lines” with macrophages in a scenario where the
macrophages lead the way (e.g., they can create a hole) for tumor cells to invade (Goswami et al., 2005). Tumor cells cooperate to create a pathway through the restructuring of matrices that allow other tumor cells to pass through (Wolf et al., 2007).

2. Collagen is present in numerous structures, depending on the type of tissue in which they are found. Each of these different structures requires different types of enzymes in order to be broken down. Subsequently, tumor cells enter the bloodstream and roll in a weakly adherent manner using the same molecules utilized by leukocytes to do so (Spiegel et al., 2016). As a result of this process, tumor cells are able to evade the immune response as well as shearing in the blood stream; however, not all cells are able to complete this process successfully. Notably, one to four million cells per gram of tumor can enter the bloodstream daily and less than .01 percent metastasize successfully (Butler & Gullino, 1975; Fidler, 1973). Circulating cells (e.g., those obtained via liquid biopsy) can provide information as to which cells may ultimately prove successful in establishing a metastasis. Furthermore, tumor cells accumulate a group of cells or matrices that can provide protection from shearing during the migration process.

3. More than 90 percent of metastases are clonal in origin. Therefore, each metastasis must be considered a separate entity with regards to treatment.

4. As tumor cells begin to grow at a metastatic site, they co-opt blood vessels, induce angiogenesis, create “tubes” in which blood can flow, and promote growth into neutrophil extracellular traps (Bridgeman et al., 2016; Maniotis et al., 1999; Naumov et al., 2006; J. Park et al., 2016).

5. There are intrinsic modifier loci that may provide predictive biomarkers to help stratify patients based on their treatment needs. Pro- and anti-tumorigenic genetics of both the tumor and host responses are involved in the metastatic process (Hurst & Welch, 2011). One example is the metastasis suppressors, of which there are now 35 that have been functionally characterized. One example is the metastasis suppressor gene KISS1, which allows tumor cells to persist and become “dormant” (Nash et al., 2007). These targets may provide a new therapeutic avenue to explore.

6. It is unknown why patients with the same disease characteristics differ in their rate of metastasis. Racial disparities may reflect a difference between patients that can influence metastasis. Notably, African-Americans develop different types of tumors and at different levels of aggressiveness than Caucasians, Europeans, or Asians; therefore, inherently different factors predict the susceptibility to developing metastasis (Hunter, 2006). In a study by Lifsted et al., various mouse genetic crosses, which can be considered analogous to race in humans, were used to map metastasis modifier loci that either promote or inhibit metastasis (Lifsted et al., 1998a). Current research is seeking to extend this work while also taking into consideration mitochondrial genetics. Results indicate that mitochondrial polymorphisms are predictive of metastatic potential via a mechanism that has not yet been elucidated.

7. The microbiome of the host plays a role in metastasis and the response to treatment.

Three major gaps in the field of metastatic cancer research:
1. While most research focuses on metastasis prevention, the focus should be on tumor cell colonization as the only tractable step for therapeutic intervention. The steps of colonization need to address organotropism (e.g., why tumor cells go to certain tissues, underlying tumor and host genetics involved in this process, the microenvironment, etc.) to elucidate what promotes or inhibits tumor cell dormancy.

2. A better understanding of tumor-stromal communication (i.e., the signals that come from that tumor and stroma that regulate each other and what differentiates these signals as either pro- or anti-tumorigenic) is needed. What distinguishes a pro- or anti-metastatic signal? How can immune cells be polarized to become either pro- or anti-tumorigenic?

3. There is a lack in the ability to detect microscopic metastasis. Since cancer outcomes improve the earlier the disease is detected, technologies are needed that detect lesions smaller than one centimeter while also monitoring lesion progression.

Collaborations required to meet these gaps: N/A.

Major barriers that inhibit progress towards extending the lives of metastatic cancer patients:

Scientific Barriers: (1) There are few if any models of metastasis for the most common tumor types. (2) There is a lack of consistency in models of in vitro tumor colonization and in vitro models are not complex enough to be accurate. (3) There are challenges in clinical trial design for the study of metastatic cancer. (4) There is a general lack of as well as access to matched primary tumor and metastatic tumor samples, particularly from multiple tissues.

Programmatic Barriers: (1) The focus should be less on treatment and more on prevention. (2) With regards to metastasis-related experimental methods, there is inadequate training for researchers. Well trained researchers and multidisciplinary collaborations are needed (e.g., physicists, biologists, etc.) (3) Metastasis research involves lengthy, complex, and high-risk experiments that often take considerable time to make it to publication. (4) The current funding model today focuses on short-term (i.e., 5-years of funding), low-risk science. A significant amount of data is needed simply to get grants funded. (5) In vivo models, which are imperative to this research, are associated with burdensome Institutional Animal Care and Use Committee (IACUC) requirements and per diem costs. (6) Non-scientists are directing research, which should be the responsibility of scientists.

Suggested ways to overcome these barriers: (1) Collaborations both within institutions and at an international level are needed to address translational issues between disciplines. (2) To advance the field, there needs to be an environment where researchers are both willing and able to take on such projects without the fear of penalty for failure.

Initiatives needed to accelerate clinical and translational research: (1) Focus on the development of experimental models for the 10 most common cancers, as well as the characterization of these models. (2) Collect matched primary and metastatic tumor samples. (3) Further define the interactions between the tumor and stroma. (4) Focus on initiatives to improve imaging technologies. (5) Establish and convene an expert panel to design a clinical trial rubric. (6) Improvements to clinical trial design such as the Response Evaluation Criteria
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in Solid Tumors (RECIST) criteria are not applicable to dormancy-related interventions. (7)
Focus more on metastatic cancer (i.e., stage IV patients) rather than on prevention. (8)
Establish biomarkers for tracking outcomes to better inform clinical decision making. (9) As patients survive longer as a result of metastatic cancer research, further study on survivorship and the psychosocial effects of metastatic cancer on patients is needed. (10) Investigate the long-term effects of cancer treatment (e.g., via cardio-oncology). (11) Focus on the recruitment and retention of researchers in the field of metastatic cancer. (12) Provide specialized training to oncologists regarding metastatic disease.

Question and Answer Session Transcript:

Exactly on time. We're going to get started with the five minute question answer period, and then we will take our break for lunch.

Danny, excellent talk. You mentioned the old paper from the 70s on the number of cells released every day, per gram tumor, which has been quoted, probably, tremendously all over. But I was just wondering if you have a prostate cancer with a proliferative fraction of 2, or 1 percent, and if you have really millions of tumor cells per gram shed every day-- I mean, I never did the mathematical calculation, but I would assume the tumor just disappears if these figures are correct. Just challenges that a bit.

All of those, are legitimate. And I think Rakesh has done some follow up, and he's seen similar types of numbers, with other tumor types. Part of the issue in doing these is technical. And I don't want to get totally into the weeds, but having a single efferent vessel where you capture everything that's coming out is part of the reason they did it. There are many issues, and we can talk about them, but your point is well taken.

I was in Gullino's lab when those experiments were being done. I witnessed those. And not only that, Lance Liotta repeated those experiments using another operation when he was a PhD student at Case Western Reserve University, working with somebody named John Sidell. It's also published in Cancer Research. Those numbers are correct. What you need for that is a special tumor operation which has a single artery, and a single vein, so you can collect everything coming out of a tumor. That's what Peter Gullino did, and that's what Lance Liotta did.

My only point was that there might be a larger range, you know, considering the different tumor types that we all have in our world.

So I will just sort of say, if you say a fact about a tumor, it's about a fact about a tumor. When I teach medical students, or graduate students, I say, here, are the rules that will give you the correct answer 90 percent of the time, you just have to address the other 10 percent, so you're absolutely right. I'm getting a lot of questions from people off the panel, I just want to make sure, Lisa?

Dan, I'm going to challenge your notion that what we need are better models for the 10 most common cancers, because I would argue that we need improved models for orphan cancers. Mostly, because if you approach biotech-- aside from that we need to understand the biology--if
you approach biotech, or pharma, with an orphan cancer, their hurdle to drug approval it's-- I don't agree with you because we've got quite a few collaborations in the lab where biotech and pharma recognize that the hurdle to approval is much lower with orphan cancers, because the impact can be huge. Mesothelioma, for example, you can improve standard of care by more than three months, you've got a drug approved, and then you open yourself up for a much broader platform for clinical testing, and evaluation. And that's the strategy we've taken. One of the reasons we went into mesothelioma research was because the road to approval was a much lower threshold for the companies, and they have bought it significantly, and they're making investments in that way. We've got lots of models for common cancers. We don't know anything about orphan cancers.

I disagree that we've got lots of models. We don't have lots of metastatic models for the common cancers. But I don't disagree with the point that there is a lower threshold. Orphan drugs do require any improvement-- Not even orphan drugs. Common drugs.

I mean an orphan tumor, an orphan disease. So I think, to bring it back, just a little bit to Bruce's point and yours-- and I do see the other question-- we made a lot of discoveries, related to the genetics of cancer RB, P53, and all those, due to relatively rare cancers. You can learn an awful lot from them. So it's not to exclude anything. I was just trying to put, we only have so much to spend, so much time, and so many investigators, and so on. Then maybe the change in metastatic disease, you know, the majority of the patients really do not have a performance status of one, and that cutoff has really changed significantly over the years. It used to be a performance status of one to two, trending all with one now. So that cuts out these types of patients that we'd like to--

Elise, do you have a question for the task force?

I just wanted to comment on the RECIST. I think you raised a really important point. RECIST is definitely focused on shrinkage, and the more classical chemotherapeutic paradigm, or driver paradigm, where you have a single driver, like when you're hitting RAF in melanoma. In the clinical trial design, one of the reasons that we've moved aggressively at NCI to randomized Phase IIs; even small ones that may have as few as 25 patients per arm, is to try and allow incorporation of a disease free interval, progression free, survival type of period, which indirectly might speak to short term dormancy questions. But you can't do that in a single arm study. Which is one of the problems with TAPUR, in effect, because they included a disease free interval, at an investigator analysis, and there's just a huge literature on the aggressive bias. I think that there's some discussion about how can be reconsidered with the new types of agents that are coming in, and feedback from researchers who are especially are focused on elements related to dormancy, and heterogeneity, may help inform the clinicians side, because those are issues that are obviously a problem. And if you're biopsying someone, as you said, and Bruce, and others, you're only getting information on that one site. So I think it's a complex area where partnership between the lab and the clinic are going to be really important for metastasis. All right. Thank you, very much.
Dissecting the Metastatic Cascade by Microscopy and Molecular Analysis

Peter Friedl, MD, PhD

Department of Genitourinary Medical Oncology, Division of Cancer Medicine, The University of Texas MD Anderson Cancer Center, Houston, TX

Department of Cell Biology, Radboud University, Nijmegen, Netherlands

Dr. Friedl discussed the mechanisms surrounding cancer metastasis and the gaps in current knowledge that may hinder clinical outcomes. In the sections below, the most important research findings that extend the lives of patients with metastatic cancer, major gaps in the field, major barriers that inhibit progress, and initiatives needed to accelerate clinical and translation research are summarized.

The most important research findings that extend the lives of patients with metastatic cancer:

1. CTCs can arise from any cancer lesion (e.g., primary tumor, any stage of metastasis) and result in metastasis (Pantel & Brakenhoff, 2004).

2. For decades it was thought that a single tumor cell could cause cancer metastasis; however, it has now been shown the tumor cell clusters are particularly efficient in establishing themselves (Figure 7) (Aceto et al., 2014; Cheung et al., 2016; Cheung & Ewald, 2016; P. Friedl et al., 1995; Peter Friedl et al., 2012; Liotta, Saidel, & Kleinerman, 1976; Wolf et al., 2007). Within these tumor cell clusters, there are leader cells and follower cells, as well as environmental sensing and gap junction communication between cells that allow for the adaptation to stress in a manner that differs from the mechanism by which a single tumor cells would respond. Metabolic stresses can trigger the release of cells from a tumor.

3. There are many mechanisms by which tumor cells can metastasize and colonize different organs (Peter Friedl & Alexander, 2011). For instance, integrins are key to cancer metastasis as they mediate invasion, migration, extravasation, growth, survival, etc. of tumor cells (Desgrosellier & Cheresh, 2010; Felding-Habermann et al., 2004). Notably, inhibition of integrins can release cells from the primary tumor under certain circumstances (Haeger et al., unpublished data).

4. Tumor cells may respond unfavorably to specific therapeutic interventions. For instance, treatment with serine proteases, cysteine proteases, cathepsins, or matrix

Figure 7. Cancer invasion, circulation, and metastasis (Friedl et al., 1995; Wolf et al., 2007; Friedl et al., 2012; Aceto et al., 2014; Cheung et al., 2016; Cheung & Ewald, 2016).
metalloproteinases can trigger tumor cells to convert to a different dissemination mechanism (e.g., “amoeboid” migration in the presence of protease inhibition) (Wolf et al., 2003; Zaman et al., 2006).

Three major gaps in the field of metastatic cancer research:

1. Preclinical and clinical studies have not adequately dissected the mechanisms by which cancer metastasizes. Therefore, there is a lack of understanding of the various ways in which metastasis can occur (e.g., invasion, survival, growth, etc.). In addition, it is difficult to encourage graduate students and post-doctoral researchers to study the mechanisms underlying cancer metastasis.

2. Additional work is needed to investigate the metastatic cascade rather than the study of a single endpoint such as tumor growth.

3. There is an inefficient understanding of the effect of therapeutic interventions at the preclinical and clinical level (e.g., the release of cells following radiation). Notably, these interventions may cause tumor cell plasticity and metastatic response.

- Collaborations required to meet these gaps: Collaborative clinical work and the establishment of common terminology are needed.

Major barriers that inhibit progress towards extending the lives of metastatic cancer patients:

Scientific Barriers: (1) The study of this topic requires a multifaceted approach involving cellular, molecular, biophysical, and imaging expertise all within a single project. This is time-consuming, costly, and beyond the capabilities of one lab alone. Collaborations can also be challenging because of the slow output. (2) There are variable standards for the monitoring and classification of metastasis as well as for therapeutic interventions that target migration. (3) The significance of CTCs and their role on cancer metastasis remains controversial. It is unknown what experiments are needed to elucidate this to reach a consensus.

Programmatic Barriers: N/A.

- Suggested ways to overcome these barriers: (1) Develop a better understanding of the mechanism of tumor dissemination strategies both within a single tumor and patient as well as between various tumor types. (2) Develop a better understanding of the mechanisms by which therapies that interfere with molecular targets and the consequences that may result. (3) Develop methods of predicting drug-induced changes in tumor cell invasion and dissemination mechanisms, as well as cell crosstalk, survival, DNA repair, and growth. (4) Research needs to be performed at both the preclinical and clinical levels.

Initiatives needed to accelerate clinical and translational research: (1) Develop biomarkers for the monitoring of tumor cell changes in migration and adaptation strategies (e.g., serial biopsies, CTC analyses, co-clinical analysis of patient-derived cells). (2) Determine therapeutic combinations that can target tumor cell plasticity responses. (3) Improve the
understanding of all factors involved in tumor cell dissemination both at the cell and molecular level that lead to metastasis and how these steps are affected by therapeutic interventions. (4) Identify pathways in tumor cell dissemination and survival that can be targeted by therapies. This would require both in silico research as well as experimental work to elucidate both aspects of dissemination and tumor cell survival. (5) Better assess the metastatic mechanism clinically (e.g., via the monitoring and analysis of CTCs prior to, during, and post-therapy and palliative treatments). (6) Rapidly develop more affordable strategies for the isolation of tumor cells as well as clinical biomarkers.

**Question and Answer Session Transcript:**

Thank you, Dr. Friedl, it was excellent. You very nicely pointed out a lot of barriers, lack of common terminology, lack of team science, a bigger issue surrounding the ability to work in teams. And we see that across the whole landscape of cancer research. But it seems to be standing out more in metastatic cancer research, lack of engaged investigators, researchers, clinicians.

The research ecosystem does not necessarily reward team science. And that's one of the subthemes we seem to keep hearing here. What thoughts do you have on that? If we need to get clinicians working more with basic scientists to validate in the clinics some of these ideas and models, and even to get what we heard this morning about trying to get a group together to look at clinical trials in metastatic patients, and how that looks and how difficult that is.

What, from your experience on both sides of the divide, are some barriers to the team science in moving forward the field the way you've described it?

I have made a personal experience in a physical science of cancer consortium. When there is an umbrella situation where an acknowledged program has been built that comes along with substantial support, over five years renewable for another five years, and if you're part of it, your much better off in order to integrating. This is a very strong strategy I have seen, and this is enforced in many fields.

I haven't seen it in the metastasis world so far. So we are all happy with the bioluminescence assay, it gives us a readout. And the need to really put this complementary expertise together to solve one problem on metastasis across campus, let's say at MD Anderson, I haven't seen this. And there I would say a dedicated focused activity like Dr. Welsh suggested, let's identify the cancer types that could serve as a role model. Identify the mouse models that could serve as a lead, and what could be a druggable pathway that are done co-clinically, where a sufficient mass of patients is available, and put this together in a dedicated, focused program. I think this could really change our understanding, and resolve the black box partly.

Sir. Lou Rivera, right here. If you could establish a collaborative team, what would be the minimum skill sets or resources that that team should have? Many of the presenters have demonstrated intravital microscopy as a valuable tool, so what are the elements, you think, of a team, specifically resources, skill sets, that would be a fundamental part of that team?

Yes. Practically everything that's being done in cancer research in a multimodal way has to be focused towards a metastatic output. So we need clinicians getting biopsies. We need omics
people doing single-cell RNA-sequencing. We need intravital researchers being able to take out cells from every step of the metastatic cascade in a co-clinical effort, in order to see what's the longitudinal drift that the cells goes through.

We need histopathologists analyzing the material, which is not the clinician, it's another entity, again. Or a cohort of already available material to look into biomarkers, like tissue microarrays. We do need cell biologists that to do organotypic 3-D culture, best organoids, and people deriving organoids for co-clinical work of patient material. We need and bioinformaticians putting all this complexity together. We talk about 10 or 15 different data sets that need to be statistically molded and brought together into one landscape.

What have I forgotten? Yeah, the traditional tumor biologist, of course. Being able to do tail vein injections and look at outcome. Geneticists doing smart interferences so that you have genetically engineered mouse models delivering human-like situations, but also PDX models modeling human material in mouse system. So how many have I counted now, 10 or 11 already? So I think this would be-- have I forgotten? Immunologists, yes, of course.

And--

As we have heard throughout this morning.

I would add you're forgetting engineers also.

Yes.

Because--

Biophysicists. Metastasis is a physical problem. Cells have to survive, withstand, shear stresses. Indeed.

I would like to comment on building upon what you say in having a consortium grants with engineers. It's been very fruitful, because there is another mindset to help develop technology, that it's another barrier that we have. We cannot see everything that we want to treat.

And from the question about team building, I think there's two layers. One is that, as investigators, we spend a lot of time writing a lot of grants to keep our labs funded. And it's a
cost-benefit decision to go into team grants, sometimes where the reward is the same or less, but the amount of work that goes into it is much larger. And it is important that the institutions that have a team of people around metastasis will get some programs, for example from the NCI or other institutions, to fund team science, beyond the immediate goal of publication but rather of cementing the team building.

And, for example, Lisa and some other people here, have spent 10 years in the Tumor Microenvironment Network consortium funded by the NCI. And after 10 years of building momentum and really understanding what we were doing, the funding was stopped. And this--this is death for a program that really matured. So continuity in funding is really essential. Those are some of my two cents.

A final comment from the Task Force, then we need to move on.

Everybody's been talking about biomarkers, and that word has a different meaning in the laboratory and in the clinic. And I just wanted to ask you when you were describing the biomarkers that are so critical, are you looking for biomarkers that are predicting that someone will develop metastasis, so a prognostic biomarker of risk? Are you talking about biomarkers of susceptibility to intervention, which would be a true predictive biomarker or a biomarker of a relationship between the co-clinical situation?

All three of them. So it's clear a biomarker is not a biomarker, is not a biomarker. So it really depends on your angle. So from my standpoint, for example, it would be important to find out biomarkers that predict stability of cells to survive circulation versus being vulnerable to sheer stress. So they will die. And then could we look at a certain biomarker that's in the metastatic marker lesion that's been biopsied relative to a biomarker that I see in the CTC's? And do they co-evolve, so to say, or is there a disparity between the two compartments?

So it really depends on the parameter to be monitored, and probably we have to live on a couple of biomarkers in one consortium effort in order to dissect the cascade, or a certain momentum that it might gain through an intervention.
Integrated Drug and Biomarker Development to Improve the Lives of Prostate Cancer Patients with Metastatic Disease

Howard I. Scher, MD
Genitourinary Oncology Service, Memorial Sloan Kettering Cancer Center

Dr. Scher discussed the development of biomarkers for prostate cancer patients with metastatic disease. In his presentation, he highlighted the most important findings that can extend the lives of patients, major gaps in metastasis research, major barriers that inhibit progress, and recommended initiatives to accelerate clinical and translational research.

The most important research findings that extend the lives of patients with metastatic cancer:

1. Prostate cancer is androgen-driven at all stages. The androgen receptor (AR) and AR signaling drive its progression. Tumors often become hormonally sensitive and are driven by upregulating the androgen biosynthetic machinery. ARs may also become overexpressed. These oncogenic drivers have been targeted successfully using the drugs abiraterone acetate and enzalutamide (Figure 8).

2. Treatments targeting the immune system or tumor microenvironment (e.g., sipuleucel-T and radium-223) can improve a patient’s lifespan without having an effect on prostate-specific antigen (PSA) level, tumor size, or tumor progression (Kantoff et al., 2010; Parker et al., 2013).

3. The Prostate Cancer Working Group 2 (PCWG2) recommends that RECIST guidelines for prostate cancer focus on individual disease sites rather than a global metric, as individual disease sites have different impacts on prognosis and different biological characteristics. The PCWG2 also developed the 2+2 biomarker rule in which new lesions must be observed in two sequential bone scans in order to be considered a sign of metastasis (Scher et al., 2008).

4. The results of the initial Stand Up to Cancer and Prostate Cancer Foundation molecular profiling effort strongly support moving towards a more biologically-based disease taxonomy. 90 percent of the 150 patients had molecular alterations that were...
clinically actionable. Molecular alterations in the AR, the PI-3 kinase signaling pathway, and the DNA repair pathway were the most common alterations observed, and there is also a high frequency of germline alterations (Pritchard et al., 2016; Robinson et al., 2015). Developing methods that predict sensitivity to DNA repair pathway treatments is consequently a high priority (Mateo et al., 2015).

**Three major gaps in the field of metastatic cancer research:**

1. Additional research must be done to develop methods that help determine the appropriate treatments and optimal treatment timing to improve patient outcomes.

2. Standards are needed for the assessment and reporting of imaging results. In addition, there is limited availability of certain imaging tracers and there are challenges with deciding which imaging technique to use. The choice of imaging modality influences biopsy and subsequent treatment decisions since individual lesions may respond differently to specific modalities (e.g., Technetium-99, fluoro-5-alpha-dihydrotestosterone-positron emission tomography [PET], fludeoxyglucose F 18 [FDG]-PET).

3. Methods for assaying predictive biomarkers, especially those located in the blood, need to be developed and validated.

- **Collaborations required to meet these gaps:** (1) The Prostate Cancer Working Group 3 convened to identify subsets of patients with castration-resistant prostate cancer for whom specific agents are most appropriate or specifically indicated, to assess the changing biology before and after treatment and to design trials that best demonstrate how to use available agents to maximize patient benefits (e.g., alone, in sequence, or in combination) (Scher et al., 2016). (2) Blood biopsy (i.e., “liquid” biopsy) provides a source of samples that can be easily obtained on a repeated basis with minimal patient risk.

**Major barriers that inhibit progress towards extending the lives of metastatic cancer patients:**

Scientific Barriers: (1) Technologies are frequently developed without a clear view of their utility or necessity. (2) Cancer heterogeneity is a barrier across the spectrum: among patients, within an individual patient, and within lesions.

Programmatic Barriers: (1) There is an insufficient understanding of the biomarker development process. Both the analytical viability and the clinical utility of biomarkers need to be defined. (2) In general, the field focuses too much on new therapies and not enough on optimizing the usage of therapies that currently exist.

**Suggested ways to overcome these barriers:** The biomarker development process should function more like Phase I–IV clinical drug trials: (1) focus on context of use (i.e., the management decision that is influenced by the biomarker result); (2) demonstrate analytical validity for its intended purpose; (3) be clinically validated (i.e., the biomarker should be linked with biological processes and clinical endpoints); and (4) have clinical utility (i.e., use of the test result to inform a therapeutic decision improves patient outcomes relative to non-use of the test). In addition, although novel technologies can be developed to measure the next generation of biomarkers, existing technologies should be exploited more.
For example, CellSearch™ remains the only CTC assay that has obtained FDA clearance for enumeration. FDA, industry, and academia are collaborating to develop an intermediate endpoint containing CTCs.

**Initiatives needed to accelerate clinical and translational research:** (1) Support the generation of evidence of clinical utility (e.g., blood profiling atlas of the Cancer Moonshot, imaging biomarkers for all contexts). (2) Increase focus on the use of standard of care drugs. (3) Support infrastructures for collaboration (e.g., dedicated programmatic administrative support). (4) Support consortia (e.g., the Prostate Cancer Clinical Trials Consortium). (5) Focus sampling at the treatment decision point rather than using samples of convenience, such as frozen samples of the primary tumor. Morphometric criteria may be developed to predict the likelihood of a successful biopsy and to determine whether a biopsy should be performed.

**Question and Answer Session Transcript:**

Dr. Scher, thank you very much for that. And you mentioned a lack of standardization, too many technologies, no clear focus. And then, at the end, you mentioned Blood Profiling Atlas in Cancer (PAC) coming out of Cancer Moonshot. And I want to give you a just bit of time to give a little more detail to the Task Force on that. What are the goals of Blood PAC, as you're a leader in that, obviously? Is that initiative to overcome some of these wide-ranging approaches that different teams, including industry and academia, have in this field of liquid biopsy? Just a few more minutes on that.

So the beauty of the Moonshot is you have all the stakeholders in the room. You have engineers, you have assay developers, you have experts in genomics, you have clinical trialists, you have industry, you have different levels of resources, and you have federal regulators. And the idea is to apply the so-called Bible of biomarker development to all of the assays.

And it starts, essentially, with an evaluation of the technology, or a critical review of what has been done from the analytical validation perspective. Again, having multiple groups test the same methodology, and show that they consistently perform is critical for me if I'm going to include it in the clinical studies and commit patient samples.

From the biomarker development point of view, we heard earlier how difficult it can be for them to get specimens, which I think is part of the reason that they'll run whatever they can. But here, we can focus the question, look at the assay, what answer will it give us, and how do we want to use that result? And set it up just the way we set up a trial with a drug.

So it was very interesting. One of the questions that comes up in the circulating nucleic acid field is what tube should you use? And we heard from Carolyn Compton that it really starts with the needle diameter that you might use to draw the blood sample from the patient. You might get a different answer if you use the first tube or second tube. So two types are commonly used. One is EDTA tube, another is Streck. Streck has a preservative, so it can be, presumably, shipped.

And we learned that amongst the group within the room, Jerry might correct me if I'm wrong, that that same experiment was probably done close to 1,000 times. If you added it up within the group, we had a statistician in the room. We said, well how many times you really have to
do this to show, in fact, that you get the same amount of DNA with the same integrity? He said, about 50. So that alone can cut down on timing.

And, again, sharing the assay procedures, sharing the data on what context they are actually showing results. There's no question that it will cut time down. It gives me access to people I would never meet or never see. And, again, what's really been interesting is how enthusiastic everybody is about it. They really want to see this work, because they know that what can be accomplished by the group can never be done by anybody alone.

Sorry, Klaus?

Yeah, Howard. Some of these goals are very similar to our cancer ID goals. And I was just wondering whether it would make sense to bridge our efforts in a certain way to save time and resources.

Jerry, pardon me here. We've only been in existence since September 10th, unofficially. In October, I think it was 17th. So we're still getting organized, but again, you and I have been colleagues for years, and I've spoken to several of the leaders within your group and absolutely would love to work with you on this initiative. But we need to be a little bit further along. Give us another two weeks.

[LAUGHTER]

After Christmas, all right.

Time for one final question. Sorry.

So, Mike Kelly from the VA. So I appreciate your focus on getting to clinical utility, because I think that is where you have to go, but how confident are you that you understand the biology of what you're measuring? For example, in the circulating tumor cells to know that you're going to get a strong association, or a strong biomarker, out of that? Or could it be that the tumor cells which are circulating are circulating for such a brief period of time that you really can't measure them until you understand what exactly it is that you're trying to measure?
OK. So obviously the choice of the biomarker is based in part on preclinical data and what is known about the particular pathway. Where it gets challenging is it rarely occurs in isolation, which is a whole other area. So there are other groups that are trying to look at the so-called output of a particular pathway, and see if that may be more informative. There's no shortcut. You really have to see what you can measure and then make that association. What has been interesting as we've looked at different cell phenotypes, there are some that seem to be strongly associated with a DNA repair-deficiency. And when we treat with a drug that targets the pathway, only that population disappears. So it's almost like you're getting to the point of antibiotic sensitivity. And I think what we'll see as we do this in real time, that we won't be using the drugs quite as long as we have in the past, we may actually be able to alter treatments in a shorter period of time.
Epidemiological Perspective on Improving Survival among Metastatic Prostate Cancer

Bettina F. Drake, PhD, MPH

Washington University School of Medicine, Division of Public Health Sciences, Alvin J. Siteman Cancer Center

Dr. Drake discussed metastatic cancer from a population-based perspective. In her presentation, she highlighted the most important findings that can extend the lives of patients, major gaps in metastasis research, major barriers that inhibit progress, and recommended initiatives to accelerate clinical and translational research.

The most important research findings that extend the lives of patients with metastatic cancer:

1. The incidence of metastasis at the time of diagnosis has increased from 2007 to 2013, necessitating an increased need to develop improved risk stratification and therapies to improve survival in patients with metastatic prostate cancer (Weiner, Matulewicz, Eggener, & Schaeffer, 2016). In addition, the U.S. Preventative Services Task Force recommendations that reduced screening for prostate cancer have resulted in diagnoses at later stages. Furthermore, there are detected molecular alterations and aggressive disease states. These observations highlight the importance of improved screening techniques and imaging capabilities that allow for earlier detection of metastatic prostate cancer.

2. A recent Surveillance, Epidemiology and End Results Program study demonstrated an increase in 5-year overall survival in men treated with radical prostatectomy (67 percent) or brachytherapy (52.6 percent) as compared to men receiving standard treatment for metastatic prostate cancer (22.5 percent) (Figure 9) (Culp, Schellhammer, & Williams, 2014; Engel et al., 2010). However, this is not currently the standard of care for metastatic prostate cancer.

3. Men with castration-resistant prostate cancer now have improved outcomes due to the discovery of novel therapeutic agents (e.g., hormonal agents, chemotherapy, immunotherapy). There have also been advances in prognostic modeling, which may lead to better treatment options.

Figure 9. Radical prostatectomy improves 5-year overall survival compared to no local treatment (Culp, Schellhammer, & Williams, 2014; Engel et al., 2010).
Three major gaps in the field of metastatic cancer research:

1. Additional studies are needed regarding outcomes following primary tumor reduction prior to the start of standard treatment for metastatic prostate cancer. Some prospective studies are currently in progress. Further, there are some retrospective studies also in progress, but they have small sample sizes. Future studies require more extensive follow-up and a standardized course of treatment.

2. Men with a family history of prostate cancer and African-American men are more likely to experience a more aggressive and progressive cancer. They are also more likely to be diagnosed with metastatic disease or experience disease progression after primary treatment. A greater number of randomized controlled trials (RCTs) that include these high-risk populations are needed. In addition, education should be targeted towards men in these high-risk populations.

3. Additional data on modifiable behaviors (e.g., exercise, smoking) that may improve outcomes and help to identify potential interventions for patients with metastatic prostate cancer are needed.

- Collaborations required to meet these gaps: Efforts should be directed toward addressing limited follow-up in clinical studies, increasing the number of high-risk populations in these studies, increasing patient access to RCTs and other therapies, and the development of guidelines and patient education efforts.

Major barriers that inhibit progress towards extending the lives of metastatic cancer patients:

Scientific Barriers: (1) Many current clinical trials and prospective studies are not directly comparable as a result of their use of different endpoints (e.g., time to progression, time to treatment failure, PSA progression, radiologic progression, and patient-reported outcomes) for the assessment of survival for metastatic prostate cancer. (2) Studies on prostate cancer Health Related Quality of Life are also not directly comparable. Patient reported outcomes are assessed differently across studies, and studies frequently choose different outcome measures (i.e., pain, fatigue, physical functioning).

Programmatic Barriers: N/A.

- Suggested ways to overcome these barriers: (1) Specific endpoints that can be compared across RCTs should be established (e.g., the development of guidelines that state that each study should look at time to progression along with any other relevant endpoints of interest.

Initiatives needed to accelerate clinical and translational research: (1) Additional translational studies on risk prediction. (2) Observational studies that identify predictors of remission in metastatic cancer should be conducted. (3) The improvement of survivorship care via the development of specific care plans that coordinate treatment regimen, follow-up care, and
behavioral recommendations. (4) A greater number of minority and underserved populations need to be included in clinical studies.

Question and Answer Session Transcript:

Thank you for that presentation. Thanks. I had a question about the epidemiology research that you've done with prostate cancer. You take out more tumor, you have a better survivor if you metastatic disease, and whether there's only a small number of METs versus a large number. How do you apply that to other cancers? Particularly ones where there are a small number of patients, or where the metastatic disease doesn't behave in the same way, there might be lots of different METs.

How do you how do you apply that? How many patients would that take? How easy would that be to do?

Right. So that is not my area of research, but my understanding in reading the literature is that that specifically works when there are a small number of metastases at the time of diagnoses. And so removing of that initial tumor burden increases their survival, and the treatment efficacy of the additional metastatic sites.

Yeah. So I had a question about the epidemiologies, the barriers, that you were talking about there at the end, because the lack of consistent standards across epidemiology--

Right.

--studies has plagued my research as well. What sort of suggestions you would have to provide standardization across different studies, and able to better integrate all of these things to provide larger cohorts and better understanding of the various epidemiological factors?

So understanding that every study will have its specific outcomes, but, for example, perhaps there could be guidelines that state that each study should at least look at time to progression. Maybe there are two or three outcomes that where there can be a consensus where if you're a randomized control trial, these are the endpoints that you should include, and open and leave it open for people to include others as well. But at least there will be basic endpoints that can be used for comparability.

With regard to survivorship, at least commission on cancer facilities are going to be mandated to maintain a survivorship program by I believe 2017 or 2018--

Right, I've heard it.
From your study population, do you know what percentage of patients were treated in institutions where there's existing survivorship program? There's going to be no requirement for survivorship programs outside of commission on cancer.

So the data that I showed you about the patients that were less likely to have follow up care was from our Siteman Cancer Center. It was from our single site where they are in the process of developing survivorship care plans. I don't want to say that the one has not been developed yet, but I know that they have started off working with breast and a couple of other cancers. And so it's not completely funneled all the way through to the patients yet, but I know it's something that they've been working on.

So I have a question about the primary tumor data. I am curious to how strong that data is. It seems like if it were really mechanistically-- I'm trying to get at it, I know that's not your area. But I wondered if we could have the data inform us better. If the primary tumor was leading to greater metastatic events, I feel the phenotype may be not so subtle. But maybe if it's allowing a patient to tolerate therapy in the future better, I wondered if it would be more subtle. And maybe that's not even the right way to think about it, but that was my first question, if the data helps with that. Does it look at overall survival? Does it look at time to progression?

And then the second question I had was about with patients that weren't following up, that wasn't required. They weren't on a trial, right? The people that you said didn't come back.

OK, so I'll answer the first question first. In terms of tumor burden, remind me. So the specific question about removal of the tumor burden.

Right, because just the background, in the basic science world more, I would say, but it comes up a lot in my world in pediatric cancer oncology, for example, whether you should be targeting the primary tumor. If it can't be resected, for example, but you can do other therapies. Or if it can be resected at maybe a big cost, I would say, like relevant other cancers.

Judah Folkman hypothesized that if you remove the primary tumor, you're enhancing this metastatic phenotype. It's taken on a life of its own over the years since then, but it was a good hypothesis I'm sure. Dr. Jain can add more about it. But I was hoping the actual epidemiology data would help to answer some of those big picture questions that have been in the field.

So the epidemiological data are mixed. It's that the data, like I've presented, is so striking when you see that it is more suggestive that it will provide a survival benefit. Although there are studies that say that prostate cancer biology is different from that of breast or colorectal cancer, where other studies, larger studies, this has been done. And it's done more routinely, and they say that the biology of prostate cancer is such that it not necessarily will provide the same survival benefit that's seen in other cancers, like breast or colorectal.
Your second question, these individuals were not on a trial. They were recruited into a prostate cancer prospective study and consented to long-term follow up. And so every year or two years, they are contacted again, either through mail or phone, to see if they've been back in, what their PSA levels are, if they've gone to another institution for further treatment. And that's when we started getting these responses and what prompted us to actually look at what the follow up was like.

All right, great. I'm sorry, I'm going to have to cut off. We're a little bit over time on the Q & A. Again, you can find a speaker at the break or after the event closes. Next up is Dr. Dizon, so we're going to change the slides up and we'll get started. So in your packets, you just flip backwards since we did change up the order there briefly. Thank you.
Looking Beyond Novel Targets: Social Networks and Survival

Don S. Dizon, MD

Massachusetts General Hospital Cancer Center

Dr. Dizon spoke about the association between social networks and survival, indicating that social isolation increases mortality rates in cancer patients. In his presentation, he highlighted studies investigating the role of social networks in extending the lives of patients, major gaps in research, major barriers that inhibit progress, and recommended initiatives to accelerate clinical and translational research in this field.

The five most important research findings that extend the lives of patients with metastatic cancer:

1. Social networks are critical to improving survival in cancer patients. However, this phenomenon and the role of social interventions on improving patient outcomes is not yet well understood. Based on a 2007 study, “support” was defined differently by women with cancer, with 47 percent describing it as emotional and 22 percent describing it as both structural and emotional support (Dizon, Gass, Bandera, Weitzen, & Clark, 2007). In addition, 54 percent of women did not identify their partners as their primary source of support. Furthermore, a 1992 study by Williams et al., indicated that unmarried patients with coronary artery disease had an increased risk of death (Williams et al., 1992). Additional studies indicate that the driver for this phenomenon is the presence or absence of emotional support, as indicated in a study of patient survival following myocardial infarction (Berkman, Leo-Summers, & Horwitz, 1992). A 2006 study by Caroline Kroenke et al., assessed more than 2,800 women with breast cancer at various stages to determine the effect of social networks on this particular study population (Kroenke, Kubzansky, Schernhammer, Holmes, & Kawachi, 2006). The results of this study indicated that social isolation defined as the absence of close relatives, living children, or friends significantly increased the risk of mortality in women with breast cancer, independent of marriage status, involvement in religious/community activities, or the presence of a confidant (Kroenke et al., 2006).

2. In a 1994 study of 525 black and 386 white women with recently diagnosed breast cancer, lack of emotional support consistently correlated with poorer prognosis in both groups, albeit more so in black that white women (Reynolds et al., 1994).

3. Interventions that address support, primarily via support groups, have yielded mixed results. A 2007 study by Spiegel et al. indicated that support group therapy did not improve survival in patients with metastatic breast cancer. The Life After Cancer Epidemiology Study published in 2013 investigated the effects of social networks on mortality risk in women with invasive breast cancer between 1997 and 2000, finding that although the size of a patient’s social network was not associated with lower mortality, the quality of the social network improved mortality in these patients (Kroenke et al., 2013).
4. In 2010, a study published in the New England Journal of Medicine of patients with recently diagnosed non-small cell lung cancer receiving either early and extensive palliative care (i.e., illness-related education, symptom management, decision-making support, coping assistance for patients and family/caregivers, referrals to additional care providers, and prescriptions) or standard oncologic care found that patients receiving palliative care had a significantly higher rate of survival than patients receiving standard treatment (Figure 10) (Temel et al., 2010).

5. A recent meta-analysis assessing the role of palliative care in patient outcomes indicated that although there was no improvement in overall survival and symptom burden, patient quality of life was improved at the 1–3 month follow up (Kavalieratos et al., 2016). However, additional studies are needed to better define the role of palliative care in metastatic cancer patients and the populations that would most benefit from this intervention. One theory indicates that a patient’s behavioral actions can affect the immune and neuroendocrine responses and ultimately improve patient outcomes (Costanzo, Sood, & Lutgendorf, 2011).

**Three major gaps in the field of metastatic cancer research:**

1. It is unknown what the future directions are in the topic of support networks and their effect on patient outcomes.

2. There is an insufficient understanding of the mechanism by which emotional support improves patient outcomes.

3. If the observed effect of social networks on patient outcomes is real, it is unknown how this impact can be maximized to benefit patients.

- **Collaborations required to meet these gaps:** N/A.

**Major barriers that inhibit progress towards extending the lives of metastatic cancer patients:**

Scientific Barriers: (1) The data currently available in this field are not conclusive and the definition of “support” is variable between patients. (2) In addition, disparities (e.g., race in terms of cancer biology as well as differences in support needs) can impact clinical trial design. (3) Currently, clinical trials are focused on patient response rates and survival as outcome measures and not on the effect of social networks on patient outcomes.
Programmatic Barriers: The science is focused on specific areas and does not take into account or focus on the potential effect of other factors, like social networks, on research and patient outcomes.

Suggested ways to overcome these barriers: N/A.

Initiatives needed to accelerate clinical and translational research: (1) Provide funding to investigate the role of social support in metastatic cancer. This should include investing in pilot trials. (2) Promote an interdisciplinary approach to clinical trials aimed at studying novel therapeutics. (3) Consider quality of life while aiming to extend the life of patients. Notably, if palliative care simply improves the emotional state of patients, it is an investment that is worthwhile.

Question and Answer Session Transcript:

All right, great. We'll start the clock for questions from the Task Force. Howard? Do you have one from Dr. Gable?

Hi, very nicely done, thanks. So what I heard was that it seems as though some things in palliative care influence survival, but we're not sure which. Any recommendations on how to tease those out?

Obviously if you were going to tease it out, it would take a multi-year commitment, and study each one of those interventions separately. And I don't think that's feasible, at all.

All right.

Well-- oh sorry.

I'm just going to suggest, I think the Temel paper showed it wasn't actually palliative care, it was a palliative care consult that they received, not to correct you too much.

Great.

And I think the theory is that what happened is those who got a palliative care consult, when they went through first-line chemotherapy in lung cancer and then progressed subsequently, when they went past the evidence-based treatments, rather than going on third-line therapy where there was no evidence for it, they opted not to go on desperation chemotherapy-- third-line, fourth-line chemotherapy-- and instead went on supportive care and palliative care at that point, rather than going on chemotherapy. And as a consequence, they didn't get the side effects, or the ill effects, of the chemotherapy at that point in time.
Which actually raises a good point, because it might have been that treatments-- Not only, did it prolong their life, that they didn't go on the extra chemo, but it also improved their quality of life, that was also improved.

Yeah, but I can say from the Mass General perspective that the palliative care consults do cover every aspect that was in the Temel paper as part of their standard. And as I've talked about the intervention with colleagues across the country, it is highly an unfeasible thing to roll out. In Boston, we are trying to do a palliative care consult in our satellite clinic, and having great difficulty even in providing it in a satellite.

There's already been a second randomized trial published which confirm the findings.

Right, that's the-- I forget the name of that. But, yeah, the thing is that the caregiver's also benefit. But to the question you have asked, is there a specific component that benefits? I don't know. Or is it the whole kit and caboodle that needs to be rolled out? But I think if you wanted to address that, it would be to take each one of those components separately.

But again, I have to caution. The lung cancer trials have been positive. I would say that it's not a safe assumption to believe that survival will be improved across cancer types. I think that that data point, we need to see.

Dr. Kohn?

Don? I'm going to start off first with my hat as a patient advocate. I think that you and I, and many of our immediate colleagues, learned from our gynecologic cancer patients that we don't salvage patients. We don't give salvage chemotherapy, we give subsequent chemotherapy.

Correct.

Right. So I think one reason that patients, certainly when I observe in my own clinic, react to terms hospice and palliative care. And may seem too many in the room that it's semantics. But when you sit on the other side, and I don't know how many in this room besides my colleague in front of me and myself and the advocates, actually do have a foot in perhaps both sides.

But it's a very different thing. So I think one, it may seem silly, issue would be to change the word. But my question to you on behalf of the Task Force is, if this is as daunting a task, can you tell us what might be needed? Are there adequate tools? Are there tools that are harmonized, or harmonizable across cancer situations so that we might be able to get adequate power and information across cancer types, which might allow us to get information more quickly? So really it's about the tools and the direction that we need to go to add to your comment about directions.
So two things on that. There was a very nice study out of MD Anderson that showed exactly what Dr. Cohen has showed. If you call something palliative care, the uptake is low. You change the name to supportive care, the people will come. So I think one of the plaguing things in palliative care research is the fact that we continue to require it be called palliative care. Perhaps that is something the Task Force can keep in mind.

To address the second question, there has been some work that ASCO, the American Society of Clinical Oncology, and the Palliative Care Society have come up with guidelines as to what can be done by the oncologist in the realm of palliative care. So that document I'm happy to send it to Elise or to somebody to look at, and make at your disposal. But it does provide a roadmap on how palliative care can be delivered across cancer centers and across institutions. I think it's ripe to be tested across cancers, but there is a bit of guidance, yeah.

So I wasn't just asking about guidance, but are there appropriate tools to investigate and to advance this area, or is the development and validation of tools an unmet need in order to move this segment of metastasis and metastatic cancer research forward?

As far as I know, and maybe, Bettina, you can answer as well, I do not know of any specific tools in the palliative care realm. Many of our studies right now are using the patient reported outcome measures—(PROMS) questionnaires-- and picking out the specific ones to roll out in the context of a randomized trial.

All right, we do have time for two quick questions. Dr. Scher, I know I cut you off before, my apologies. Please go ahead. Can you turn your mic on?

So if you had, let's say, a blank slate, and you would approve this concept, where would you start, and how would you do it?

If I had a blank slate, I would roll it out in the context of a Phase of an early clinical trial, preferably randomized Phase II. Because I think we are all going more towards more precise subgroups, and I think the less variability introduced into the patient selection, the easier it's going to be to answer such a question as social support, and its impact on survival. So I'd do it in the context of an early clinical trial, preferably with a randomization.

I would try to choose an intervention, and this is where the ground is still moving quite quickly. But I would try to test an intervention that was acceptable to an advocacy group. And, quite frankly, the interventions I'm most interested in testing are on social media, the role of health care communities on social media, and see how that influences survival in the context of a randomized Phase II trial. That's what I would do.

All right, and our final question. Ma'am, back there. The mic on?
Yes, I think the most successful social support, actually, comes from patients that are going through exactly the same thing. Those are the ones they relate to, and that's probably why the spouses weren't mentioned more frequently, as much support as they are, that they're not going through the same thing. My non-profit's developed a really good program along that line. I'd like to speak to you about it later, you might be interested.
State of Metastatic Cancer Research – Thoughts from a Dermatologist and Cancer Geneticist

Hensin Tsao, MD, PhD
Director, MGH Melanoma and Pigmented Lesion Center
Professor of Dermatology at Harvard Medical School

Dr. Tsao discussed the role of targeted therapy and immune cells in metastatic melanoma. In his presentation, he highlighted the five most important findings that can extend the lives of patients, major gaps in metastasis research, major barriers that inhibit progress, and recommended initiatives to accelerate clinical and translational research.

The most important research findings that extend the lives of patients with metastatic cancer:

1. Survival of metastases is a direct function of tumor thickness (Figure 11) (Balch et al., 2001). Notably, there is a direct correlation between thickness and metastatic potential. Genetic drivers have less impact on risk than pure growth kinetics.

2. The identification of some of the major pathways involved in melanoma that can be exploited in the development of targeted therapies has been a major advancement in the field. In melanoma, BRAF and MEK are two well studied targets. In addition, receptor tyrosine kinases such as KIT, and cell cycle inhibitors such as CDK4 inhibitors are also targets of melanoma. Targeted treatments with vemurafenib, a BRAF kinase inhibitor, resulted in a significant reduction in metastatic lesions in patients with metastatic melanoma that had a BRAF V600E mutation (Chapman et al., 2011). Six months post-treatment, overall survival was 84 percent (95 percent confidence interval [CI], 78 to 89) in the vemurafenib-treated group and 64 percent (95 percent CI, 56 to 73) in the dacarbazine-treated group. In the interim analysis for overall survival and the final analysis for progression-free survival, vemurafenib was associated with a relative reduction of 63 percent in the risk of death and of 74 percent in the risk of either death or disease progression, as compared with dacarbazine (p < 0.001 for both comparisons). After review of the interim analysis by an independent data and safety monitoring board, crossover from dacarbazine to vemurafenib was recommended.

3. Melanocytes are immunogenic and 3 percent of patients with stage IV melanoma develop vitiligo. Vitiligo-like depigmentation in patients with melanoma is associated with a more favorable clinical outcome. In a recent study, vitiligo was associated with 75 percent reduction in mortality (Teulings et al., 2015). Furthermore, immune cells are able to...
recognize native melanocyte antigens without the use of immune therapy. As a result, many agonist antibodies and inhibitory antibodies are currently under development. An example of such drugs ipilimumab, which is an anti-CTLA-4 receptor antibody that has been shown to be effective in patients whose tumors have a greater number of missense mutations (Boussiotis, 2014).

4. It is possible to inherit metastatic potential lethality. For example, because BAP2 loss facilitates metastasis, patients with germline BAP1 mutations are more likely to develop lethal ocular melanomas (Njauw et al., 2012). Therefore, survival of melanoma may be effected by heritable defects in pathways involved in metastasis and autoimmunity.

Three major gaps in the field of metastatic cancer research:

1. There is a lack of understanding of the high rate of recurrence following the use of targeted therapies, such as BAP kinase inhibitors. It has been suggested that the metastatic cells are not completely eliminated. In addition, multiple resistance mechanisms have been identified that do not presently have solutions to overcome them.

2. There is a lack of understanding of the metastatic phenotype of melanoma. There is a specific feature of melanoma, ulceration, which has been characterized as decreasing survival rate and increasing the risk of metastasis by approximately 10 percent. The molecular pathways underlying ulceration are yet to be defined; however, it serves as a phenotypic marker of melanoma aggression.

3. Society is still plagued by the lack of early melanoma detection. There is no barrier to visualizing a melanoma; however, there is a lack of melanoma recognition.

- Collaborations required to meet these gaps: N/A.

Major barriers that inhibit progress towards extending the lives of metastatic cancer patients:

Scientific Barriers: (1) There is a need for new murine models that are not inbred strains. (2) There is a need for better tissue engineering to develop improved host-derived tumor models that represent both non-tumor and tumor tissues. (3) The immune system needs to be incorporated into functional assays. (4) There is a wealth of data but not enough bioinformaticians with a background in cancer to analyze the data and create standardized approaches. (5) There is a need for improved ex vivo methodologies that better predict outcomes.

Programmatic Barriers: (1) There are too many clinical trials aimed at developing new drugs or analyzing the best combination of therapeutics (in the correct sequence and dose) and not enough patients to participate in these studies. Trials are aimed at developing new drugs and not invested in better defining already existing drugs. (2) There is a lack of motivation to track patients once the FDA approves a drug and its use becomes “ad-hoc” within the community. (3) There is too much competition securing grants and publishing and too few collaborations.

- Suggested ways to overcome these barriers: (1) Initiate a national bioinformatics approach
to big data that would create standards of practice for all researchers to follow. (2) Develop a community outreach program to track when study participants are taking a drug, the sequence in which the drug is taken, and outcomes from patients and healthcare providers. (3) New models of collaboration, new rewards, and new incentives from academia and funding agencies. For instance, academia could begin to change the criteria required for promotion and funding agencies could offer a greater number of multiple primary investigator grants to incentive cross-disciplinary collaborations.

**Initiatives needed to accelerate clinical and translational research:** (1) Allot funding for the creation of platforms that facilitate rapid preclinical testing of therapeutic combinations to determine mechanisms of drug synergy. (2) Create improved methods of capturing outcomes in the non-trial (i.e., community) setting through the use of EMRs, crowdsourcing, new technologies, etc. (3) Use vanguard technologies, such as liquid biopsies or circulating DNA, to track disease burden. (4) Redefine the way academic institutions promote primary investigators, encourage multiple primary investigator grants, and create better avenues for bench scientists to think about and access “big data.”

**Question and Answer Session Transcript:**

Hensin. Great talk, enjoyed that. One question I have is about, if you are going to create these platforms for rapid pre-clinical testing, and the problem is that you have all these different various combinations, is your goal to test all the combinations in these pre-clinical models? Or do you, how do you prioritize which combinations you're going to be testing?

There are different ways you can approach it, I believe. I think you start with obviously, what's known as standard of care. You wouldn't sort of just randomly do all of them. There must be a strategy, per se, that you might be able to layer upon different ways of analysis. So for instance, if you're looking at, you're looking at the first drug and you're looking at the ones that are most effective. And you're layering on top of that, for instance, a second drug looking at combinations, and this is what I'll talk about. What you may want to do, is choose something not necessarily at a toxic level, but see where you might start developing synergistic effects. So I think one of the things I did talk about, was if you're going to start thinking about combinations, you have be more and more rigorous in terms of really calculating synergy, calculating antagonism, and seeing how these sort of combinations sort of work out. But certainly I think, if you're moving towards the animals, you're moving towards human trials, you start at least at the backbone of what's already been approved, what's known to work at some level. And it's hard. You know, melanoma, we think of as a common skin malignancy sometimes. But it's a relatively rare cancer, still with 10,000 deaths. I think the kind of leveraging you want to do really will start when the more common cancer's out there, for sure. So following up the discussion we had after my talk, so how would you formally link co-clinical pipelines for your mouse model or in vitro models, to the clinical works? So what would be the integrating principle? When do you do what? Midair when you were talking. Perhaps you can just quickly give me a 10-second thing. What was the pipeline you were talking about? Because I wasn't here for your part of the talk, unfortunately.

So it was about that we learned from pre-clinical models, how different steps of the metastatic cascade, kind of intravasation, survival in the bloodstream, extravasations, survival in the secondary site, growth, how that aligns with what we see clinically. And there is, number one, a black box in the pre-clinical world. And number two, clinically the concepts are very immature.
When do we see metastatic progression? When do we see survival, secondary outgrowth, new arrival versus outgrowth of preexisting clones? So that was the punchline. And so, you touch upon exactly the same points here.

Yeah, I think some of the vanguard technology that I was thinking, and I'm sure you probably brought up a lot of that in terms of trying to capture, for instance, circulating cells, trying to get some of the signatures through circulating DNA. Trying to understand, for instance, whether the circulating cells themselves are the ones that are contributing more to the survival within the different organs. I think, obviously, it's a barrier out there for capture, in terms of trying to get some more deposits in that. One way has been sort of rapid autopsies, for instance, to try to get to as many tissue specimens as possible, as rapidly as you can, obviously. In terms of mice models, certainly I think, to understand the progression of tumors in different backgrounds that you could potentially CRISPR in, like BAP1, something that we're doing. And perhaps looking at how that influences the metastatic potential. Allows you to start playing again, with changing some of the germline influences for metastases.

So how would you link this to the clinical pipelines?

In terms of the therapeutics?

In terms of target selection, in terms of procedures. Are they synchronized? Are they independently occurring?

Well, I think an ideal setting, which you have a large cancer center that has funding to capture all of that information. I think the electronic medical record is huge. That's what you're talking about in trying to capture some of the phenotyping. I think we need to standardize the kind of information we're willing to capture within the electronic medical record. And not sort of base it on ad hoc texting of information. I think we need buy-ins from pathology, again, to do the exact kind of things we're talking about. I think what we could do is first line analysis upfront when the tissue's still fresh, and have a virtual repository of data. Next gen sequencing information of tumors have been exposed to this drug. And have that as a virtual repository information that you can sort of mine at some point. I think right now there's a lot of tumors being captured. They're sent to different individual places. And individual places are looking at different individual markers. If there's some way to track that back so that one of the obligations, for instance, of getting tissue from a certain center is to return the data to a large shared pool. I think that'll be very helpful to tie into the original medical records system. So I think it has to do with a lot of the relationships that we build on the team level, the incentivizing. And obviously, finding the funding to sort of do all of that information. But I think a lot of data are being generated and perhaps some of it redundantly. And one of the ways to get to what you're talking about perhaps, and streamlining it, is to get all those sort of groups again, to commit to returning some of the data back to a central place.

Right. One quick comment and then we'll be moving on.

The very tight correlation between sickness and metastatic activity in melanoma is a little bit surprising because, on the other hand, you have a very strong influence of immune surveillance. And you would think this immune surveillance co-factor should make the correlation between tumor thickness and metastasis less strong. Unless the immune
surveillance only plays a role for the primary tumor growth, but not for the metastasis.

It's possible that's a local surveillance problem. One thing I didn't mention is, we do know that ultraviolet (UV) light is an immunosuppressant. And that has been shown over and over again in different, in fact, one of the therapies is UV light to suppress the immune system. So I think what you're getting at is incredibly insightful. That the local immune reaction, what is happening there, is obviously a critical component of what's going beyond systemic.

So my understanding is that Dr. Judah Folkman had suggested the possibility that thickness is related to microvascular density in that region. And microvessels are needed for cells to leave. So that, what he proposed, I think, at least in one article as a potential reason why thickness correlates with the metastasis. Similar to what, he had a paper with one of his fellow in New England Journal of Medicine about microvessel density and hot spots in breast cancer and metastasis. Whitener, is that the name? Who went and became Chief of Pathology at UCSF.

I think there's a good about, Judah did a lot of beautiful work on that. On whether certain subclones of melanoma, microsatellites, as they're called, certainly locally, are more antigenic, for instance. And perhaps recruit in the scaffolding of the vessels that allows it to sort of go. And perhaps as they progress deeper in the anatomy, that sort of phenotype gets switched on in some ways. And then it becomes more and more metastatic potential because of it.
Ovarian Cancer Metastasis: Mechanisms and Therapy

Anil K. Sood, MD

Vice Chair, Translational Research in the Departments of Gynecologic Oncology and Cancer Biology

Co-director, Center for RNA Interference and Non-coding RNA

Director, Blanton-Davis Ovarian Cancer Research Program, MD Anderson Cancer Center

Dr. Sood discussed the highly variable, histologically diverse characteristics of ovarian cancer that have various routes of metastasis (Naora & Montell, 2005; Rose, Piver, Tsukada, & Lau, 1989). In his presentation, he highlighted the five most important findings in ovarian cancer research that can extend the lives of patients, major gaps in ovarian cancer metastasis research, major barriers that inhibit progress, and recommended initiatives to accelerate clinical and translational research.

The five most important research findings that extend the lives of patients with metastatic ovarian cancer:

1. Identification of patient-specific oncogenic vulnerabilities early in the disease progression is key to selecting the appropriate therapy. Germ-cell, stromal, epithelial, and metastatic ovarian cancer types are very diverse. Even within serous tumors of epithelial cancers, which represent approximately 70 percent of ovarian cancer cases, there are significant differences in the genetic characteristics of low grade and high grade serous tumors (see call out box). These genetic differences provide insight into the treatment that is predicted to have the most therapeutic potential.

2. Implementation of a personalized surgical care strategy for ovarian cancer patients. The recently developed Anderson algorithm provides a laparoscopic quantitative assessment of seven different regions within the abdomen and pelvis to predict the success of completely resecting the visible tumor (R0). Each region assessed receives a score of zero to two. If the aggregated score is less than eight, then primary tumor reductive surgery is considered feasible. If the aggregate score is greater than or equal to eight, the patient has a poor chance of achieving R0 resection and instead receives three to four cycles of neoadjuvant chemotherapy before undergoing tumor reductive surgery. Since implementing the Anderson algorithm, primary cytoreduction R0 rates improved from 25 percent to 86 percent (n = 103) (Nick, Coleman, Ramirez, & Sood, 2015). Patients who underwent neoadjuvant therapy followed by interval cytoreduction had improved R0 rates from 60 percent to 81 percent (n = 204).
3. Clinical trials designed around tissues that receive an Anderson score. The tissues obtained from initial laparoscopy are used as a baseline. Patients with an Anderson score of less than eight are administered a novel or standard therapy for 1–2 weeks. After treatment, patients undergo cytoreductive surgery and the retrieved tissue samples are matched to the site from where it was originally obtained for pharmacodynamics studies. Patients with scores greater than eight are treated with a novel drug along with neoadjuvant chemotherapy. After interval cytoreduction, additional tissue samples are obtained without having to implement an extra procedure.

4. In 2014, two biologically targeted drugs, Bevacizumab (anti-VEGF) and Olaparib (PARP inhibitor), received FDA approval to treat ovarian cancer. Prior to 2014, the vast majority of drugs used to treat ovarian cancer were cytotoxic agents.

5. Overall survival rates previously used to measure therapeutic benefits of new drugs or therapies are not a good endpoint for determining effectiveness in ovarian cancer. Instead, selecting endpoints within the progression-free survival (12–28 months) and post progression survival (12–38 months) phases are more realistic endpoints.

**Major gaps in the field of metastatic cancer research:**

1. The metastatic mechanisms of ovarian cancer are poorly understood.
2. Mechanisms of tropism for unique metastatic sites are also not well understood.
3. There are variations in therapeutic response rates at different metastatic sites.
4. There is no way of reliably assessing a small amount of metastatic cancer.
5. There is a lack of understanding of clinically meaningful predictors or determinants of tumor dormancy/latency versus rapid re-growth.

- Collaborations required to meet these gaps: N/A.

**Major barriers that inhibit progress towards extending the lives of metastatic cancer patients:**

Scientific barriers: (1) A lack of a highly sensitive imaging and detection methods for ovarian cancer. (2) Multi-dimensional models of cancer cell and microenvironment interactions have not been tested. (3) Models reflective of human disease patterns are not consistently available.

Programmatic barriers: (1) Research in the field of ovarian cancer has been performed in silos with limited cross-disciplinary investigation.

- Suggested ways to overcome these barriers: To move the field forward there is a need to incentive more collaborative research between disciplines.

**Initiatives needed to accelerate clinical and translational research:**

1. Promote information-rich (tissue and liquid assessment) clinical interventions. (2) Develop systems and multi-dimensional understanding of metastasis. (3) Require cross-disciplinary investigation (4) Provide
Question and Answer Session Transcript:

Hi, there. Jeremy Perkins. I'm a medical oncologist, so constantly fascinated with gyn-onc and because it has such a distinct paradigm on going after disease that has clearly spread beyond the organ and the regional lymph nodes. What's being done in ovarian cancer that kind of stuns you as not being extrapolated to other tumor types? And then maybe another way of looking at it is, what's occurring in other tumor types that you really wish could be translated better into ovarian cancer?

Very important questions. With regard to ovarian cancer, that perhaps offers opportunities for other cancer types, as well, there are many such areas. But one perhaps area is that, we know that only about 1/3 of a high grade serous ovarian cancers have T cells within the tumor islets. And those patients tend to do well, no matter what you give them. The remaining 2/3 don't. They have peri-tumor or very poor immune cell penetration. So understanding what those mechanisms are that prevent T cell entry and how to improve immune access, I think are opportunities for ovarian, as well as other solid tumors, as well. Another area I think, would be to really define which patient groups are those that would truly benefit from surgical resection to the extent that we defined here. Again, in some of the other tumor types, there are small studies that keep, that perhaps are intriguing where surgical resection may indeed play a role, even with a metastatic disease. With regard to learning from other diseases, one example would be that for triple negative forms of breast cancer, neoadjuvant therapy at MD Anderson has really become the way that treatment is started at this point. And more than chemotherapy, there are some neat opportunities for introducing novel drugs that can have remarkable effects in that space. So far, I think we've not exploited the neoadjuvant space in ovarian cancer to the extent that we could or should moving forward.

I was going to ask about that. In the study that you were proposing where the scores are high and they need neoadjuvant chemotherapy first, and you're adding novel drugs, how do you actually know the benefit of the novel drug, without randomizing those patients into the carbotaxol alone versus the novel drug?

Great question. So after the neoadjuvant therapy's completed, at the interval setting, randomization can actually also occur. So that if you start off with neoadjuvant therapy alone, after that you can randomize adding a new drug or continue with your chemotherapy. So far, the trials that we're doing are primarily looking at either molecular or immune-based endpoints. But to truly gain, to truly figure out the magnitude of effect, you're right. You would absolutely need randomization. But we think there are different nodes where you can randomize, including after the point of interval debulking.

I'm assuming in these studies you're also evaluating quality of life outcomes, as well.

Yes, we are. Yes. And not just quality of life, but even other patient-reported outcomes, yes.

I got a question. Great job. It's similar to pancreatic cancer in the sense you can have an R0 resection, no lymph node positivity, and then we can see the patient die with not any operative complications six months later. So you said something, unless I missed it, that you said that in
some of these patients that you downsize with neoadjuvant, they become R0. They don't do as well, right? So does that imply maybe that there's a chemo-resistant selective pressure that we're putting on these patients? That those micro, metastatic disease or something might be selecting for more powerful clones? Can you comment on that?

So that's a theory. That there may be subgroups of patients where that indeed may occur. But you know, but the patterns of response are so different and we understand so little about that. Let me give you an example around that. I don't think I knew that in ovarian cancer, you could achieve a pathologic CR just with neoadjuvant therapy. Well, now we know that about 5 percent of the patients, you can actually achieve a pathologic CR. Well, who are those patients compared to those where there's limited response, if any? Those are some of the questions we're now trying to tease out, both at the molecular and immune level, as well. And part of the reason why some of those who progress rapidly after the interval debulking are very likely those patients that you alluded to, where you're selecting for more resistant disease.
Towards Curative Approaches for Metastatic Cancer

David E. Fisher, MD, PhD

MGH Dermatology, MGH Cancer Center, Harvard Medical School

Dr. Fisher discussed the development of targeted therapies and immunotherapies for metastatic melanoma. In his presentation, he highlighted the most important findings that can extend the lives of patients, major gaps in metastasis research, major barriers that inhibit progress, and recommended initiatives to accelerate clinical and translational research.

The most important research findings that extend the lives of patients with metastatic cancer:

1. Recent successes in immunotherapy are a result of an increased understanding of the genomics of melanoma and its underlying driver and passenger mutations. UV mutations are extremely common in melanoma; specifically, UV-associated neoantigens have been found in passenger genes.

2. Melanoma is one of the few cancers for which the primary carcinogen has been identified. However, despite the known risk from UV radiation, unsafe behavior is still quite prevalent. One potential explanation is that there is evidence of UV-associated endorphin synthesis and addiction-like behaviors.

3. There have been two major breakthroughs in targeted therapies in the last 5–10 years:
   a. The discovery of the negative side effects of V-Raf murine sarcoma viral oncogene homolog B (B-RAF) inhibitor therapy used as a monotherapy. B-RAF-targeted therapy using B-RAF kinase inhibitors has been used in the past because ~50 percent of metastatic melanomas contain an intrinsically activating kinase mutation and the B-RAF oncoprotein. This mutation activates the mitogen-activated protein kinase (MAPK) pathway, and has an antagonistic relationship to C-RAF. Thus, B-RAF inhibitors (e.g., vemurafenib, dabrafenib) hyper-activate C-RAF signaling. B-RAF inhibitors are therefore associated with very significant toxicities, including malignancies.
   b. The second breakthrough is a partial solution to the first: the combination of B-RAF targeted therapy plus a MEK inhibitor (e.g., trametinib) is more effective and less toxic. Individuals with the B-RAF mutation have a high rate of response to this combination therapy (80–90 percent), but the magnitude of response is limited and complete remissions are relatively rare.

4. There have been two major breakthroughs in immunotherapies in the last 5–10 years:
   a. The first breakthrough is in the use of individual immune checkpoint blockade with CTLA-4 or PD-1. There is a correlation between the magnitude of mutational burden and neoantigen burden. Patients with a higher mutational burden and neoantigen load have a higher likelihood of responding to CTLA-4
b. The second breakthrough is in the use of combination immune checkpoint blockades (CTLA-4 and PD-1). In a preclinical mouse model of immune-intact melanoma, the presence of UV-neoantigens conferred responsiveness to immune checkpoint blockade. The neo-antigen devoid cell line derived from the immune-intact model provided a model of immunotherapy resistant cancer. Thus, if there is an inflammatory microenvironment within a melanoma (i.e., a “hot” tumor), there is a significantly elevated chance that immune checkpoint blockade is going to be effective, whereas “cold” or sterile tumors are unlikely to respond. When this melanoma devoid of neoantigens is treated with the combination of thermal injury (via fractional laser), topical imiquimod (a Toll-like receptor 7 agonist), and immune checkpoint blockade (e.g., anti-PD-1), the melanoma is bilaterally cleared (Figure 12). This response is dependent on cluster of differentiation 8 positive (CD8+) T cells.

Three major gaps in the field of metastatic cancer research:

1. Syngeneic preclinical models in immune-intact mice are needed across cancer types, especially immunotherapy resistant cancers. Opportunities to rescue the immune recognition and immune response should be identified because there is a window of autoimmunity that can be therapeutic and not toxic.

2. A more systematic study of pro-inflammatory treatments to “rescue” immune checkpoint responsiveness is needed. Some questions about immune checkpoint responsiveness are: Can we trigger an inflamed microenvironment and the neoantigens capable of being recognized by the immune system? Could there be strategies to restore an immune response if a tumor does not have its own genomically encoded neoantigens? Could we provide non-genomically encoded neoepitopes? Can we induce autoimmunity against normal proteins or normal peptides within the tumor microenvironment?
3. Additional work is needed to identify drug targets in “epigenetically” mutated human cancers. In these cancers, global regulation of gene expression is impaired and global misexpression results in particularly devious cancers. One potential way to treat this would be to target the synthetic lethality (i.e., unique vulnerability) of these epigenetically mutated cancers.

- Collaborations required to meet these gaps: (1) Clinicians working with laboratory researchers to integrate clinical observations with biopsy programs. (2) Cross disciplinary collaboration (e.g., immunologists and tumor modelers). (3) Immunologists working with clinicians to investigate tumor biopsies before, during and post-therapy.

**Major barriers that inhibit progress towards extending the lives of metastatic cancer patients:**

Scientific Barriers: (1) Preclinical immune-intact models of disease are vital, but very difficult to test in the laboratory. (2) Availability of human tumor biopsies before, during, and post-treatment. (3) New and better drugs (e.g., new checkpoint inhibitors, immune modulators, systems for preclinical assessment).

Programmatic Barriers: N/A.

- **Suggested ways to overcome these barriers:** N/A.

**Initiatives needed to accelerate clinical and translational research:** (1) Multi-cancer initiative on preclinical understanding and testing immune modulators would enable learning between malignancies, learning lessons from one disease, and applying them to others. (2) Rapid clinical testing of candidate immune modulatory approaches, and linking the results with biopsies. (3) Preclinical and clinical testing of epigenetic targeted therapies.

**Question and Answer Session Transcript:**

That was lovely. I want to connect Dr. Sood's talk. He very briefly mentioned that high grade serous cancers are a cancer of copy number. They're not a cancer mutation. Obviously, you can still disrupt and get funky proteins, my very scientific description.

The question that I have is, since there are a number of different cancers that either have quiet genomes or have a different mechanism of genomic disruption, how can you take the lovely work that you've done there and how would you suggest or direct or, the way you can move it forward in a setting where it's a copy number or it's a quiet genome. Where there's still this excitement that this has to be the curative approach.

So I would say, I think that if we are able to, in a sense, the strategy that I was describing is inducing autoimmunity. And it is inducing autoimmunity against normal proteins or normal peptides within the tumor microenvironment.
So the goal actually, is to instruct the immune system to destroy and target normal proteins that are on the surface of, for example, we had a pancreatic cancer cell line. BRAF, I'm sorry, Kirsten rat sarcoma viral oncogene homolog (KRAS P53), that had absolutely no response whatsoever to anti-PD1. But when this thermal injury plus imiquimod and then anti-PD1, 70 percentagesystemically were disappearing.

We are, the only thing we can imagine that is being recognized, I mean it is possible, there's an NK response. We've actually done a huge amount of immunophenotyping. We don't think that's the case. We believe that there is a window of autoimmunity that can be therapeutic, and not toxic. And that I would say is one theoretical approach.

I should actually mention another that is being studied by quite a few people. There actually are certain cancers that have a surprisingly good response to anti-PD1. In fact, renal. Kidney, happens, although it's not funded as well as it should be, as we heard about before, actually has shown significant response over many decades to immunotherapy for reasons that just aren't clear.

Now the genome has largely been studied by TCGA. And it's not like melanoma. It doesn't have that vast, heavy mutational load. And yet it's unmistakable. Not just to checkpoint inhibitors, but all sorts of other immune therapies that have been used over the years.

So one hypothesis that is being proposed, that's I think quite an attractive one, is that there may be embryonic genes that are not expressed. They're expressed during embryogenesis, they're not expressed neonatology or perinatally around the time of immune education and tolerance education.

So the immune system never saw them, never tolerized to them. But later on, as we know many tumors dedifferentiate and show embryonic features, some of these embryonic proteins may come back on. And those may be sufficient to elicit an immune response.

This is an area of testing. And that actually opens, this is an interesting intersection with epigenetic therapy, because when you can manipulate gene expression, things can get turned on that weren't supposed to be there. And sometimes that's a good thing from the perspective of potential immune targets.

Have a, right here, ma'am.

Is it clear at all what the passenger mutations are that are driving this immune response?

So tomorrow, Steve Rosenberg will talk, and I'd be shocked if he doesn't talk about this because he's done probably the most elegant work in dissecting. And it is Herculean. You have to work at NCI and have a budget. Whatever, we can't afford to do this. But it is very, very, very, very difficult to predict. OK, I shouldn't have said that. Forget it.
I can just say that we're not able to do it. It is very difficult to predict the epitope that a T cell receptor will see, because it sees not only the peptide epitope, but it is linked to HLA Class I. And so there are many algorithms, and computationally it's not so hard to do it. Computationally it's not right very often.

What Steve has been able to do is predict and then test hundreds of peptides individually in separate clones of T cells from tumor infiltrating lymphocytes that they surgically resect. Take each of these clones. You know, test peptide by peptide and see one in 20 that really works and is really private for that patient and they know, and those are the instances. So there are some beautiful examples where the neoepitope was neoantigen, even genomically-encoded through the peptide and a T cell clone could be identified that was able to recognize it. The predictability of that is still not very high. There are attempts to make it more predictive, that 50 percent, 70 percent would be right. But one point is they're going to be different for every tumor.

Because these are mutations that are randomly distributed throughout the genome. They're going to be restricted by that person's HLA. So it's not like they'll be some generic vaccine. But when it works, you know, it's really spectacular.

Steve actually also had a paper in the New England Journal last week on a T cell response against a KRAS mutation, which is, that's the dream of dreams. If it might not be a passenger, but a driver mutation that the immune system sees. Of course, in their paper their proof was a clone that had kicked out the KRAS mutant allele and that resisted the therapy.

Question from Dr. Gable.

Yes, so you've shown and others, that the vitiligo is associated with tumor response. And that sort of makes sense. But what about other autoimmune phenomenon that we see with the PD1s and the CTLA? Are they associated with responses, as well?

That's a really good question. So in the case of PD1, I think generically people would say tends to correlate, but not very well. So other types. Like the odd autoimmune, like hypophysitis, for example, that that tends to happen. And of a variety, obviously, inflammatory bowel disease.

That was a little clearer in the case of anti-CTLA4, in the previous days. The overall response rate is significantly lower anyway. But seeing evidence of inflammatory bowel disease tended to be a sign of, you know, all hope is not lost. You might be one of the lucky responders. But even then, vitiligo would be seen. And I don't know the relative numbers, if anybody did them side by side.

Generally speaking, evidence of autoimmune side effects is a good thing to have. Ranking it relative to vitiligo would actually be a really great question. I don't know of anybody who's actually done that. But one point that I think is quite interesting is that the vitiligo, we think of it and we say well, it's autoimmune. And actually, no melanoma patient would forego immunotherapy because of the risk of vitiligo. But if you had pancreatic cancer, risk losing your pancreas. Lung cancer, your pulmonary epithelium. You know, these could be fatal.

It's really important that even when these patients develop vitiligo, they're getting it somewhere
on a patch. They might even get it on a large patch. But the vast, vast, vast, vast, vast majority of their melanocytes are still intact. And so there is a suspicion, and in our mouse models, we could often see a patch of vitiligo. But again, the vast, vast, vast bulk of the melanocytes were there.

So it could be that this kind of approach to immunotherapy, like other approaches, which actually are successful, cytotoxic therapy in leukemia in children, for example, does have a toxicity associated. Measurable, perhaps phenotypic, maybe not even phenotypic. But in order to barrage a new armamentarium against the tumor, the concept would be that there may be actually a window available for us. In fact, we even have some reason to suspect it's happening already. Because this vitiligo is happening in these patients, that already the neoantigens may be triggering the response. But we don't know how much of the actual tumor killing is happening from recognition of wild type epitopes.

All right. Final question here from Dr. Rivera and then we'll move to the panel.

Have you looked at other mechanisms of injury? Heat might not be safe in some organs, like hollow viscous, even pancreas. And then, is it is it improving immune access or surveillance? Do you have a sense?

Yeah, so we've actually looked at that a huge amount. We've also looked at some chemical modifiers that put Hapten's cross linking agents, and they have actually better activity actually. But we're very much in the midst of doing this. Some of those might be even treatable in vitro, and then you can inject it as a vaccine. I mean it opens up a zillion possibilities.

So we've done a good deal of immunophenotyping of the tumor. So in the studies I showed with the heat, especially, that's where we have the most data. Arlene Sharpe is an immunologist at Harvard Medical School. And she's done a lot of immunophenotyping with us. And basically what we see is complex. So we see a vast increase of activated CD8+ T cells, as opposed to suppressors, T regs. Inhibitory T cells. But there is actually an influx of inhibitory populations of cells, as well.

So it is a very polyclonal, very heterogeneous response. When we've sequenced the T cell receptors we're not seeing a few dominant clones. It's extremely heterogeneous. So much so that you can't actually make out exactly what is the signal. It's just a vast pro-inflammatory process.

So we know there's a cellular infiltrate. We know there's a cytokine storm within that microenvironment. But it's somewhat brute force at this point, I would say. It's a blunt
instrument. And the initial goal really was efficacy. And then perhaps tease out refinements at a later stage.
Targeting Metastatic Cell Heterogeneity to Extend Life of Stage IV Patients

Julio A. Aguirre-Ghiso, PhD

Tisch Cancer Institute, Icahn School of Medicine at Mount Sinai, New York

Dr. Aguirre-Ghiso discussed the heterogeneity of metastatic cancer and the state-of-the-science of dormant tumor cells. In his presentation, he highlighted the most important findings that can extend the lives of patients, major gaps in metastasis research, major barriers that inhibit progress, and recommended initiatives to accelerate clinical and translational research.

**The five most important research findings that extend the lives of patients with metastatic cancer:**

1. Dormant cancer cells persist in patients both with and without overt metastasis and can evade chemotherapy. Both dormant and proliferative cells can co-exist in patients with metastatic cancer (Harper et al., 2016; Hosseini et al., 2016; María Soledad Sosa, Bragado, & Aguirre-Ghiso, 2014). The process is driven by cross-talk between the cancer cells and their microenvironment and involves factors including adhesion signaling, stress-signaling, epigenetics, etc.

2. New markers and gene expression profiles are beginning to allow for the identification of tumor cells that are either dormant or reactivated. In addition, via the study of various tumor microenvironments (i.e., lungs and bone marrow) in an animal model, mechanisms of dormancy that involve factors such as TGFβ2 and NR2F1 have been recently discovered (Bragado et al., 2013; Maria Soledad Sosa et al., 2015).

3. There is currently a better understanding of and research investigating the reprogramming of malignant cells into a dormant state. In particular, the use of drugs such as azacytidine and retinoic acid, which epigenetically target the molecular mechanisms involved in dormancy, are being investigated in clinical studies to convert proliferating cancer cells into dormant cells.

4. Single cell transcriptomic profiling of cells from the bone marrow of prostate cancer patients with no evidence of disease after radical prostatectomy (but no other therapy) and prostate cancer patients with advanced metastatic cancer have been performed. Expression profiles of cells differed between the two patient groups and the cells from patients with metastatic cancer carry both proliferative and dormant cells, the latter of which were similar to the cells found in patients with no evidence of disease (Chéry et al., 2014; Maria Soledad Sosa et al., 2015). Similar dormancy gene signatures were also found in experiments using cells from breast cancer patients (Klein, Aguirre-Ghiso, unpublished data) (Kim et al., 2012).

5. Studies have also examined the origin of dormant tumor cells. Specifically, a recent study investigated the location within the primary tumor from which this cell type arises, finding that cells that arise from hypoxic areas of the primary tumor contain a higher proportion of dormant tumor cells than those arising from normoxic areas (Figure 13) (Fluegen et al., 2016). In addition, these dormant cells are resistant to treatment and are therefore associated with
a poorer patient prognosis. For instance, cells that arise from a normoxic environment are susceptible to treatment with cisplatin; however, cells that arise from hypoxic environments are resistant to this chemotherapy (Fluegen et al., 2016; Harper et al., 2016; Hosseini et al., 2016). Furthermore, at least one drug has been discovered that specifically kills dormant tumor cells and there is hope that drugs like this could be combined with anti-proliferative therapies.

**Three major gaps in the field of metastatic cancer research:**

1. A better understanding of the genetic composition of individual metastatic lesions (i.e., the entirety of primary tumors) as well as the genetics and gene expression of dormant tumor cells is needed.

2. Greater knowledge is needed regarding the tumor microenvironment and immune environment involved in cancer metastasis, including the differences in microenvironments that host dormant tumor cells.

3. There is a lack of understanding of the effect of aging on the behavior of dormant tumor cells.

- **Collaborations required to meet these gaps:** (1) Collaborations between basic scientists and clinical programs are needed to help access metastatic cell samples, which include single dormant tumor cells. There are currently few sites with the capability to perform rapid autopsies and it is also difficult to access bone marrow aspirates. (2) Collaborations are needed between clinical programs, genomics, single cell biology specialists, and single cell proteomics specialists. (3) There is a need to better understand the mechanism of survival of dormant tumor cells.

**Major barriers that inhibit progress towards extending the lives of metastatic cancer patients:**
Scientific Barriers: (1) There is a need to reverse the culture of primary tumor-centric research and focus more on metastatic cells. (2) Greater access to human metastatic cancer samples is required. (3) Changes need to be made to how clinical trials are currently conducted to better understand the biology of both the dormant and proliferative cells. (4) Novel tools and imaging technologies that can detect minimal residual disease and are needed to image dormant tumor cells. (5) Additional surrogate biomarkers, such as those that can be detected in blood samples, are needed to provide information regarding relapse rates of dormant cells.

Programmatic Barriers: N/A.

- Suggested ways to overcome these barriers: (1) Education regarding the basic biology of residual disease post-therapy is needed for regulators and funding agencies in an effort to emphasize the need for a better understanding of dormant cells and to better adapt clinical trials. (2) Promote the education of industry, such as through the government, to encourage the development of therapies that are not modeled solely on primary tumor-based studies. (3) Additional funding is needed to establish Centers of Excellence with basic and clinical research aims to better understand dormant tumor cell biology. (4) Access to and the study of biological samples from patients in remission following treatment of metastatic cancer as well as the development of better experimental models to study this in vivo.

Initiatives needed to accelerate clinical and translational research: (1) Better understand of minimal residual disease and the biological characterization of metastatic tumor heterogeneity and dormant tumor cells is needed. (2) Develop therapies to reprogram cancer cells to sustain a state of minimal residual disease as a chronic, asymptomatic disease. (3) Develop therapies targeted at killing dormant tumor cells. (4) Better understand the effect of the microenvironment on dormant tumor cells. (5) Develop clinical trials targeting dormant tumor cells, such as through combination therapies (e.g., anti-proliferative therapies with anti-dormant tumor cell therapies). (6) Collaborate with engineers to develop novel technologies for the analysis and detection of dormant tumor cells. (7) Consider and fund multidisciplinary programs that incorporate other models of dormancy in biology (e.g., dormant states observed in bacteria, viruses, worms, plants). (8) Develop a better understanding of differences between hosts (e.g., polymorphisms) that can influence cancer relapse rates.

Question and Answer Session Transcript:

Thank you, Dr. Aguirre-Ghiso. I've got a couple of questions. Excellent, excellent points. And actually, as I start to ask this, I'm going to prep Dr. Dumler. I think he's in the room. Right? Steve, you're here? I'm going to ask you about programs for rapid autopsies. So, if you could just give that thought for a minute and sort of how many of those are in the country and what it takes to set something like that up. Something you sort of just quickly went past but mentioned, but struck me, was you said something to the effect that it's very hard to get metastatic samples in the US. So, as I think about that-- and many of us here in the task force have been running the Department of Defense-funded biobanks for years. And there is a lack of metastatic samples.

And, as I thought about it during your talk, some of the restrictions we have are, a lot of our Institutional Review Board (IRB) protocols are for clinically directed biopsies only. And so much metastatic therapy is given based on imaging, nowadays. They don't even need to biopsy
it. And when they do, of course they want the most minimally invasive biopsy. And I understand this. And the pathologists need to exhaust the specimen to get the diagnosis right, so there's very little left over. And educating IRBs is part of it. But anytime any of us go to our IRBs and try to get-- and we want to take extra samples of the metastatic deposit for this exact, important reason-- lots of pushback. And it was occurring to me that we've tried to educate IRBs over many years, and that probably has not a good rate of success.

We have several advocacy organizations in this room. And it occurred to me, if we're moving more towards empowerment and patient-reported outcomes-- in fact, I wrote down, maybe we can have patient-requested biopsies, where you-- you know, you mention to the advocacy community how important this is.

Absolutely.

And that people, patients just allow for or are empowered to say, you know, I understand this needs to be biopsied. Do you have a program that, you know, supports the use of this and putting it in some type of biobank for folks like yourself to study? Because otherwise, we're not going to make any progress. You're right. Everything is centered on the primary tumor. And unless we change the culture of IRBs, empower patients to demand this be done on behalf of science and moving the field forward, I don't think we're going to make much progress. But before I ask Dr. Dumler to comment on rapid autopsy, could you respond to, why did you specifically mention it's hard to get these in the US? Is it because of the things I've mentioned?

It's been difficult to get physicians to incorporate, for example, access to bone-marrow samples. This is changing a little bit. I know some centers now are doing it more routinely. But we have, at least in Sinai and other places that I've interacted, we got a lot of pushback from the physicians at the time of, you know, doing this. And so, who's going to pay for it? You know, I need to incorporate a hematologist to do this, or I need a trained nurse. Who's going to pay for it, if you don't have the money to do it, you know? And so there's a lot of logistics. Consent. Another consent form that we have to put through the patient, you know? So, again, it's educating not only the IRB, it's also kind of educating our physicians to help the research programs.

I think the access to metastatic samples in patients that are undergoing treatment, that is-- it's tricky, and it depends on what you can sample. Right? But the rapid autopsy programs are usually the source of these metastatic samples where you can obtain the material. And you can not only obtain the material from the lesion. You can also sample other bones. The rapid
autopsy program at the University of Washington samples around 40 bones of these prostate-cancer patients, so they get the metastatic sample and then many other sites. And I think this is very rich information that you can obtain from this. But they need support. And, I don't know, maybe Howard can mention to this. But there are not a lot of these autopsy programs across the country. There may be four or five.

Steve, did you want to respond to my question?

Yeah. So the responses I can give are actually quite limited, because there are very few programs like this in the United States that I'm aware of. I actually kind of cut my teeth in pathology at the University of Maryland School of Medicine, where they had a rapid-autopsy program at the time. And there were a number of deficiencies with autopsy materials for these purposes, including ischemic times and things like that that are less well controlled than if you were getting operative samples. So I've asked my two colleagues next me who work at Walter Reed, in Pathology, whether they have any comments. And currently we do not have a program in place there. We're willing to do so. There are obstacles that have been noted because of IRB restrictions and IRB protocols that have to be accessed and general reluctance of IRBs to kind of agree to these things all are limitations, too.

Do we have time for one question?

It's not a question.

OK.

Maybe a statement. We do biopsies routinely of bone. And the biggest issue-- I mean, we have a targeted sequencing assay that's routine. It's done on virtually all the castration-resistant patients we can do. It's fully integrated with our Interventional Radiology group. But our yield on bone of sufficient tissue for profiling is only about 50 percent. And that's looking at directed lesions. A big issue with bone is, how do you process the specimen? And that's been more of a limitation, from our end, as clinicians who will put the effort in to get it, to standardize the SOPs for doing so. I would be curious of, how many cells approximately are you analyzing on each patient? You know, Klaus and I did an editorial on this recently-- not that recently. But, in many cases that are reporting on post-treatment DTCs, the number of cells that you're analyzing is quite small.

Very small.

And that gets get you a little bit uncomfortable, clinically. I mean, the biology is fascinating. There's no question you want to target that.

Yeah, but we have to start somewhere, and--
I'm ready. So we'll talk later. But--

So it's still a research, but, you know--

Understood.

--you've seen the profiling of-- the few studies that do genetic profiling of multiple metastases and prostate cancer, they're extremely revealing about the heterogeneity, about--

I understand that.

--the evolution. So I think we need to start somewhere.

Well, we're ready. And we do have a warm-autopsy program and an IRB that's friendly that allows metastatic biopsies

Ma'am, you had your hand up. We're going to let you ask your question or respond.

So I'm absolutely a huge fan of biopsy. And when I give my talk, I'm going to say, we really need to collect this information. And that's my research side, 100 percent. But my clinical side, having-- have a trial open right now, that you have to have a biopsy to go on study, I really can relate to the problems that physicians are having and their reticence to do biopsies.

Absolutely.

And that's why I totally agree with you, that we need engineering and technology to make better sense. One, I'm interested in the microenvironment, so I don't want just the tumor cells when they biopsy. I want a good sample. Two, what about tracks? You know, in certain patients, like Ewing's sarcoma, you worry every time you put in a needle that you couldn't get a track and you'll end up causing more harm than good in these patients. Sometimes you're inducing inflammation. So, potentially therapies that could target that in that peribiopsy period or perioperative period. And maybe we should be going for, like, metastasectomies more, getting more tissue for you than just biopsy. So I just raise that side, because I feel conflicted, myself, being on both sides of that.

I agree completely, and I don't want to give the impression that I'm not paying attention to the patient side. But I think we need to push the boundaries. And maybe, by really pushing it, we bring in engineers, we bring new thoughts. And maybe, after a few lessons, we say, well, we could stop doing this, because we have this solution. Right? But--

Exactly.

--if we don't get into it, we will not learn.
All right, we have one final question from the task force, and then we need to move on.

So, a comment, and then a question. So I'm also, as Rosie is, at NIH, but we also have adult patients, which may be a difference. Because we actually require biopsies pre and post therapy on almost all of our patients, in all of our studies.

That's excellent.

And the patients, you know, are unique. The patients who walk in the door are willing to have those biopsies. But we're not unique in that, I think, lots of academic institutions, you've heard from Howard, are doing this in patients. You get limited material, and you're somewhat restricted, in that the patients can't-- you know, you won't do a dangerous biopsy that you might do for a diagnosis just for research cores. But we could get four or five cores from most of our patients. The question I had, I guess, is just thinking about your dormant cells from a different aspect. Killing them would be the best. But, rather than putting cells into dormancy, have you ever tried driving them out of dormancy and then treating the mice to see if you can flush them out, and--

Yes. Every time we try this is a disaster.

Worse, not better.

So I would not awaken them.

[LAUGHTER]

Our groups, then, are trying to mobilize cells from marrow. They're doing it as a protocol at Hopkins, where they're intentionally stimulating the cells out-- the idea that they can kill them when they're not--

Well, if you have very good drugs, you know, then try it. But I don't know if we have that good drugs yet.
Clinical and Translational Research on Metastatic Lung Cancer

Sarah B. Goldberg, MD, MPH

Yale School of Medicine and Yale Cancer Center

Dr. Goldberg discussed clinical and translational research on metastatic lung cancer. She shared scientific evidence illustrating the three most important research findings that have extended the lives of patients with lung cancer, major gaps in the field, major barriers that inhibit progress, and initiatives needed to accelerate clinical and translation research.

The most important research findings that extend the lives of patients with metastatic cancer:

1. The identification of molecular drivers on lung cancer. Over the last twelve years, the Lung Cancer Mutation Consortium, a group of 16 sites across the U.S., has collaborated to share patient samples, resources, and data that helped to identify molecular drives for lung cancer. The identification of molecular drivers has transformed lung cancer treatment. Patients with an identified molecular driver that have received targeted therapy have improved survival rates compared to those who do not receive targeted therapy (Cardarella & Johnson, 2013).

2. Improved understanding and ability to overcome resistance to targeted therapy. Patients with lung cancer can benefit from targeted therapy, on average, for 1 year. In some cases patients can benefit for up to 10 years but eventually acquired resistance develops. Five mechanisms of acquired resistance have been identified: (1) secondary mutations in the drug target (e.g., T79DM is a secondary mutation in the drug target of the epidermal growth factor receptor), (2) activation of bypass signaling pathways, (3) mutations in downstream pathways, (4) phenotypic changes in the tumor, and (5) small-cell transformation (Ohashi, Maruvka, Michor, & Pao, 2013). Because of this understanding, there is host of other drugs that have been developed to treat resistance. One such drug is osimertinib, which has been successful against T79DM.

3. Immunotherapies have provided significant improvements in overall survival for lung cancer patients. In particular, PD-1 and programmed death ligand 1 (PD-L1) inhibitors have been very successful in treating lung cancer. In the survival curve below, a Nivolumab a PD-1 inhibitor (blue line) and standard chemotherapy (green line), Docetaxel, were both used as second line therapy for non-small cell lung cancer (Figure 14) (Borghaei et al., 2015). Patients treated with Nivolumab had a 42percent 1-year overall survival compared to the 24percent 1-year survival with Docetaxel, and this survival continues into the second year. Other groups have reported 3-year and 5-year survival benefits of Nivolumab. Immune therapy, such as Nivolumab, is also better tolerated than Docetaxel.
Three major gaps in the field of metastatic cancer research:

1. Lack of understanding of drug sensitivity and resistance.

2. Lack of biomarker-driven treatment options for the majority of patients. A minority of patients with lung cancer have an actionable molecular target. The remainder have a target for which there is no available drug or do not have a known target.

3. Lack of understanding of the etiology and treatment of various sites of metastatic disease, particularly brain metastases. Brain metastases are a common problem in patients with lung cancer. The microenvironment of the brain, difficulty of drugs to cross the blood-brain barrier, and relative exclusion of patients with brain metastasis enrolled in clinical trials are responsible for the poor prognosis in these patients.

- **Collaborations required to meet these gaps:** (1) Incentivize collaborative research between basic scientists and clinical researchers across multiple centers or hospitals. (2) Provide resources and the ability to biopsy tumors in patients who are responding to and progressing while on various treatments. (3) The ability to not only repeat biopsy after treatment progression, but to biopsy after effective therapy to learn what is going on in residual cells. (4) Include patients with brain metastases in clinical trials of systemic therapies.

**Major barriers that inhibit progress towards extending the lives of metastatic cancer patients:**

Scientific Barriers: (1) Ability to analyze large amounts of genomic and proteomic data. Advances in technology have provided a significant influx of data but there is difficulty accessing and interpreting it. A major challenge exists in integrating molecular, histologic and clinical data. (2) Ability to store and share data. (3) Outdated clinical trial design that is not adapting to the rapidly changing landscape of cancer science. (4) Lack of collaboration between scientists and clinical/translational researchers.
Programmatic Barriers: N/A.

- **Suggested ways to overcome these barriers:** (1) Redesign clinical trials and implement more combination trials and novel trial designs (e.g., basket trials and umbrella trials). Trials must incorporate biomarker development in an organized manner. Use adaptive randomization and ability to work with statisticians and bioinformaticians who understand the science.

**Initiatives needed to accelerate clinical and translational research:** (1) Promote collaboration between clinical researchers and scientists and between multiple centers. (2) Coordinate efforts towards a data storage infrastructure and mandate data sharing. (3) Improve clinical trial infrastructure.

**Question and Answer Session Transcript:**

Thank you, Dr. Goldberg. That was excellent. And this task force really needs to hear from clinicians doing research. And so we appreciate your coming and speaking to us. Working through a couple of your important points, you mentioned data-- getting the data available to the public. And so the Genomic Data Commons, as you know, was opened, to great fanfare, by Vice President Biden at ASCO, in June. Is that part of the solution, things like NIH-driven Genomic Data Commons? They're going to open a protein data commons, an imaging data commons. Is that sort of some of the solution to that problem you mentioned?

You know, I think-- I think it could be. But I think-- I think it has to be easily accessible, because, I think, if it's not going to be easy for people to access and put their data into it and then get data out, I don't think it's going to be useful. So I'm not sure that that's going to be entirely a solution.

And then you brought up the important point of, you know, in any health care system, you leak out some of the patients, as you say, to the community, where then they're not in your system. Now they're getting some targeted therapies, sort of standard-care therapies. And so yesterday we heard from Cliff Hudis about the ASCO LinQ. And so what's your thoughts about that, as part of a solution to that important problem you just mentioned?

Yeah, so I think actually that's happening-- we've seen that already. And I think I've heard from other academic centers that that's happening more, now that these drugs are more available. So I think it's happening more and more and will. Yeah, you know, I think, again I think that that could be part of the solution. And I haven't seen that, I guess, in action, so I'm not sure that that- I'm not sure that that is going to be the solution. But I think that that is the right idea, to try to get that data into a place that can be useful. But I guess that that's the right thinking. I agree with that that line of thinking, to try to bring that together. Again, I don't know if that's the right way to do it. I don't know enough about it.
You bring up important points. I'm just exploring whether the solution is some national organization. So, like, the data-sharing. The NIH should be responsible for that.

Yeah, you know--

The getting data from community organizations-- you know, some national organization like ASCO should be responsible for that-- that sort of thing.

I think some of these things are bigger than just an individual site, right? It can't just be a hospital or an individual site. I think it can't be, because, I think, the cost is too much. And, I think, it doesn't make sense for each individual hospital or cancer center to have their own system, because then that's not sharing either, right? But I don't know-- I guess I don't know how big it needs to be. Or maybe there can be one overarching system that then each site can have their own piece of it. I guess I'm not sure exactly what it would look like or how big it would need to be. But I think it does have to have some broader reach.

And you mentioned the important point of clinical trials. I mean, we're in a new era. And you mentioned a few times, we need to redesign clinical trials. So, in your opinion, who drives that conversation? Like, who should be the organizer of the national conversation on new clinical-trial designs, in the biomarker era, the targeted-therapy era? And specifically when we probably will need to do multiple targeted therapies synchronously to patients, rather than just one and then resistance develops, and you go on to the next one.

Right. And I think there are several people in this room who know better than many people and many others who treat patients and who develop trials, how, I think, trials need to be developed and how patients need to be treated. And I think creating groups that can develop trials is the right way to do it. And I think some of that is happening already. There are trials that are starting to develop that address these issues. But I think getting these trials funded is sometimes challenging. They're big. Right? They're big trials. But I think it's a multidisciplinary group. Right? It's clinicians, and it's some basic scientists that need to be on the biomarker side of it, and statisticians that have experience with designing trials like this and, like I mentioned, creative statistics, not just the standard. So I think it has to be a group effort.

Thank you.

We have time for one more. Dr. Scher?

Yeah.

The lung-cancer community is one of the most organized. They were one of the first to pool data on mutations.

Yep.
It's a national group. You have outstanding statisticians. You've already done battle trials--very creative, innovative. So I'm not sure--I don't think you need the entire universe--

Nope!

But you already have--

No, and I think it's true--

You have an outstanding group that exists.

I think that's true. And I think a lot of it has already happened, and that's a lot of what I've showed you, is that it's led to a lot of really great results for us. I think it's true.

But it's not going to stop. I mean, Paul Bunn gave rounds at Memorial and just traced the history of the evolution of how you've been learning more about the biology, how you've changed the biology with first- and second-generation compounds, how you've adopted, now bringing in immunotherapy. You're doing really well!

I agree. I agree. No, I agree, and I think that that's for lung cancer, and it's one disease, and there's still more. Right? That's lung adenocarcinoma and not other parts of it. But I agree.

All right. I have to keep an eye on the time, so I apologize, but we're going to have to move on to our next speaker. So, thank you. And our next speaker is Dr. Neugut. So we're going to get the slides changed up here. As a reminder, you can find presenters during breaks and lunch and ask any questions you weren't able to ask during the Q&A session. Thank you.
Epidemiology of Cancer Metastasis: Risk Factors and Prevention

Alfred I. Neugut, MD, PhD
Columbia University

Dr. Neugut discussed risk factors for and prevention of metastatic cancer. In his presentation, he highlighted the most important findings that can extend the lives of patients, major barriers that inhibit progress, and recommended initiatives to accelerate clinical and translational research.

The five most important research findings that extend the lives of patients with metastatic cancer:

1. Preventative measures are inexpensive, nontoxic, and are responsible for some of the largest reductions in cancer rates. They should be an even larger area of focus. In addition to the primary prevention of cancer, the prevention of recurrence or metastasis should also be prioritized. Adjuvant therapy can help prevent metastasis (Sundararajan et al., 2002).

2. Many patients are not treated with the adjuvant therapy they should be receiving. Access to care is a significant problem in the U.S. For example, African-Americans are much less likely to have access to treatment for ovarian cancer (Figure 15) (Hershman et al., 2004) and colorectal cancer. Thus, recurrence rates are higher in this population.

3. Non-compliance is another problem in cancer treatment as the average adherence rate is 50 percent. Non-adherence to medication is correlated with poorer prognosis and higher health care costs; therefore, patient compliance should be factored into treatment plans. Notably, RCTs have demonstrated that oral Cytoxan had a better response rate than intravenous Cytoxan, but adherence was better with intravenous Cytoxan. In response, intravenous Cytoxan became more commonly used. In another study, higher prescription copayments were associated with both non-persistence and non-adherence to aromatase inhibitor therapy in women with early-stage breast cancer (Neugut et al., 2011). Without compliance, patients do not receive the full benefit of therapy, thereby affecting recurrence and mortality rates.

4. Environmental and lifestyle factors can influence the occurrence and site of metastasis (Table 2).
Table 2. Risk Factors for the Development of Various Cancers.

<table>
<thead>
<tr>
<th>Cancer Type</th>
<th>Risk Factors for Metastases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast Cancer</td>
<td>• Smoking and lung metastases (Murin &amp; Inciardi, 2001; Scanlon et al., 1995)</td>
</tr>
<tr>
<td></td>
<td>• Obesity and axillary node metastases (Daniell, Tam, &amp; Filice, 1993)</td>
</tr>
<tr>
<td>Colorectal Cancer</td>
<td>• Hepatitis B virus infection protective against liver metastases (Song, Chen, Ou, &amp; Su, 2001)</td>
</tr>
<tr>
<td></td>
<td>• Cirrhosis protective against liver metastases (Gervaz et al., 2003)</td>
</tr>
<tr>
<td>Esophageal Cancer</td>
<td>• Smoking and lung metastases (Abrams, Lee, Port, Altorki, &amp; Neugut, 2008; Araujo et al., 2016)</td>
</tr>
<tr>
<td>Head and Neck Cancer</td>
<td>• Tumor thickness and cervical lymph node metastases (O-charoenrat et al., 2003)</td>
</tr>
<tr>
<td>Prostate Cancer</td>
<td>• Smoking and metastases (Moreira et al., 2014)</td>
</tr>
</tbody>
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5. Aspirin reduced the incidence of breast cancer, prostate cancer, and colon cancer, and it may also prevent recurrence and metastasis in these cancers (Figure 16) (Elwood et al., 2016). As adjuvant therapy, aspirin may prevent recurrence and metastasis by preventing adherence to vessel walls as well as via COX-2 inhibition (Langley et al., 2011).

Major gaps in the field of metastatic cancer research:

N/A.

- **Collaborations required to meet these gaps:** N/A.

Major barriers that inhibit progress towards extending the lives of metastatic cancer patients:

- **Scientific Barriers:** It is very difficult to study what exposures are causing metastatic disease over a patient’s lifetime. Some exposures stay constant and some change.

- **Programmatic Barriers:** (1) Access to care. (2) Adherence to treatment. (3) Clinicians are generally unaware of the extent of their patients’ noncompliance.

- **Suggested ways to overcome these barriers:** (1) Develop ways to ensure access to care and adherence to treatment. (2) Preventive measures post-diagnosis, as well as chemopreventive and therapeutic measures aimed at risk factors for metastasis may be helpful. (3) Prevention/reduction of metastasis could be a tool for improving survival and cure and is inexpensive relative to life prolongation.
**Initiatives needed to accelerate clinical and translational research:** (1) Research regarding the prevention of metastasis and recurrence should be prioritized over treatment as preventative measures cure the disease rather than merely prolong life. (2) Additional research is needed to improve the effectiveness of adjuvant therapy and also to improve adherence and compliance to adjuvant therapy. (3) Preventative research should focus on lifestyle and environmental factors associated with metastases. (4) Additional research on aspirin as adjuvant therapy is crucial, and aspirin should be made the standard of care as adjuvant therapy for prevention of colorectal and breast cancer metastases. Notably, the Department of Defense (DoD) Breast Cancer Research Program (BCRP) recently funded a Phase III clinical trial for aspirin as adjuvant therapy for breast cancer patients. There are other RCTs in progress in different countries. (5) Research is needed regarding the role of financial strain on non-adherence and non-compliance. Controls on both price and overtreatment are also critical.

**Additional comments:** Some patients are not treatable; they have truly fatal conditions and need palliative care instead. We need to address research on how to put limits on the use of chemotherapy and how to decide when to stop therapy and refer a patient for supportive care. Novel, population-based solutions might be needed. Social media and support groups may be used to encourage patients to be more compliant with medication.

**Question and Answer Session Transcript:**

Thank you, Dr. Neugut. So, on behalf of the, um-- you bring a very interesting perspective. And one of the reasons we appreciate your being here is the population-based and the patient-based. And two of your sort of focused initiatives, I want to just ask you to speak more to it. And in our audience is Dr. Bob Browning. And Bob, I'm going to ask you to comment on smoking-cessation programs and screening programs. And then Dr. Neugut brings up tobacco cessation in patients diagnosed with cancer. I wonder if you could just talk about the program that you have at Walter Reed. But you mentioned that medication compliance is an important component and certainly can be related to failure of therapies for patients with metastatic disease. And so it was occurring to me that almost sort of population-based, novel solutions might be needed. As more and more patients come out of this generation of social media and devices, maybe reminders that get sent out to patients-- you know, take your medicine today--you know, especially the upcoming generation. Better education of patients. And then even using support groups. Support groups are used for a lot of things, but maybe support groups could be educated to be used to encourage patients to take medications. But are these some of the ideas to get at a population-based solution to patient compliance?

So, we have a randomized trial that's just finishing, where we randomized 750 women with breast cancer to either get text messaging to remind them to take their aromatase inhibitor or not. And so I don't know the result yet, but we'll see how that worked. And that's been used for patients with HIV taking antiretroviral therapy and in some other contexts, similarly. I think part of the problem is just awareness by the clinicians. Clinicians are totally unaware, in the general community, how non-adherent their patients truly are, because nobody wants to tell them. I don't tell my dentist that I don't floss. Every time he asks me, I tell him, oh, yeah, I've been flossing, you know-- yeah, yeah. I lie all the time, you know.
But that's true of everything-- for hypertension drugs, you know, I skip-- well, look, OK, I'd better not talk-- be personal. But most patients do that, and it's very common.

Dr. Browning, so, my point was, when we do lung-cancer screening for high-risk patients based on the NSLT trial, we have a tobacco-cessation program aligned with that. Is the same thing natural for patients who are, once they're diagnosed with lung cancer, to try to get them in a cessation program?

Yes. So, we have lung-cancer screening, and we'll find these patients. But when they're diagnosed or, our early lung-cancer patients, we have lung-survivorship clinics. And a big part of that is the smoking cessation, obviously. I mean, if these patients continue to smoke, they continue to get cancers. And we pick them up in the lung-cancer screening or the lung-cancer survivor programs-- these early stages, that we think they're going to survive. Unfortunately, 50 percent of even the Stage I cancers will recur, and their mortality is low over a five-year period, as well. So it's an important part of any program for sustaining life with lung cancer.

Do you know what your success rate is? I mean, we just heard from Dr. Neugut that if patients continue to smoke, their risk of metastasis is higher. Do you talk to that about with your patients?

Their risk for--

Recurrence is higher.

--Recurrence is higher? It is. I don't have each individual patient-- I don't have a stat on that for our group. But we find a lot that do recur. And actually most lung cancers will recur, even at early stage.

Col. Rosner?

So I'm just wondering if you can comment on exposure. So, exposures over a patient's lifetime change from the time of being an adolescent child to adulthood. And sort of really trying to correlate exposures and cancer risk. And I find that it's often difficult, especially in the Department of Defense, different exposures and how to really catalog and see what exposures may be causing metastatic disease, potentially, or an initial disease.

That's a terrific question. And it's very hard to study, epidemiologically. Some exposures stay constant throughout your life. If we talk about things like physical activity or obesity or diet,
some things change through your life. You eat a certain diet, because your mother makes you do it, and then you go to college and you start eating hot dogs and, you know, Lord knows what. And then you become a yuppie, and then you go out to eat fancy foods. And then you get married, and who knows what you eat. And then you have children. You start to eat better, because you've got to make the kids eat vegetables. And then you get divorced, and you go back to eating hot dogs.

[LAUGHTER]

So things do change, through your life, and things like that. And smoking changes, through your life. Everything does. And that's why it's very hard, in truth, epidemiologically, to know-- you can usually only capture one moment in time, and it's hard to get serial measurements like that. And in part that's why epidemiologic studies are often very difficult clash because you get different time frames, and you have to be very-- that's a whole new area, now, what's called "life-course epidemiology," where they try to get handle on adolescence through young adulthood through middle age and sort of get serial measurements like that.

All right, we do have one final comment from the task force. Then we have to move on.

Yeah, hi. Just a follow-up about your recommendation for aspirin. I don't know if you're aware that the DoD BCRP just funded a Phase III clinical trial for aspirin in breast cancer that is run by Eric Weiner and Michelle Holmes, up in Boston. So that's just getting started. My understanding is it just got highlighted at the San Antonio meetings. So--

You mean, as an adjuvant treatment?

Correct. To prevent recurrence. So that has really highlighted how-- Bayer is board with it. They're providing the drug. They're collaborating with the UK clinical trial that's ongoing with other cancers. And they have reassurance for follow-up funding from a different organization.

So that's where it's taken time for them to build that infrastructure. And that's partly why it got funded, because it really took bringing in all the players that needed to be part of it.

There are about three or four randomized trials in progress, in different countries around the world. I would argue that the observational data is so powerful, at this point, for colon cancer. There are at least six or seven good cohort studies that show that it improves survival. And it's a relatively harmless drug, as compared to say, FOLFOX, which is what we use. So I think the evidence is strong enough, we should be giving it already as standard of care, even as we test it with a randomized trial. But the randomized trials are in motion.
Metastatic Breast Cancer Research

Alana L. Welm, PhD

Huntsman Cancer Institute, University of Utah

Dr. Welm presented a high-level overview of the answers to the questions posed by the Task Force with specific regard to metastatic breast cancer research. In her presentation, she highlighted the most important findings that can extend the lives of patients, major gaps in metastasis research, major barriers that inhibit progress, and recommended initiatives to accelerate clinical and translational research.

The five most important research findings that extend the lives of patients with metastatic cancer:

1. Breast cancer is a heterogeneous disease with a wide variety of clinical subtypes that are primarily driven by the estrogen receptor, progesterone receptor, and expression of HER2, but there are many more additional subtypes as well. Approximately 20–30 percent of breast cancers become recurrent or metastatic disease. Although breast cancer can present initially as stage IV at the time of diagnosis, the larger problem in this field is disease recurrence.

2. The biology of metastatic breast cancer differs in non-metastatic or non-recurrent breast cancer. Therefore, it is often more than just an issue of early detection that results in cancer recurrence or metastasis. In addition, there are no clear genetic drivers of metastatic breast cancer as have been identified for some other cancer types.

3. Early stage breast cancers can metastasize prior to diagnosis and can remain dormant for years or even decades. As a result, it is important to consider how to prevent metastasis to reduce the number of breast cancer-related deaths.

4. The tumor microenvironment is key to the successful outgrowth of metastasis. A better understanding of the tumor microenvironment will yield opportunities to better target both this specific niche and the tumor itself.

5. Immune control of metastasis has been shown in many different models, but to a lesser extent in breast cancer. By better understanding how the immune response controls metastasis, targeted therapies can be utilized to improve the treatment of breast cancer.

Major gaps in the field of metastatic cancer research:

1. It is not well understood why 20–30 percent of breast cancer tumors result in clinical metastasis. Assays such as Oncotype DX® and Prosigna® for breast cancer can predict the likelihood of recurrence and can be utilized in clinical decision making (e.g., to identify which patients should receive adjuvant therapy). Since it is not well understood how these breast cancer tumors differ from those that do not metastasize, and there is a problem regarding the overtreatment of breast cancer (i.e., seven out of 10 patients must be treated to benefit three patients) Better understanding which tumors are metastatic and targeting treatment more specifically and precisely to those at earlier stages would increase the likelihood that metastasis could be prevented.
2. It is not understood how tumors change when within metastatic sites. In addition, the mechanism of drug resistance of metastatic tumors needs to be elucidated.

3. Further work is needed to determine how the microenvironment within each organ promotes the growth of or protects metastatic tumors (e.g., via the facilitation of drug resistance). A better understanding of this microenvironment may lead to improved methods of treating metastatic breast cancer.

4. Unsuccessful metastases present an opportunity to learn from the tumor cells that remain dormant and non-metastatic as well as their microenvironments; however, this is an understudied area of research.

- **Collaborations required to meet these gaps:** N/A.

**Major barriers that inhibit progress towards extending the lives of metastatic cancer patients:**

**Scientific Barriers:** (1) There is a lack of effective and efficient models for the study of metastatic cancer. Genetically engineered mouse models and PDXs have been shown to be the best models of metastasis so far; however, these models are imperfect. Genetically engineered mouse models do not reflect the heterogeneity of human breast cancer. Furthermore, PDXs are incredibly robust and do provide a model of reliable, spontaneous metastasis; however, they are very slow and difficult models to use in the laboratory as metastasis can take 8–9 months to establish following tumor implantation. In addition, these animal models are often immunodeficient, thereby prohibiting the study of mechanisms of tumor-immune system interactions and immune therapies. Current work is attempting to humanize mouse models via hematopoietic stem cell transplantation; however, this work is still in its infancy. Models that exhibit metastasis to clinically-relevant sites, reflect the heterogeneity observed in human breast cancer patients, and can recapitulate immune function observed in human patients are needed. (2) There is a disconnect between basic science and clinical trials. Therapies should be used in the adjuvant setting (i.e., post-surgery and initial treatment) to prevent breast cancer metastasis; however, the testing of new drugs, is typically completed in the metastatic setting where tumors are already well established. This results in the failure of drugs within trials when their mechanism of action is at an earlier stage within the biological process. (3) The majority of studies assess the impact of novel interventions on established, drug-resistant metastases and not chemo-naive micro-metastases as a result of a lack of efficient experimental models. Therefore, additional work aimed at determining how to treat existing drug-resistant metastases is needed. (4) Tumor-centric dogma in that many scientists are solely focused on the tumor and neglect the tumor microenvironment, which is important to consider when...
elucidating the best methods by which to treat cancer. Furthermore, since there are not clear genetic drivers of breast cancer, it may be more of a disease influenced by epigenetics to result in hormone-dependent cancers. (5) Metastasis is difficult to study as a result of experimentation being slow and expensive, which leads to productivity challenges. In addition, the same experimental designs are consistently repeated within this field of study.

Programmatic Barriers: There may not be sufficient reviewer expertise and study sections as there are few researchers investigating breast cancer from the broader “whole physiology” perspective necessary to understand metastatic disease.

- **Suggested ways to overcome these barriers:** The DoD BCRP releases a state-of-the-science document highlighting the topics in which research is needed. This helps to guide scientists in addressing important questions in the field and can be used as a model for other programs and cancer types. In addition, appropriate expertise is needed within the peer review process. To achieve this, a Metastatic Cancer Research Program could be developed to focus on the common mechanisms of cancer metastasis versus the separation of specific cancers by pathology or origin.

**Initiatives needed to accelerate clinical and translational research:** (1) Align preclinical and clinical studies to facilitate the execution of research that will most effectively translate into clinically-relevant findings and reduce subsequent failures that can result from a lack of understanding of therapeutic combinations or the biology of a disease. (2) Facilitate collaborations and greater interactions between scientists, ensuring that all research is applicable to the clinical setting. (3) Promote well-designed clinical trials with clear scientific objectives and appropriate clinical correlates. (4) Continue to support and prioritize research on cancer metastasis. (5) Establish special interest panels, study sections, and requests for applications mediated by the appropriate expertise.

**Question and Answer Session Transcript:**

So, with that, I'll end and take any questions, if there are some.

Great. We'll start the five-minute question-and-answer period. Dr. Hamilton.

Yeah, thank you Dr. Welm. I'd like you to expand a little bit on one of the last things you commented on. Congress has asked us to address metastatic cancer almost as if it's one disease process. And yet, in your slides, you comment on the heterogeneity of breast cancer. We heard it from Dr. Sood with ovarian cancer, also with lung cancer, that's actually many, many different diseases. Are they taking these common themes and metastasis in each disease process, co-opting these mechanisms in different ways? What's the best way, philosophically, for this panel and for the research community to look at this problem?
That's a tough question. I mean, I think we have to acknowledge that every cancer is different, in particular genomically. Lung cancer is very different from breast cancer. And when breast cancer metastasizes to the lung, it's not that it looks like lung cancer. Right? So we have to take into account the nature of each tumor type. But I think that is very, very dominant over taking into account the microenvironment that the tumor's in. And so I think that the metastatic niche and things that can lead to drug resistance can lead to immune suppression will have commonalities, amongst many cancers. So I think we have to take it at a two-pronged approach and really consider not only the nature of each tumor but the commonalities of what happens in the metastatic disease, in order to address that.

Thank you, Dr. Welm. And we appreciate the extra effort you made to get here, considering the blizzards and the travel in the Midwest over the weekend. So, thank you. And thank you for focusing on the task force questions and speaking so clearly about your recommendations. So, we did hear yesterday-- and you seem to be talking sort of the same thing but the other side of the coin-- we heard, yesterday, a lot about the research funders being more tolerant of failure and extending lifecycle grants, because of some of the issues that you brought up, as well, which is, this is just-- it takes a long time to do this research. The cycles of the grants are out of the cycles of the cell lines and everything you're working on. And so we did hear that from numerous experts, as well as yourself. Can you-- because we happen to have, as you know, the director of the CDMRP and the Breast section, both, in this task force, what additional guidance would you like to see? Or what would you like to see in a perfect environment, in terms of that, in terms of more detail, having grants align more with the realities of metastatic research?

[SIGH] Another hard question. I think-- I think what we need to do is, in some ways, come back to a blank slate. And I think we need to say, what are the questions we want to answer? And we need to build the models, in order to answer those questions. And I think what's happened is, we all have our favorite pathways, and we all study things that we know are important. But I think that that direction is unfortunately giving us much more incremental progress than we would like to see. So maybe there's something to be said for saying, you know, we really want to address established metastatic disease and how we can affect that. Maybe we put out an RFA-- I don't know if it's the CDMRP or somewhere else, but-- let's make the models and show some proof of concept that we can treat metastatic disease or try to understand these pathways. And then we have to acknowledge that this is a tough, tough problem. Cancer biology already is tough enough-- the heterogeneity and the different mutations, drivers, passengers, therapeutic resistance. But now, when you talk about metastasis, you're talking about it in a completely different context from which it's normally studied, which is the primary tumor. So I think that I agree that we need longer time on grants, to look at that. But I think we need to say, you know, maybe it's not OK to take the fast, easy models and try to address, the best we can, those questions. Maybe we need to say, what is the best way to do this and build-- I don't know if it's a center, a collaborative team, an individual. I don't know the best way. But somehow we have to say, this is the best way to address the problem. And, you know, here are some resources, and here's the way to start. Because if we keep doing what we're doing, I think
we are making progress, certainly, but it's a little bit more incremental than I think that we want to see right now.

OK, we have time for one more comment. Doctor?

I think there was a comment made yesterday that the NCI's program on tumor microenvironment had been curtailed. And I'm wondering if you or anyone else, really, in the room has any insight into why that happened? Because, in fact, that was a program designed to provide expertise and provide funding to people who were looking at this as a specific and a longer-term question.

Yeah, I actually don't know, but Dr. Coussens, I'm sure, can help.

Yeah, hi. That was a program that Dinah Singer and Suresh Mohla really pioneered, fabulously, with a lot of help from many of us in the room, over the last 20 years, to sculpt the program. The initial RFA came out, and, as you know, there were two cycles of that. And, like many of the U54s, after two cycles the attention span from NCI diminishes, leadership changes, and you lose enthusiasm for the program. And I think that the mandate to Dinah was to move on. And so the program wasn't renewed. But we never thought it would be renewed beyond two. And I think that, as Julio mentioned yesterday, it's a real shame. Because now we are a mature field and poised to be impactful in the clinic. And now the program is gone.
Priorities and Unmet Needs in Metastasis Research

Cyrus M. Ghajar, PhD
Public Health Sciences Division/Translational Research
Program Human Biology Division
Fred Hutchinson Cancer Research Center

Dr. Ghajar discussed primary findings and research gaps in the field of cancer metastasis research. In his presentation, he highlighted the most important findings that can extend the lives of patients, major gaps in metastasis research, major barriers that inhibit progress, and recommended initiatives to accelerate clinical and translational research.

The five most important research findings that extend the lives of patients with metastatic cancer:

1. Metastasis is not a linear process, but one that occurs in parallel to the primary tumor (C. A. Klein, 2009). In many cancer types, cells leave the primary tumor prior to detection and move to distant sites where they evolve in parallel to the primary tumor. As a result, there is limited benefit in sequencing the primary tumor when studying metastasis.

2. Cancers have been stratified based on their status of hormone and growth factor receptors. Therapies have been developed specifically toward these cancer subtypes, which has resulted in substantial improvements in survival. Sequencing can further stratify cancer subtypes with specific vulnerabilities. For example, a multiplex sequencing assay was used to assess mutations in 20 DNA-repair genes associated with autosomal dominant cancer-predisposition syndromes in 692 men with documented metastatic prostate cancer (Pritchard et al., 2016). The frequency of germline mutations in genes mediating DNA-repair processes among men with metastatic prostate cancer was 11.8 percent, compared to 4.6 percent among men with localized prostate cancer ($p < 0.001$). Instead of treating a patient with a drug typically administered for prostate cancer, patients could be treated based on the identified mutations. These findings can change the standard of care in metastatic prostate cancer.

3. Metastatic cells rely on the “normal” cells around them. The microenvironment, or niche, is required for disseminating tumor cells to engraft distant sites. Likewise, the microenvironment can be targeted to treat metastases or metastasis initiating cells (Ghajar, 2015; Psaila & Lyden, 2009).

4. Exosomes, nano-sized particles derived from tumor cells, mediate pre-metastatic niche formation (Alderton, 2012). Exosomes may be exploited for diagnostic and therapeutic purposes to help prevent the spread of metastasis.
5. Immunotherapy, which is the concept of harnessing the immune system to combat cancer in solid tumors has led to limited but at time spectacular results in the metastatic setting.

**Major gaps in the field of metastatic cancer research:**

1. There is no way to predict which patients will develop metastases and where the metastases will be located. However, we can predict whether the patient is at a high-risk of developing metastases in breast cancer. In breast cancer, the presence of micrometastases in the bone marrow at the time of diagnosis is associated with a poor prognosis (Braun et al., 2005b). Patients with micrometastases are at a four times higher risk of relapsing over the next five years.

2. There are no therapies to target micrometastases.

3. There is a lack of treatments based on the organ-site of metastasis.

4. Each cancer exhibits a predilection to metastasize to certain organ sites. Tumors cells are present in other organs, such as heart, kidneys, and skeletal muscle, but do not grow tumors. It is unknown why cancers do not emerge in other organs.

- **Collaborations required to meet these gaps:** N/A.

**Major barriers that inhibit progress towards extending the lives of metastatic cancer patients:**

Scientific Barriers: (1) Lack of immune-competent models (e.g., animal models that have a full immune system) to study the progression of metastasis and the efficacy of treatment. Models are needed that allow us to see cancer cells and follow disease progression while animal is alive. In addition, we need to be able to label cancer cells with a marker that is not antigenic. Studies cannot use transgenic mice because they are under an abnormal transcription factor. (2) The majority of metastasis research is focused on elucidating clinical relevance and, as a result, biological studies are rarely driven by population science-driven observations. (3) Improve methods to separate cells from solid tissues, maintain viability, and enable single cell sequencing.

Programmatic Barriers: (1) The method in which metastatic specimens are banked and made available to other researchers. (2) Conceptual barriers/biases that present a bottleneck to new/potentially transformative ideas breaking through.

- **Suggested ways to overcome these barriers:** (1) Incentivize cross-disciplinary research between epidemiologists and cancer biologists to examine population data and formulate research studies to address the questions in the data. (2) Fund high-risk and high reward research studies. (3) Start a new tissue banking program and preserve specimens in various manners to have a repository of tissue that can be utilized in 10–15 years.
**Initiatives needed to accelerate clinical and translational research:** (1) Develop immune-competent models for metastasis research to enumerate metastatic progression and quantify what remains after treatment. (2) Incentivize conducting experiments with the appropriate pre-treatment, treatment, and post-treatment schedules. (3) Maximize analytic power on studies, such as single cell genomic profiling, by collaborating with experts in data analysis. (4) Characterize anti-metastatic tissues and cells to learn why metastases do not emerge in certain tissues and to determine whether anti-metastatic factors can be delivered to sites to convert permissive sites. (5) Improve imaging, characterization, and targeting of disseminated tumor cell studies to determine frequency and predictive capabilities of future metastases, as well as novel methods to target metastases. Results from this effort can answer the question, “should stage IV cancer be re-defined?” (6) Start with a clean slate – reevaluate the grant system, review process, and ways clinical trials are run and then implement better methods or processes.

**Additional comments:** The processes that have been in place nationally, such as funding, labs, clinical trials, and grants, are not built to look at the questions surrounding metastasis. Rather they are built around the primary tumor. There is a need to reimagine the entire scientific ecosystem and this may need to be done at the national level. A national resource is needed to fund a central repository for storing tissues with multiple metastases, mandate tissue sharing, and ensure open access to data obtained from the tissue.

**Question and Answer Session Transcript:**

OK. I just want to note that we do have to limit this to five minutes exactly, so I will cut it off, as we're a little bit behind schedule.

Thank you, Dr. Ghajar. That was excellent. And it's interesting. Over the course of the two days, these themes start to emerge, when we hear the testimony from all of you experts, and what you've said. And I've written down four things here. But I think you summarized it right at the end. It almost occurs to me that the processes that have been in place nationally--funding, labs, clinical trials, grants, are not built to look at the question around metastasis. They're built around the primary tumor. We've heard about, over the last two days. And so you rightfully bring up this idea of reimagining the whole ecosystem. And even focusing just on the tissue banks. And again, I mentioned at the other talk that we've been funding a lot of tissue banks. But you're right, in the metastatic realm. And so researchers like you get stuck, because there's nowhere to move out of pre-clinical models to really move into. And as we would look at that, you're right. It can't be retrospective. You have to almost start afresh. It's almost, just from that standpoint, the tissue banks, you'd almost need national resources, with best practices of attainment of the samples, including CAP accreditation, CP tax standards for preanalytic variables, and making sure ischemia times were proper. So when you move beyond genomics and get into the protein assessments, that those samples were ready for that. The multiple metastases would have to be addressed. You'd have to get samples of them, a resection of them, instead of needle biopsy, for reasons we've heard from prior speakers. And it's almost
like there needs to be a centrally funded commitment of a resource that then all researchers could go into and tap into.

Right.

But unless there's some big effort to address all these multiple issues of a metastatic tumor bank, even those of us and other organizations who've established tumor banks, they're going to remain focused on the primary tumor, and we're reaching the limits of what we can earn from that.

Yeah. And so there are a few fantastic rapid autopsy programs, but they're primarily in prostate cancer. And the Sloan Kettering one was referenced there. The UW Fred Hutch one is amazing. There's one at Michigan. There's one at Johns Hopkins, and then there's a pancreas one in Arkansas. And there's not a great and consistent breast one. Hopkins has started one that stopped. We don't need a whole bunch of them. We need one really, really good one. And it could involve multiple sites where it's standardized, and then maybe there's some review process of when people want specimens. But it's a pretty accelerated one. And then if the science makes sense, or there's enough applications asking similar questions, you pull out the samples, you do the tests, and then you send out the data. I think that could be a working model. You need to have the right group of experts guiding the design of the whole thing to begin with, but I think that could be a working model. And that could be a working model for other things too.

Ma'am?

Thank you. Do the adult co-operative oncology groups have the resources to establish a bank like we're describing?

If I could. The adult network, the National Cancer Institute, National Clinical Trials Network, does support funding for collection of blocks or required tissue samples, but not in a repetitive fashion. And those go to the groups that are funded through their U24, for their bank. It doesn't have the resources to do the kind of situation that you're describing. The NCI early therapeutics clinical trials network, which is really the Phase I and early Phase II program, is funded at a higher level, does have encouragement for repeat biopsies, and is developing the appropriate banking situation for those. Although currently, those are banked at the primary site of that ETCTN study. It is creating an opportunity for collaborative resources.

Yeah. And I think the key is there's a lot of sites that do this on their own. And then when you want access to them, it's hard to get them. So there needs to be some kind of mandated sharing, but also some kind of measure to prevent wasting of those tissues also, if they are being shared.
Tissue-Specificity and Immune Response to Primary versus Metastatic Disease

Lisa Coussens, PhD
Knight Cancer Institute
Oregon Health Science University

Dr. Coussens discussed the role of immune cells in primary and metastatic disease. In her presentation, she highlighted the four most important findings that can extend the lives of patients, major gaps in metastasis research, major barriers that inhibit progress, and recommended initiatives to accelerate clinical and translational research.

The most important research findings that extend the lives of patients with metastatic cancer:

1. Chronic inflammation drives cancer progression. There is compelling histological evidence of a significant expansion of immune cells that are present within tumors. For example, there is a significant increase in the presence of leukocytes in tissue stained with CD45, a lymphocytic marker, in non-small cell lung cancer and asbestos-associated mesothelioma when compared to normal homeostatic tissue of the lung or pleura of the thoracic cavity.

2. Tumor-associated chronic inflammation is tissue-specific. The immune microenvironment for specific tissues or tumor types needs to be targeted when using or testing immunotherapies.

3. Myeloid inflammation dampens anti-tumor T cell cytotoxicity. As a result, myeloid inflammation correlates with decreased survival outcomes, whereas CD8+ T cell inflammation correlates with improved outcomes. In theory, if myeloid-mediated inflammation could be targeted, then we could change the outcomes for the patients with myeloid-dominated inflammation in their tumors.

4. Combined immunotherapies neutralizing tumor-promoting myeloid inflammation, with relief of T cell inhibition, plus cytotoxic therapy provide a survival advantage in patients with tumors containing a low mutation burden.

Major gaps in the field of metastatic cancer research:

1. Inadequate understanding of tissue-specific biology.

2. Inadequate models of de novo primary and metastatic disease.

3. Therapies are advanced to the clinic based on preclinical success with primary disease and not metastatic disease. However, primary disease does not drive patient outcomes. Metastatic disease and the associated chronic pathologies that are driven by
inflammation, which occur after the primary disease has been resected, is responsible for patient outcomes.

4. An absence of biomarkers for patient stratification and response monitoring. There is a need for a diagnostic assay to determine which patients are most responsive to particular therapy.

5. Limited access to healthy tissue.

- **Collaborations required to meet these gaps:** (1) Improve funding for collaborative cross-disciplinary science, such as biology, immunology, physics, chemistry, clinical, etc. (2) Make more funding available for biomarker discovery studies.

**Major barriers that inhibit progress towards extending the lives of metastatic cancer patients:**

Scientific Barriers: (1) Limited access to annotated clinical samples (primary and metastatic disease, paired biopsies, linear blood) for biomarker and target discovery or validation. This will require a patient registry. (2) Lack of warm (i.e., rapid) autopsy for diseased and “normal” tissue. (3) Lack of annotated cohorts. (4) There is a need for more big data analysis and bioinformatics discovery and validation.

Programmatic Barriers: (1) The rapid growth of primary tumors in most mouse models precludes the ability to effectively study metastasis because IACUC protocols mandate that a certain tumor burden, the tumor must be removed or animal euthanized. As a result, science is moved forward without a proper understanding of the primary and metastatic tumor microenvironment. (2) Increase funding to support the creation of new models of primary and metastatic disease. (3) There is no policy that requires all clinical trials to report their data regardless of success or failure. (4) It take one full time staff member to maintain IACUC regulatory licenses, but funding mechanisms do not provide the resources to maintain this required staffing need.

- **Suggested ways to overcome these barriers:** (1) Revise IACUC protocols that mandate when to remove a tumor or euthanize an animal to allow for more time to study metastasis. Provide interdisciplinary funding and access to areas outside institutional expertise. (2) Increase incentives for industry and academic partnerships. (3) Improve data sharing for positive and negative results. (4) Promote collaborative inter-institutional preclinical and clinical trial networks. (5) Revise funding mechanisms so that enough resources are given to primary investigators to support staff members who maintain IACUC regulatory licenses. (6) Provide educational opportunities for academics to learn about new statistical techniques or bioinformatics that will help advance research being conducted in their laboratories.

**Initiatives needed to accelerate clinical and translational research:** (1) Create repositories of annotated clinical samples for biomarker and target discovery and validation. (2) Implement a warm autopsy program where tissues are banked from diseased as well as “healthy” individuals at all stages of life. (3) Create big data analysis
and bioinformatics discovery and validation submission portal. (4) Promote interdisciplinary collaboration. (5) Require all clinical trials to report their results, whether they fail or not, and mandate that tissue and linear blood samples are made available for evaluation.

**Additional Comments:** One way to incentivize other disciplines to collaborate is to have academic institutions change their guidelines for tenure and promotion and to request examples of collaborative research. If junior faculty do not have to maintain independent investigator portfolios and only publish senior authored papers, and instead are told that they will be rewarded with promotion and tenure for team science, then cross-disciplinary collaborations will happen.

**Question and Answer Session Transcript:**

All right. Great. We'll start. Are there any questions from the task force, before we go to the general audience? Sir?

Yes. Excellent talk. Thank you. This whole time, I've been listening, and everybody continues to talk about collaboration, which I completely agree with. And unfortunately, it seems like in the medical and scientific training pipelines, we're taught to be individuals and stand out. So how do you think, and I think it's a great word that he used, the prior speaker, "incentivize." In your mind, with how long you've been, and working with young investigators, how do you think it's possible to incentivize other disciplines to be involved with you? How could we incentivize that?

Well, one way would be to provide funding that works. So institutions can rethink tenure and rethink promotion and tenure guidelines. If junior faculty don't have to maintain independent investigator portfolios and only publish senior authored papers, if they know from the get-go that they will be rewarded with promotion and tenure for team science, I think collaboration is a lot more fun than being an island. It's a no-brainer. But that's what we have to do, in order to maintain our programs within academic institutions. At OHSU, over the last five years, because we're making significant investments in team science, we have completely redone our P&T process. It's been an expense administrative output, in order to do that. And we were able to do that with philanthropic support administratively. All the institutions aren't able to do that. And so I think that if there are mechanisms that can incentivize either for accreditation or to simply throw some money at it, so that institutions can make it happen, that I think junior faculty will grow up in a different environment. Many of us old dogs, we're not going to change. But where we need to target is that next generation, so that they can think differently about their research programs.

Dr. Pantel?

You made a very good point about our illiteracy, and I speak about myself too, on bioinformatics, which causes me sleepless nights, to be honest. We have now, in our cancer ID, made ring try, where we gave the same next sequencing and generation data to four different bioinformatics groups—With different answers.
I don't think you get the same answer. Actually, it reminds me of our discussion in Germany, right now, how the computer will take over our lives in the future, and we are not needed anymore. And I think in science, we are already at that point. We give our data into a machine or to some young guys that do something, and they come out with some results that we don't understand. We have no way to even check plausibility, right?

Right.

And if you give them two, three different young guys, we get three different answers. This, to me, is really dangerous. And you're absolutely right, that we have to find a way to shed light into that, because we rely on the answers, and we are responsible for these projects, and also, for these young people that are doing this work. And I think I feel very uncomfortable, if there was a black box.

Yeah. I completely agree with that. I don't even know how to design effective controls for the bioinformatics. I would call people like Dr. Hunter here and say, help. Stupid question number 99. What do I do? It's a problem.

Call somebody else.

[LAUGHTER]

It's a significant problem across all of our laboratories.

I would love to become a student again with Dr. Hunter, or anybody else. Really, I would love to spend some weeks of my life to learn that.

We have time for one more question. Dr. Lee?

Yeah. Just a real quick point, back to Lisa. I know the vice president helped us launch the GDC, as Dr. Shriver mentioned. On this side, we were surprised on the NCI end that since June 6th until now, we've had 5 million people accessing download. So those 5 million people are looking for homes, I'm sure. And if there are things that we are building, we've been trying to think about this problem a little bit with DARPA and with the VA. I know Mike Kelly is helping us out with an initiative like that. So if that's something that we could help out with, happy to chat about it, because that is going to be an issue.

Great. Thank you.
The Revolutionary Advances of Immune Therapy as a Cancer Treatment Modality

Charles M. Balch, MD
University of Texas MD Anderson Cancer Center

Dr. Balch discussed the utility of checkpoint inhibitors as immunotherapy. In his presentation, he highlighted the most important findings that can extend the lives of patients, major gaps in metastasis research, major barriers that inhibit progress, and recommended initiatives to accelerate clinical and translational research.

The five most important research findings that extend the lives of patients with metastatic cancer:

1. The majority of cancer patients are in a state of immune tolerance. Stimulating them with different biological agents and vaccines will not change the status of a patient unless the tolerance is compromised. Immunotherapy does not treat the cancer, rather it treats an abnormal immune response. Lessons learned from immunotherapy for one cancer type often apply to other cancers.

2. There are many different types of agents that can be used to break immune tolerance or activate the immune system, increasing the repertoire of the immune system to have a more robust and durable immune response (Figure 17) (Mellman, Coukos, & Dranoff, 2011). These agents are being tested as monotherapies and combination therapies.

3. One important type of immunotherapy is the use of immune checkpoint blocking antibodies. Checkpoint inhibitors break immune tolerance and induce an inflammatory response in and around the tumor. There are three powerful checkpoint inhibitors that
can reverse immune tolerance in humans: anti-CTLA-4 (ipilimumab), anti-PD-1 (nivolumab or pembrolizumab), and anti-PDL-1 (atezolizumab). Checkpoint inhibitor activity has been demonstrated in clinical trials for several different cancers (e.g., melanoma, lung, head and neck, kidney). Metastatic melanoma patients who have not responded to conventional therapy have had long-term and durable response to monotherapy with checkpoint inhibitors. Criteria to stop therapy used in chemotherapy trials do not apply when using immunotherapy.

4. Checkpoint inhibitors are better than standard cytotoxic chemotherapy for patients with metastatic lung cancer, melanoma, head and neck cancer, and kidney cancer (Brahmer et al., 2015; Ferris et al., 2016; Reck et al., 2016; Seiwert et al., 2016). More trials are needed for other cancers.

5. Another way of treating the immune system is with a genetically engineered virus as a vector. This is now being tested in combination with checkpoint inhibitors.

**Major gaps in the field of metastatic cancer research:**

Investigation of checkpoint inhibitors in combination with other immune strategies and alongside standard modalities of treatments with targeted therapies, endocrine therapies, radiation therapy, and surgery.

- **Collaborations required to meet these gaps:** We need to invest in training doctors as clinical investigators, both in academic centers and in the community, where patients are first diagnosed.

**Major barriers that inhibit progress towards extending the lives of metastatic cancer patients:**

Scientific Barriers: Because checkpoint inhibitors such as CTLA-4 and PD-1 work on different sites within the immune system, their profiles of complications and toxicities are very different. We need immunological biomarkers to help select the most effective therapies depending on the different mechanisms of action. Currently, the only biomarker is PDL-1. PDL-1 biomarker expression in human cancers correlates with the incidence and duration of response to anti-PD-1 treatments.

Programmatic Barriers: (1) We have lost our leadership in conducting clinical research in cancer therapy and diagnostics. Investigators have not had sufficient support at the federal level for supporting the training of clinical investigators, including import roles such as clinical biostatisticians. Currently, much of the discoveries and leadership in clinical research and oncology is now coming from Europe and Asia, where governments are investing to a greater extent than we are in the U.S. (2) We are in a steady state that doesn’t allow for new programs to come in and be funded at a robust level. There is less money for new people coming into the system.
• **Suggested ways to overcome these barriers:** The study of checkpoint inhibitors as immunotherapy needs the support of federal funding. This type of therapy can benefit patients with a wide variety of cancer types.

**Initiatives needed to accelerate clinical and translational research:** (1) Standardized criteria for evaluating immunotherapy responses, which are different from evaluating cytotoxic chemotherapy responses using RECIST criteria. (2) Immune diagnostic tests that assess immune status in individual patients (e.g., state of tolerance, need for amplifying tumor-specific T cells, predictors of responses. (3) Novel approaches for patients who are unresponsive to immunotherapy or who relapse while on or after treatment. (4) Develop commercially available vectors for delivering immune modulators to the tumor (e.g., T-VEC). (5) Adaptive clinical trials for therapies with new endpoints for evaluating efficacy of agents and diagnostics.

**Question and Answer Session Transcript:**

Thank you, Dr. Balch. It's Craig Shriver here. And, first, for myself, the task force, and all audience members, please accept our gratitude for your giving this presentation and our best wishes for your wife and her recovery. I'm going to ask the--

Thank you. And you know I would be there if it weren't significant.

Yes, sir. I'm going to ask the only question just in the interest of the distance involved. As you know in the audience and on the task force, we actually have leadership from the Congressionally Directed Medical Research Programs. And in the audience, we have senior leaders from the National Cancer Institute. You started your presentation by commenting that we have lost our leadership in cancer research and treatment due to poor federal support. My question to you, and you can make a few comments on it, is I think as far as a dollar amount funding-- and, today, President Obama's going to sign the 21st Century Cures Act you almost unanimously passed through Congress and the Senate. It's going to increase funding federally for research, including cancer research and the Beau Biden Bill. So is money the issue or is it the way that the money is being used or what's the problem? How have we lost our leadership worldwide as you indicate?

Remember, I'm just making a general statement because I do consultations all over the world now. And I'm seeing the tremendous investments that are being made including federal support. Good examples of this are in Japan and China and some parts of Europe. And I think the issue is not the dollar amount that is being spent now, but that we are in a steady state, which doesn't allow for new programs to come in and be funded at a robust level. The pay line is so severe that the senior investigators may be funded, but there's less money for new people coming into the system. I worry about the support for the infrastructure for conducting multi-institution trials in the United States through the cooperative groups and other mechanisms that we need an increased infusion of funds if we're going to accelerate our progress. I also worry-- the previous speaker mentioned that we need to invest in training of doctors as clinical investigators, both in academic centers, but also in the community, where the patients who are first diagnosed are first seen. And as I had mentioned, I see a deficit that is very impacting of not having enough clinical biostatisticians is just one example, who are a critical partner with us in the design and the conduct and the evaluation of clinical research.
So if we were in an era where there were significant advances, both in biology of our understanding of human cancers, but also in having new tools to work with. And that's going to require I think a greater infusion of dollars in the support of clinical research, clinical investigations. In fact, the more we can be a leader in the world-- as all of you in the audience know that a number of the major advances that I presented in this era did not come from leadership in the United States. They came from outside of the United States. And, at a global level, that's good. But I think we need to continue to invest in these programs because now in baseball parlance, instead of hitting a few singles and doubles, we're getting home runs and grand slam home runs with new clinical tools that are making a very significant advance in cancer therapy. And in order to let American patients benefit from that, I think investment of new dollars will allow patients who are currently diagnosed or will be in the next two years to benefit from those as we advance the fields through clinical trials and not empirically-based medicine.

Thank you very much, Dr. Balch. Again, we appreciate your calling in and testifying to the task force on behalf of your service to the nation.

And I'd be pleased to work with you, Colonel Shriver, in any way as you do the follow-up of your report in January to the Congress.

Thank you, sir.
Pancreatic Cancer is a Systemic, Metastatic, and Complex Disease

Jonathan Brody, PhD

Director, Surgical Research, Thomas-Jefferson University

Dr. Brody brought to the audience’s attention that by the year 2020, it is predicted that pancreatic cancer will be the second leading cause of cancer related deaths in the U.S. (Rahib et al., 2014). The NIH funding leveling for pancreatic cancer has not increased since 1990 despite the rising rate of deaths that result from pancreatic cancer. As a result, the most important research findings that have extended the lives of pancreatic cancer patients date back to 1996. In the sections below, the most important research findings that extend the lives of patients with pancreatic cancer, major gaps in the field, major barriers that inhibit progress, and initiatives needed to accelerate clinical and translation research are summarized.

The most important research findings that extend the lives of patients with metastatic cancer:

1. A study completed in 1996 illustrated that Gemcitabine minimally increased pancreatic cancer survival to 5.6 months compared to 4.4 months with 5Fu.

2. A study completed in 2013 demonstrated that the combination of Gemcitabine/Abraxane increased pancreatic cancer survival to 8.5 months compared to 6.7 months.

3. A study completed in 2011 illustrated that Folfirinox increased pancreatic cancer survival to 11.1 months compared to 6.8 months with Gemcitabine.

Three major gaps in the field of metastatic cancer research:

1. The field is overly focused on the genomics (specifically the coding region) of pancreatic tumor cells but the progression model for pancreatic cancer has not changed. The next generation sequencing of multiple genomes has only demonstrated that the same signaling pathways remain – the progression has not changed. Personalized medicine to treat pancreatic cancer has not had many successes. The few studies that have had successes examined the primary tumor and recurring tumors and were able to effectively treat the mutation and have a therapeutic response in patients (van der Heijden et al., 2005).

2. The tumor microenvironment is complex and not well understood. The degree to which the microenvironment, such as the stroma, is a barrier to the treatment of pancreatic cancer remains unknown (McDonald, Maitra, & Hruban, 2012). The tumor microenvironment needs to be considered when selecting the appropriate oxygen and glucose levels for cell culture studies.

3. Increased early detection and improved treatment strategies are needed. Pancreatic cancer patients who are classified as stage I or stage II have such a significantly shorter life span that they are most likely already metastatic. To extend the lives of patients with pancreatic cancer, there is a need to detect the cancer much earlier.
Collaborations required to meet these gaps: N/A.

Major barriers that inhibit progress towards extending the lives of metastatic cancer patients:

Scientific Barriers: (1) Only a small window is available for early detection if it is going to be clinically beneficial. (2) There are a limited number of clinical trials for the enrollment of pancreatic cancer study participants.

Programmatic Barriers: N/A.

Suggested ways to overcome these barriers: N/A.

Initiatives needed to accelerate clinical and translational research: (1) Expand targeting strategies to reach beyond genetic mutations and epithelial tumor cells. Invest in efforts examining regulatory elements in the non-coding regions of the genome. (2) Invest in high-risk, high-reward studies, but expand the length of grant support to facilitate advancements. (3) Increase the number of clinical trials for pancreatic cancer. (4) Place more investment in postdoctoral fellows, who work more than 50 hours per week.

Question and Answer Session Transcript:

Dr. Brody, thank you very much for that. And, in one of your opening slides, it was appropriate that the applause line came at ASCO for increasing the survival albeit. But, at the end of the day, that brings us back to the fact that that's really the charge of this task force and its report to Congress is what can be done. All that we've been talking about is all excellent and is going to be rolled up into it, but those types of strategies-- and it's hard cause, yes, as we've heard long term we need investment in biology. We need investment in marathon funding grants that are longer term to really get at some of these models of metastasis and so forth. Is there anything else on the immediate horizon in your field that can be like the ASCO? Obviously, the trial you've put together is very provocative and seems like the next step. So I'm hope-- there are a lot of really bright people who I think are in our field. And I think, correct me if I'm wrong, I think Dr. Coussens got a grant from Lustgarten. And I think bringing people like-- smart people like her in and others who are thinking out of the box and thinking differently is what we-- is, certainly, what we need. If I had to-- if you were literally-- I think there are a lot of very interesting trials. Unfortunately, maybe, I feel like I'm too old and that's why we need new people. I'm a little bit cynical in the sense that I think we need to take-- and I know this isn't like the big thinking, I think we need to take a step back and realize that in 40 years the clinical outcomes for pancreatic cancer has not changed much. So what point in time do we as a community look in the mirror-- and I'm not just going to blame it on funding. I know I ended with that joke cause I felt pressured to. But, seriously, at what point in time are we going to realize that genetics explains a lot. It's not everything. How are we going to have better models? Everything that everyone else said. How are we going to go deeper into the science? How are we going to look at different pathways? How are we going to target different things? I'm more excited about the trial. I hope it works. Obviously, I'm the PI of the grant, so I hope it works. But I'm most excited because what we're going to learn and what we're going to learn from every patient. So I don't have a problem looking in the patient's eyes and saying we're going to learn so much from your tumor. I think those are the type of trials we need to run. I'm not excited about the agents that we have access to in pancreatic cancer. All these other agents
in these other tumors work great. But, again, the point of my slide that the three most important clinical trials in pancreatic cancer to-date, large evidence based, have all been cytotoxics. They're all chemotherapy, right? So I think that's something we need to think about. I think we need to even think about surgery. We have a trial going, a wash trial, where we're using lavage to wash the peritoneal. And the question is, is does dissemination happen at surgery? Why do R0 lymph node-negative patients succumb to disease within six months? Don't tell my chairman that, but-- who is a surgeon.

All right. Sir?

You and others have talked about the tumor microenvironment and implicit of that have been focus on other cells, other than the tumor cells, or the matrix, but there's been a little bit of mention about the microbiome. I wonder if you could comment on microbiome as far as pancreatic cancer.

Yeah. So I was just at a meeting where Dr. John Marshall at Georgetown is very into this concept and believes that the microbiome is really going to tell a difference of why we have some cancers that are more aggressive than others. And it's not my field, but I think within my field it makes a lot of sense because you have inflammation that's probably contributing to pancreatic cancer or there's pancreatitis that goes to pancreatic cancer. And there's a lot of idiopathic reasons of why is that inflammation there. And so I think that microbiome as well as how it relates to even some of these polymorphisms and why certain people are more affected than others is going to be very important. I think it's a great point.

All right. We have 30 seconds left, so one final comment from Dr. Pantel.

Very quick question. Did you ever look at tumor cells in the blood before and after surgery?

We actually did do that, and it might be the fact that our platform that we worked out was not that sensitive. I actually just published a paper on liquid biopsies and found that within liquid biopsies, we weren't able to even close—90 percent to 95 percent of pancreatic cancers have a K-RAS mutation. We were barely able to detect 50 percent of them, even from metastatic patients. But, if we can get the right platform, that is something that my colleague, who's a surgeon, is actually writing in as one of his grants. It's a great idea.

[INAUDIBLE]

OK. Well, maybe we can collaborate.
Immune Checkpoint Blockade for the Treatment of Metastatic Cancer

Andy J. Minn, MD, PhD

Assistant Professor, Department of Radiation Oncology, Assistant Investigator, Abramson Family Cancer Research Institute, University of Pennsylvania

Dr. Minn discussed some of the seminal studies in cancer immunotherapy that serve as the foundation for current and future experimental use of immune checkpoint blockers in combination approaches to treat cancer. In the sections below, the most important research findings using checkpoint blockers to extend the lives of patients with cancer, major gaps in the field, major barriers that inhibit progress, and initiatives needed to accelerate clinical and translation research are summarized.

The most important research findings that extend the lives of patients with metastatic cancer:

1. Immune checkpoint blockade, which has been used in chronic viral infection, has been translated to treat cancer. Efforts to restore latent anti-tumor immunity have focused on PD-1, PD-L1, and CTLA-4. Antibodies targeting either PD-1 or PD-L1 have been able to restore immune function in the tumor microenvironment whereas antibodies targeting CTLA-4 restore tumor immunity at the priming phase. A RCT using Ipilimumab, or anti-CTLA-4, with or without gp100 peptide vaccine, as compared with gp100 alone had improved overall survival in patients with previously treated metastatic melanoma (Hodi et al., 2010). The overall median survival was 10.1 months among patients who received Ipilimumab alone (hazard ratio for death in the comparison with gp100 alone, 0.66; \( p = 0.003 \)). Patients who received Ipilimumab + gp100 had a median survival of 10.0 months as compared to 6.4 months among patients who received gp100 alone (hazard ratio for death, 0.68; \( p < 0.001 \)). Although Ipilimumab can produce durable long-term responses in patients with advanced melanoma, it is associated with significant immune-related toxicities. By contrast, antibodies targeting either PD-1 or PD-L1 have produced significant anti-tumor activity with considerably less toxicity.

2. The tolerability of PD-1-pathway blockers and their unique mechanism of action have made them ideal backbones for combination regimen development. Combination approaches involving cytotoxic chemotherapy, anti-angiogenic agents, alternative immune-checkpoint inhibitors, immunostimulatory cytokines and cancer vaccines are currently under clinical investigation (Sharma & Allison, 2015).

Major gaps in the field of metastatic cancer research:

1. It is unknown how successful immune checkpoint blockers can be when treating T cell and neoantigen poor tumors, which may be the majority of the most common and/or deadliest human cancers (e.g., breast, prostate, non-MMR colorectal, and pancreas).
2. It is unknown how durable responses are to immune checkpoint blockers.

3. There is an incomplete understanding of the mechanisms of resistance to immune checkpoint blockers.

4. There is an incomplete understanding of the mechanism of action of combination therapy with immune checkpoint blockers. Without an understanding of the mechanism of action, there is no real way to properly target combination therapy and avoid resistance.

- Collaborations required to meet these gaps: Incentivize more research done by interdisciplinary teams of basic and clinical scientists.

**Major barriers that inhibit progress towards extending the lives of metastatic cancer patients:**

Scientific Barriers: (1) A lack of mechanistic preclinical modeling that provide translationally actionable information for early phase clinical trials. There are limitations to current models for the study of immune responses and cancer dormancy. Furthermore, small samples sizes used limit reproducibility of this work. (2) There is a lack of understanding of the clinical relevance of experimentally discovered mechanisms. Clinical trials are resource intensive and there is a lack of study design standardization. (3) There are variations in human genetics that can play a role in outcomes. (4) Clinical trials have significant challenges that include their high cost, time, the need for appropriate end points, and the need for regulatory approvals. (5) Collection of biospecimens presents challenges due to small samples sizes, a lack in the ability to collect pre- and post- treatment samples, and tumor heterogeneity. In addition, it is difficult to select an analyte platform.

Programmatic Barriers: N/A.

- Suggested ways to overcome these barriers: N/A.

**Initiatives needed to accelerate clinical and translational research:** (1) Co-clinical trials, or integrated human/mouse studies, require a multidisciplinary team and the integration of information between mice and human patients (Clohessy & Pandolfi, 2015; Twyman-Saint Victor et al., 2015). (2) There is a need for rapid deployment of next-generation clinical trials informed by research findings and an integrated analysis between animal and human studies. (3) Ongoing research investigating immunotherapies are needed.

**Question and Answer Session Transcript:**

I'll take on Colonel Shriver's role here in making sure I'm asking a question. So CTLA-4 and PD-1 blockade, those are gross levers on the immune system, and you relate to how the body responds to viruses. And there's much more elegant cascade of events that is involved in the body responding to viral infection, including dendritic cells. And you can use killed virus, so you're zapping tumor and releasing antigen. You can use adjuvants. There was some discussion on Imiquimod, and you can use a lot of that with antiviral therapy. Do you see the field on this immunotherapy being more directed on trying to drive these T cells more specifically, or trying to involve? Or do you see it more as trying to engage other aspects of the
immune response?

Yeah. No, I think that's a great question. And my bias is the latter. I think that we do have to, in order to generate the most effective immune response, we're going to have to engage other cells, cells of the innate immune system. Dendritic cell activation, as you pointed out, is an important step. Identifying very suppressive mechanisms in the tumor microenvironment that Lisa pointed out, too, is going to be important. And those suppressive mechanisms can arise from macrophages. They can rise from dysfunctional NK cells, for example. It's not just T cells. Ultimately, to get the most durable and effective responses, you're probably going to have to marshal a whole collection of immune cells to try to really make the antitumor response the most effective.

So Andy, you and others have talked a lot about checkpoint inhibitor therapy. And for metastases, I mean, what is showing a ton of promise in leukemia and lymphoma, which is systemic. And I mean, essentially, the same problem are Chimeric antigen receptor (CAR) T cells and directed against a specific antigen. For solid tumors, that's a problem, too, because what's the antigen going to be, right? But where do you see the next big steps happening in that?

In CAR T cells?

Yeah, in CAR T cells. What is the barrier to employing CAR T cells in stage IV?

Yeah, that might be a better question for the next speaker, I believe, is coming up. But that's a big barrier, obviously, like solid tumors and trying to understand what is so difficult about solid tumors to get the CAR T cell therapy to work. I don't think I have anything that intelligent to say about it right now, especially given the lack of time. But let me take a pass on that and maybe we can talk offline.

Commander Rivera?

Seems like there's a little bit of similarity with Dr. Fisher’s work with an injury mechanism that supports immune checkpoint blockade. With regard to radiation, it's nice because it's limited, so you can treat one area. So I guess you can re-dose. Have you tried re-dosing or escalated dosing to perpetuate the duration of response?

Yeah. No, so in the clinic, anyways, I think that's a great idea. In mice, we've done a little bit of that. But what I can say is, usually higher doses are better, maybe not so much how many times you treat. Usually, at least in our hands, the higher dose is better. But I think in the clinic, because we have the technology now to go after, there is some talk about oligometastases, metastatic patients have very few lesions. With some surgical approaches, with target radiation, you could treat many, if not all, of these lesions. And is there going to be a benefit to that in terms of durability response? I think that's a very fascinating and unanswered question that we would actually like to pursue.

Do we have a comment from Dr. Kohn?

I thought it was really interesting when you were introducing your topic, before you really
(started talking about abscopal and that interaction, you made the comment about the tumor dormancy and the duration of the dormancy that is observed, certainly, in ER-positive breast cancer and in some other settings, and putting the different topics we've been listening to. I wanted to get your thoughts, and then I'm going to throw it open to everybody in the panel later about how immuno-oncology approaches can be leveraged, specifically to address dormant tumor cells.)

Yeah. Well, I think that what Joan Massagué presented yesterday, I think, was very enlightening, just trying to understand some of the mechanisms that maybe the immune cells may play in trying to keep cells in a dormant state. His data on the NK cells, a lot of what Julio talked about earlier today. So I'm interested in terms of a viral infection, is there really just a window of opportunity with all these different immune therapies? What is that window that we're creating? And with the dormancy problem, it's likely, I would imagine, that the dormant state is probably going to outlast maybe some of these windows that we can generate. So how do we go about that? Can we, again, combine agents that may specifically attack the dormant state in order to maybe shrink that window but still allow the therapeutic window to take over? These are all unexplored questions that I think we have to, as a group, solve.)
The most important research findings that extend the lives of patients with metastatic cancer:

1. Novel therapies for the treatment of high-risk tumors (i.e., metastatic disease in children > 18 months old and/or MYCN amplification) are urgently needed (Noll et al., 2013). Survival of neuroblastoma patients with recurrent disease is currently less than 10 percent. In addition, particularly since this is a pediatric population, there is a need for novel therapies that are more effective but have less severe side effects. Recent clinical progress in the treatment of metastatic disease include myeloablative chemotherapy followed by bone marrow transplantation (Matthay et al., 2009) and retinoic acid and anti-GD2 therapy for treatment of minimal residual disease (Yu et al., 2010).

2. Anaplastic lymphoma kinase (ALK) mutations are present in 12 percent of neuroblastomas. The use of ALK inhibitors to treat neuroblastoma has been tested in clinical trials, but patients developed resistance to treatment. Another proposed treatment is the use of targeted radiotherapy with the norepinephrine analog $^{131}$I-MIBG.

3. Neuroblastoma metastasizes mainly to the bone, bone marrow, and liver. Metastatic factors include: BDNF/TrkB acting via PI3K/Akt and MAPK pathway (TrkB inhibitors in clinical trials); Dkk1, a Wnt pathway inhibitor; COX-2/PGE2, IL6, and RANKL involved in bone invasion; SDF-1/CXCR4 involved in homing to bone marrow; PHOX2B suppression; and the Stathmin/RhoA/ROCK pathway.

4. Ewing sarcoma is a cancer that develops within the bones and soft tissues of both children and adolescent patients. The survival rates of patients with localized Ewing sarcoma are greater than 70 percent; however, the 3-year overall survival rate for patients with metastatic disease is approximately 20 percent (Grier et al., 2003). Novel treatment strategies for Ewing sarcoma include: the targeting of the IGF-1 pathway, which has resulted in a response within a small population of patients; PARP inhibitors used in combination with DNA-damaging agents; treatments targeting EWS-FLI1 or its downstream targets (e.g., LSD1, HDAC, DNA methyltransferases); immunotherapy; and zoledronic acid.

5. Ewing sarcoma metastasizes mainly
to bone, bone marrow, and lung. Thus far, Dkk2 (acting partially via SDF-1/CXCR4/Rac1 pathway), the ERBB4/PI3K/Akt pathway, and the Wnt/β-catenin pathway have been identified as factors involved in Ewing sarcoma metastasis (Figure 18) (Pedersen et al., 2016). EWS-ETS fusion protein down-regulation has been proposed as a treatment for this disease, but the safety of this treatment has not yet been demonstrated.

6. Hypoxia increases the metastatic potential of Ewing sarcoma and neuroblastoma. Notably, Ewing sarcoma cells that have been exposed to hypoxia metastasize to the bone. This finding is clinically relevant because lung and bone metastasis are indicators of poor prognosis in Ewing sarcoma patients.

7. Neuropeptide Y (NPY) release and circulation is associated with worse patient outcomes as it is associated with metastasis and may promote metastasis in the tumor microenvironment (Galli et al., 2016).

8. Prenatal stress results in greater rate of metastasis in a murine model of neuroblastoma.

**Major gaps in the field of metastatic cancer research:**

1. The role of non-genetic factors in pediatric malignancies is well understood and is currently understudied. Since pediatric tumors are considered genetic diseases, there is significant research that focuses on the identification of novel mutations, typically on the basis of primary tumor analysis. Although this has led to a better understanding of the genes that contribute to a predisposition for neuroblastoma as well as novel fusion proteins in Ewing sarcoma, the underlying mechanisms of metastasis for these cancers is not well understood. For both neuroblastoma and Ewing sarcoma, the same mutations or translocations are responsible for both localized and metastatic tumors, highlighting the point that other factors may be involved in the metastatic process of these diseases.

2. The role of tumor microenvironment in metastatic progression remains unclear. Similar to overall metastatic pathways, the role of tumor microenvironment in progression of pediatric tumors is understudied. In addition, little is known regarding the specific interactions between tumor cells and the stroma (e.g., Schwannian stroma, bone marrow). Therefore, it is unknown whether the pathways, such as NPY, are involved in metastasis can be targeted more universally.

3. It is not yet understood how a patient’s physiological state and systemic responses impact tumor growth and the effect of cancer treatment. For instance, it is unknown how the immune system is impacted by stress and how this impacts disease progression. Differences in host response versus differences in tumors should be further investigated.
Collaborations required to meet these gaps: N/A.

Major barriers that inhibit progress towards extending the lives of metastatic cancer patients:

Scientific Barriers: (1) There is an overall lack of interest in the study of pediatric tumor metastasis (e.g., the role of the tumor microenvironment, tumor cell plasticity, etc.), as the majority of pediatric cancer research focuses on genetics and epigenetics. (2) There is a lack of human samples to investigate neuroblastoma and Ewing sarcoma metastasis. Tissue banks primarily contain primary tumor samples and blood samples collected at the time of diagnosis. Furthermore, biopsy or resection of metastatic tumors are usually not medically indicated and are therefore not performed, which results in a lack of matching primary tumor and metastatic tumor samples. (3) There are challenges in the experimental modelling of neuroblastoma and Ewing sarcoma as there are no good transgenic models that recapitulate the metastatic process. Although some metastatic models for these diseases have been developed, they have technical challenges. (4) Because these are rare cancers, there is a lack of available tissue samples, patients for clinical trials, and a lack of interest from pharmaceutical companies.

Programmatic Barriers: N/A.

Suggested ways to overcome these barriers: N/A.

Initiatives needed to accelerate clinical and translational research: (1) Stable funding is needed to promote research on tumor plasticity and metastasis in the pediatric cancer population. Incremental research is needed to build on the studies and results that are already available. (2) The creation of collaborative/shared resource laboratories that have expertise in metastatic models and can execute experiments to elucidate the mechanism of disease progression, the testing of select agents to combat the disease, and provide tissue samples from metastasis in the animal models. (3) Tissue banks are needed to match primary and metastatic tumor samples when they are available. In addition, blood samples are needed throughout the course of disease progression. Because these are rare diseases, these samples would have to be collected collaboratively from multiple institutions.

Question and Answer Session Transcript:

Hi, Wanda Salzer at the CDMRP. Thank you for the presentation. Can you tell me how easy it is to find the circulating tumor cells in patients with neuroblastoma or with Ewing sarcoma?
Probably not. I mean, this is all still underdeveloped. And I'm not saying that those methods are developed, they're not. But I think there should be more effort put into trying to develop this.

So we don't even know if we can find them?

Yeah.

Thank you.

Any other questions, task force? Commander Rivera?

This is probably going to be a silly question, but I think neuroblastoma represents a unique opportunity, and it's the only metastatic disease that can regress spontaneously.

Yes, that's a very good point. Thank you, I didn't have time to bring it up. But it's coming back to our looking at the whole global physiological setup of the patient. We don't think about it, but neuroblastoma is really a perfect example. So there is a specific type of neuroblastoma called 4S neuroblastoma. When you have systemic very early in life before its infancy, really, and those children are often born with a systemic disease. But then when they get to about one year of age, the disease starts to spontaneously regress, or it will differentiate to Ganglion neuroblastoma. So those children are not even treated, and we have no idea what is the mechanism. But I think it's a perfect example because something has to systematically change in those children that those metastasis stop growing. And that's a great opportunity.

Yeah, it really is, and not because it's really only the skin metas--

It's the skin and liver and bone marrow, but no bone involvement.

So is there something unique about those immune environments that can cause tumor regression?

It could. So there are different ideas. So the one is the immune response, another one is the level of nerve growth factor (NGF). NGF is the differentiation factor. So the idea is that it's possible that there is increasing NGF levels during development of the child, and this is what stops those metastases from growing. But again, we don't have samples. I mean--

OK. We've got a question four rows back.

I have a question, but I want to make a few comments first, just speaking about pediatric oncology in particular. I thought you did a great job with your talk. And it really highlights, I think, despite the fact that these are very aggressive and often metastatic cancers, we don't know very much about the metastatic part of pediatric oncology as other fields. But I will say that pediatric oncology as a whole, I think, can be a role model, because most patients have
been enrolled in Children's Oncology Group (COG) trials. And we've made great progress based on the fact that the number of patients that are enrolled, whether you're at a site in Kansas or in New York City, most patients are enrolled on clinical trials. And that's very important. There is a resource for researchers. The COG does make samples available. They have Biology Committees where you can present your data and get samples. I think the biggest challenges are related to the fact that there are not many patients and the fact that biopsies, its IRBs are much less friendly. Stan mentioned how we do so many biopsies at the NIH. But even a research hospital like the NIH, the IRBs are not that reticent, they're reticent to do biopsies on children. And then the third point I want to make about 4S versus 4, and neuroblastoma in general-- and it gets to a point you made about dormancy not being important in oncology, so I wanted to ask you about that-- and pediatric oncology, is immunotherapy. A lot of the immunotherapy field was started very early on in pediatric oncology, in particular, in neuroblastoma. The first to recognize that 4S can regress and maybe that's an immune component, but that there were actionable targets that could be targeted with antibody therapy, mostly to the GD2, and has really altered stage 4, not S-- so aggressive bone, bone marrow, liver, metastasis-- in patients that had very poor survival improved it. So I think it led the way a lot for immunotherapy in adult cancers. And the dormancy issue is, as we've gotten better at treating patients, I think we see more and more dormancy. I've seen neuroblastoma patients out where they've responded to immunotherapy, let's say, and chemotherapy, and they're out five years later. But they can have late recurrences. Ewing's, a perfect example, also a tumor that you can see late recurrences as we get better at it. So I think it's important to keep that in mind.

Yeah, I want to comment about COG, yes. COG is Children's Oncology Group. And it's a great consortium. And really, you can get samples. The problem is that, again, you can get primary tumor samples. And this is how we did our studies. I mean, the blood samples had diagnosis, everything is focused at diagnosis point, unfortunately. And then also, they are overloaded. So they take care of clinical trials for treatment. So the biologists like me, when I go ask for samples, I will eventually get it. But believe me, the study I showed you, it took us five years, because we have to wait for the samples, we have to wait for statistical analysis to be done by COG. We need the resources assigned to studying biology, I feel.
Cells as Drugs: A Personalized Immunotherapy for Cancer

Steven A. Rosenberg, MD, PhD

Surgery Branch, National Cancer Institute

Dr. Rosenberg discussed the use of immunotherapy for the treatment of patients with common epithelial cancers. He discussed the recent advancements and success stories of such treatments, in addition to the direction that the research is headed to improve upon such therapies.

The most important research findings that extend the lives of patients with metastatic cancer:

1. Cell transfer therapy is a technique in which cells with anti-tumor activity are administered back into the patient from which they were collected. A large number (>10^{11} cells) of highly selected immune cells with anti-tumor activity can be grown and given back to the patient. This technique can enable the identification of specific cell subpopulations with certain effector functions needed to fight the cancer in the patient. In addition, the host microenvironment can be manipulated prior to cell readministration, allowing these cells to have greater anti-tumor function.

2. This technique is performed by excising the patient’s tumor and culturing the lymphocytes that have infiltrated it, which can be considered anti-tumor lymphocytes. Once these cells have been cultured, they are tested and the exact population of anti-tumor cells are grown to large numbers and readministered to the patient. In addition, patients are lymphocyte depleted prior to receiving these cultured lymphocytes to eliminate the immune cells...
that might hinder anti-tumor activity of this treatment (Figure 19).

3. Adoptive cell transfer studies have investigated the effect of lymphocytes cultured from melanoma tumors that are then administered back to patients for the treatment of melanoma. Of the 194 patients treated with this therapy, objective responses are observed in 55 percent of them. In addition, 23 percent of patients had complete regression of their metastatic disease, which is almost always a durable phenomenon. Of these patients, only two patients went on to have a later recurrence, highlighting the point that, if one is able to reach complete disease regression, it is unlikely that the cancer will return following treatment. Notably, there is no relationship between the extent of the cancer (i.e., tumor volume) and the likelihood of developing a complete regression following treatment. For instance, a melanoma patient with aggressive, extensive tumors had almost complete tumor regression within a month of treatment and continues to have an ongoing complete response at today at 13 years post-treatment. In another example, a patient with a large cutaneous lesion had a complete response to treatment within two weeks. A third patient with a difficult to treat lesion was treated with this therapy; however, the tumors began to recur so the patient was treated a second time and achieved complete regression of disease that is still ongoing 11 years post-treatment.

This patient is an example of one of the only two patients that had complete regression of their disease following treatment that were treated twice as the remaining patients with complete regression only required one treatment. Once a patient receives this treatment, the cells circulate and proliferate for the life of the patient. Lastly, while the brain has a lower rate of response to this treatment than other sites, a good response can still be obtained. Overall, based on the studies in patients with metastatic melanoma, adoptive cell therapy can confer a complete and durable response based on the recognition of immunogenic cancer mutations by lymphocytes.

4. Research has sought to determine whether cancer mutations are recognized as antigenic by these lymphocytes. For a mutation to be recognized as antigenic it must both be able to be constructed to form a 9–11 amino acid peptide as well as to fit the appropriate major histocompatibility complex (MHC) molecule. A protocol for the development of T cells that are reactive to mutations present in common cancers was developed (Robbins et al., 2013; Tran et al., 2014). The advantages of this approach are that prediction of MHC-peptide binding is not necessitated and no tumor cell line is needed. Furthermore, in a melanoma patient with 71 nonsynonymous tumor mutations, 12 tandem minigene constructs were developed and placed in the patient’s antigen presenting cells. Only one of the 12 minigenes, which contained six 25-mer peptides, was recognized; therefore, by mutating these mutations back to their wildtype configuration, a T cell co-culture assay could be performed to identify the mutation that is responsible for the anti-tumor activity of the T cells, in this case being a KIFC mutation. From 30 patients studied with melanoma, 76 mutations were identified that were also recognized by the patients’ own T cells. Notably, in every instance, these mutations were unique in that each T cell that mediated tumor regression recognized a different antigen. Therefore, it is likely that the inability to develop cancer vaccines thus far results from there being no or very few shared immunotherapy targets.

5. In a patient with metastatic bile duct cancer that was treated using the tandem minigene approach to target unique mutations (CD4+ T cells recognized only the ERBB2IP
mutation), a 2.5 year objective response resulted. This treatment has now been performed on 44 patients with epithelial cell tumors (i.e., colorectal, pancreas, bile duct, ovary, and endometrial cancers) and 117 neoepitopes were recognized by the patients’ own T cells. All except for a KRAS mutation was unique. KRAS mutations are present in many different cancers and by identifying a T cell receptor that recognizes this mutation, T cells from the patient can be made to exhibit antitumor properties against this mutation. In one patient with metastatic colon cancer that had failed to respond to previous treatments, this adoptive cell transfer approach using KRAS-mutation reactive CD4+ T cells resulted in tumor regression (Tran et al., 2016). Overall, 77 percent of all patients studied with metastatic epithelial cancers had immunogenic mutations that were unique, except for the KRAS mutations.

6. Notably, studies have shown that T cells recognizing specific tumor mutations can also be isolated from a patient’s peripheral blood based on their expression of PD-1, which presents an advantage over having to collect these cells directly from the tumor (Gros et al., 2014, 2016). T cells that are stimulated by antigen repeatedly upregulate PD-1 and contain antitumor activity, whereas PD-1 negative cells do not possess anti-tumor activity.

Major gaps in the field of metastatic cancer research:

Additional research is aiming to improve the targeting of somatic mutations in epithelial cancers. Some of the research that is ongoing is the purification of tumor reactive cells, the identification of multiple mutation targets expressed by the tumor, cell infusions with anti-PD-1, the transduction of mutation-reactive TCRs, growing cells in media to promote the growth of more naïve cells, knocking out CISH or PD-1 in transferred calls, and the vaccination of patients with mutations recognized by transferred cells.

- Collaborations required to meet these gaps: Collaborations between researchers and industry are needed to make this type of treatment feasible on a larger scale to cancer patients.

Major barriers that inhibit progress towards extending the lives of metastatic cancer patients:

Scientific Barriers: These types of therapies are highly personalized and therefore not something that pharmaceutical companies typically like to be involved with. This makes it difficult to make these treatments available to a broad population of patients with cancer.

Programmatic Barriers: N/A.

- Suggested ways to overcome these barriers: N/A.

Initiatives needed to accelerate clinical and translational research: Greater collaboration between researchers and industry to extrapolate this type of research to an increased number of individuals with metastatic cancer.

Question and Answer Session Transcript:

Well, I would be lucky if I were a patient of yours. That was remarkable. It just shows me what sort of forces you are bringing to bear against each and every one of these patients. While we're not talking about money here, what sort of resources do you-- is this an approach
This is a highly personalized treatment. Clearly, we're using a patient's own cells to target that patient's tumor, and also targeting a unique mutation that's in that patient's tumor and not others. Now, this is not what big pharma likes. They like a drug in a vial. And they don't care if they spent $500 million developing the first vial, so long as they can make the second vial for $1. That's the way biotech and big pharma now think, but that hasn't changed death rates from cancer in the last 100 years, or at least had minimal impact, except for our ability to prevent some cancers by stopping smoking. And so I think we need these highly personalized approaches. Now, when we first published our first cell therapies for patients with melanoma, it was considered that cell therapy would be too difficult to bring to large numbers of people. But there are now 20 commercial companies that are trying to commercialize CAR T cells for the treatment of lymphomas and tumor-infiltrating lymphocytes for patients with melanoma. So it's a highly personalized treatment. It's technically laborious, but it can work. And what we've done is concentrated on what can work, not worried too much about the practical aspects, realizing that the genius of American industry will find ways to do it if, in fact, you could find something that would actually work against these common killers. We can develop the treatment for an individual patient in the course of six to eight weeks. And the way this is now working with the commercial companies that are trying to develop it is you ship a tumor or peripheral blood lymphocytes to that common site, they'll do the exomic sequencing, raise the T cells, and ship them back in a cryopreserved bag for therapy. And that's, in fact, how that's now being done by Kite Pharma, Novartis, Celgene, Bluebird, and other companies that are doing this. So I think it can be made practical, although right now, it's highly experimental.

OK. Question from Colonel Perkins.

So one of the common themes that has come across was the need for response criteria that are specific to this new age of immunotherapy, which is not new to you. So you talked about CRs and PRs, which are classic RECIST response, not really the clinical benefit rate on stable disease. And what are your thoughts about, do you see the same flares? What are your thoughts about the need for immunologic response criteria?

I think these new immunologic response criteria that have been proposed only confuse the situation. What we want to see in patients is the tumor going away. We don't care whether it flares first or doesn't, so long as it ultimately disappears. And I think RECIST criteria are the ones that should be used. You have a tumor, you know what the volumes of those tumors are, you have to shrink them down by at least 50 percent, and not have growth of any lesions or any new lesions. And I think that's a perfectly adequate criteria. I've never seen the need for introducing new immune response criteria for immunotherapy. It's whether the tumor grows and kills you, or whether you can make it go away.

Right, I believe we have time for one last question. I believe there was a question in the back. Sir?

Hello. About a month ago, there was a paper in Science where, quite surprisingly, it was discovered that the proteasome actually played a major role in doing a post-translational protein editing generating neoantigens. Can you comment on that and potentially comment on the role of direct analysis of neoantigens and how that might help the field?
Right, so this was a paper that talked about a new way to create epitopes, not neoepitopes, by post-translationally splicing parts of a protein together to form a protein that wasn't directly encoded by the genome. The problem with that in immunotherapy is that happens not only in tumors, but it happens to normal cells. And those new epitopes are subjected to negative selection in the thymus, and so they don't represent neoantigens. And so whereas I think biologically it's a surprising and very important point, I don't think it adds to the mutational burden of those cancers.
Defining the Influence of Hereditary Variation on Metastasis

Nigel Crawford, MB, ChB, PhD

National Human Genome Research Institute, National Institutes of Health

Dr. Crawford provided evidence supporting the hypothesis that the ability of tumor cells to metastasize is significantly modified by germline polymorphism (i.e., host genetic variation) and varied environmental exposure. Dr. Crawford shared scientific evidence illustrating the most important research findings that have extended the lives of patients with metastatic cancer, major gaps in the field, major barriers that inhibit progress, and initiatives needed to accelerate clinical and translation research.

The most important research findings that extend the lives of patients with metastatic cancer:

   
   a. These modifiers were initially identified using a transgenic mouse models of mammary tumorigenesis known as the polyoma middle-T mouse (PyMT) model. The PyMT model was crossed with a variety of different inbred strains of mice. Transgene-positive females from these progeny were taken and metastasis was quantified in their F1 strains. It was found that F1 strains had significant degree of strain-specific variation in metastasis. Since transgene expression was equal among each strain and expressed at the same time point, it was concluded that germline variants were modulating metastasis. Modifier locus mapping identified Sipa1 as the first example of germline metastasis susceptibility gene (Lifsted et al., 1998b; Y.-G. Park et al., 2005). Since this discovery, other breast cancer metastasis susceptibility genes have been identified using the PyMT mouse model: Rrp1b, Brd4, Ndn, Ard4b, Cadm1, and Cnot2.

   b. Using the same approach, an aggressive model of mouse neuroendocrine prostate carcinoma (TRAMP model) identified three genes, CENPU, RWDD4, and CASP3, as germline modifiers of metastasis in prostate cancer (Patel, Molinolo, Gutkind, & Crawford, 2013). In a cohort of 498 patients with prostate cancer, 12–13percent had dysregulation of one or more of these candidate genes (Winter et al., 2016). Patients that have dysregulation of CENPU, RWDD4, and CASP3 have a poorer disease-free survival and overall survival compared to patients that have normal levels of these genes within their primary tumors.

2. Independent confirmation that germline modifiers are present in the human population. Epidemiological studies and genome wide association studies (GWAS) have proven that hereditary variation impacts metastasis and cancer outcomes in prostate and breast cancer patients (Hemminki, Ji, Försti, Sundquist, & Lenner, 2008; Lindström et al., 2007; Mirabello et al., 2015).
Three major gaps in the field of metastatic cancer research:

1. There is an incomplete understanding of the mechanisms underlying germline susceptibility to metastasis.

2. There is an incomplete understanding of how germline variation influence the somatic architecture of primary tumors and metastases.

3. It is not known if race-specific hereditary variations influence metastasis susceptibility. There is a 1.6 fold higher incidence of prostate cancer in African Americans compared to Caucasians and 2.6 fold higher incidence than in Asian Americans. Similarly, African Americans have a two time rate of mortality than Caucasians and five times higher than Asian Americans.

- Collaborations required to meet these gaps: N/A.

Major barriers that inhibit progress towards extending the lives of metastatic cancer patients:

Scientific Barriers: (1) Lack of adequately powered, non-Caucasian clinical cohorts. (2) Current understanding of the genome is predominantly based on studying Caucasians. (3) Paucity of in vitro and in vivo models of metastasis for most solid tumors. For example, there is a lack of reliable cell lines of spontaneous metastasis. PDX cell lines are difficult to use and not widely available. Cells lines used to study bone metastasis are poor. Similarly, mouse models do not reflect the biology of metastatic prostate cancer. Adenocarcinoma models do not produce bony metastasis and there is a lack of models of spontaneous metastatic prostate adenocarcinoma.

Programmatic Barriers: (1) Poor integration between basic and clinical science. (2) Difficulties in recruiting and retaining bioinformaticians. (3) Data sharing is limited. There is a need for more timely and complete access to human genomic datasets.

- Suggested ways to overcome these barriers: N/A.

Initiatives needed to accelerate clinical and translational research: (1) Define new ways to encourage high-risk and high reward metastasis research. (2) Develop new models of metastasis. (3) Incentivize collaborative research and data sharing. (4) Re-emphasize the importance of basic science in the study of metastasis. (5) Improve training in critical areas to develop metastasis research, such as laboratory techniques that focus on metastasis and training to analyze genomic datasets. Also recruit and retain bioinformaticians and metastasis researchers, and encourage training of physician-scientists. (6) Encourage data sharing and create policies to facilitate data sharing. (7) Re-evaluate how the scientific measure of success. If data sharing is encouraged then it may slow down the rate a primary investigator can publish. If this is the case, the field needs to change their thinking about publishing in peer reviewed articles as the best way to measure success.

Question and Answer Session Transcript:
We have Colonel Rosner.

Nice talk. I agree about the bone models for prostate cancer metastatic to bone, but have you done anything with lymph node or visceral disease and metastasis, because I think clinically, that's a little bit more difficult to manage.

Yes, yes, yes, definitely. So I can certainly tell you, in the mouse models, is that one of our primary data points is nodal metastasis, as well as distant metastasis. So yes, we've used that as one of our most important end points. And then attempting to correlate that with the human metastasis data, but often, human genome-wide association studies, for example, and GWAS that I've used are poorly annotated. And the same data is just simply not available for human cohorts. So I do think that's a problem.

Any other questions from the task force? Commander Rivera?

What are the clinical implications of your research? So if I have a patient, let's say, with melanoma and you're able to identify a germline variation of clinical significance-- so if they have a thin melanoma with otherwise no adverse features, should I do a sentinel node? If they have breast or colorectal, should I routinely screen them or surveil them with imaging now, or--?

This is very much a developing and understudied field. But I think, at least from my point of view, the most important implication of this is for more accurately assessing prognosis at the time of diagnosis. I would argue that the germline does significantly impact the ability of tumor cells to metastasize. Knowledge of specific germline variants that promote or suppress metastasis, I think, could be invaluable. But there's still a lot of work to do, so it's risk assessment at the time of diagnosis.

Colonel Hamilton?

Yeah, we will discussed this a little bit before lunch, but I'd go ahead and pose it again, maybe we can talk about it in the panel as well. We keep hearing the issue of bioinformatics and the bioinformatic bottleneck come up over and over and over again. Is there an answer to this? Or do you want to philosophize on this other than encourage young scientists to go into bioinformatics? I mean, what's the answer here?

I think it's quite simple, there aren't enough bioinformaticians. It's a very difficult area to study. I know from personal experience, it's much easier to work on cell culture, western blots, than sit in front of a computer and do coding. I think it needs to be incentivized, and incentivized in a way that just makes kids want to go into bioinformatics. I think it's as-- money, yeah-- I think it's as simple as that.

OK. Ma'am?
Hi. So I've sat in on hundreds of peer review panels in my capacity. And hearing your fellow scientists comment on each other's ability to carry out the work, that's one of the criteria, right, for most of our evaluations of whether a study should get a good score or not. So do you have any ideas? You note that it's a peer review problem, but at the same time, if we don't have that as a criterion, we're going to be faulted for funding people who aren't capable of doing the studies or haven't demonstrated some kind of--

Absolutely, and I think this goes back to the whole team science aspect of it in that I think these are broad questions that we're asking and they need to be approached in a broad way. So rather than talking about one PI-funding mechanisms, I'm talking about more, not quite consortia funding mechanisms, but mechanisms where the risk is spread, where there's multiple PIs working on this problem, whatever the problem is, where essentially the risk is shared, and whether it's a question that would fall into that high-risk, high-reward broad category. Giving funding to an extremely established researcher is not really high-risk, it's low-risk.

But I should also point out that we have, at the CDMRP, had some award mechanisms where peer review was done in a blinded fashion. So we had no idea-- or the peer reviewers and the subsequent panel that reviewed afterwards had no idea who submitted the proposal. It was based purely on the idea. We haven't done it extensively, but there are some programs that have done it. And it's served in that capacity, being able to judge the science for what it is.

I think that's a brilliant idea. That's a very good place to start, just blinding reviewers. And I think it would be a fantastic place to start. It's a complex problem for sure.
Targeting the Metastatic Niche – Niche Biology in Metastasis

Rosandra Kaplan, MD

Tumor Microenvironment and Metastasis Section, Pediatric Oncology Branch, National Cancer Center, National Institutes of Health

Dr. Kaplan discussed the nuances of the metastatic niche and current models used to study metastatic disease. In her presentation, she highlighted the most important findings that can extend the lives of patients, major gaps in metastasis research, major barriers that inhibit progress, and recommended initiatives to accelerate clinical and translational research.

The five most important research findings that extend the lives of patients with metastatic cancer:

1. Understanding the “pre-metastatic niche” can aid in understanding the systemic nature of cancer. The pre-metastatic niche is a specialized, dynamic environment that supports disseminated tumor cells. Patients can have multiple stages of metastases co-existing in different tissues, at different times.

2. The pre-metastatic niche is composed of bone marrow-derived hematopoietic cells (e.g., hematopoietic progenitors, myeloid-derived suppressor cells, neutrophils, macrophages) (Kaplan et al., 2005). Bone marrow-derived cells can be recruited to and accumulate at distant sites. This process may be promoted by factors secreted by a localized tumor. Recruitment of bone marrow-derived cells seems to precede the arrival of tumor cells or promotes growth of tumor cells at that site.

3. Activated stromal cells upregulate expression of fibronectin in the extracellular matrix to create the pre-metastatic niche (Kaplan et al., 2005). This enhanced expression of fibronectin may make sites more receptive to incoming tumor cells.

4. There is a signaling cascade within the pre-metastatic niche.

5. The metastatic niche is a dynamic environment with recruited cell populations (Figure 20).

Major gaps in the field of metastatic cancer research:

1. Every tumor is different, and tumor

Figure 20. The metastatic niche is a dynamic specialized environment that recruits many cell populations.
cells differ at each tumor site and at different times. Cancer has many unique subtypes, and smaller subtypes with each subtype. Furthermore, every microenvironment is different, and each microenvironment varies at different sites, at different stages, and at different ages. Predisposition to cancer can differ on many levels (e.g., environmentally, genetically).

2. There are several deficiencies in understanding niche biology. Which microenvironmental cells are important in each cancer type and each individual with that cancer? What is that microenvironmental cell doing to support the disseminated tumor cell? Where are the disseminated/metastatic tumor cells? At what times do we see specific changes in the microenvironment or tumor cell?

- Collaborations required to meet these gaps: N/A.

**Major barriers that inhibit progress towards extending the lives of metastatic cancer patients:**

Scientific Barriers: (1) Faithful, accurate, and reproducible models of metastasis are needed.
   Human xenografts most faithfully represent genetic heterogeneity and main driver mutations/epigenetic alterations, but lack a complete immune microenvironment. There is large variability in mouse models. There are few spontaneous models for breast cancer, and no good pediatric genetically engineered mouse models that metastasize.
   (2) There is limited ability to assess impact of treatment and resistance over time.

Programmatic Barriers: N/A.

- Suggested ways to overcome these barriers: (1) Using syngeneic murine model tumors is not ideal genetically, but they can provide a normal host background in C57BL/6 mice. There are murine models of spontaneous metastasis for melanoma, breast carcinoma, and embryonal rhabdomyosarcoma. (2) Define the pre-metastatic window for modeling the metastatic microenvironment. (3) To assess impact of treatment, conduct deep sequencing of the metastatic tumor (including tumor, immune, stromal, and endothelial cells) before and after treatment, conduct exosomal and growth factor analysis over time, and develop preclinical models that incorporate treatment (i.e., chemotherapy, surgery) to evaluate disease status/niche alterations after these procedures. (4) Use information gathered from correlative studies in clinical trials to inform preclinical trial design to better understand mechanism of action, resistance, and rationale combinations. (5) Develop strong preclinical correlative studies. (6) Repurpose drugs that had limited efficacy in the advanced metastatic setting; they may still have benefit in the adjuvant setting or in a different schedule. (7) Study mixed responses (i.e., patients removed from study with new disease despite stable or responding metastatic lesions).

**Initiatives needed to accelerate clinical and translational research:** (1) Sample often (e.g., CTCs, exosomes, tissue/bone marrow biopsies, blood) to understand cell-cell communication and horizontal transfer of genetic material, protein, and RNA during metastatic progression and during therapy. (2) Treat oligometastasis. Use novel combination approaches with
radionucleotides or isotopes conjugated to antibodies, and use more curative approaches such as body radiation, radiofrequency ablation, and combine all with adjuvant therapy. (3) Novel trial design. Combine microenvironment targeting with tumor targeting as adjuvant and neoadjuvant setting. Bring forward novel therapies earlier to patients who are failing standard of care. Steeg, Camphausen & Smith (2011) discuss novel ways to develop trials for metastasis (Steeg, Camphausen, & Smith, 2011).

Additional comments: The use of antibiotics to treat metastasis would enhance the metastatic process by enhancing the microenvironment response to chemotherapy. The microbiome can directly regulate the immune system in ways that are not currently well understood.

Question and Answer Session Transcript:

Are there any questions from the task force? OK. Colonel Perkins.

So just listened to Dr. Massagué yesterday. By the time that cancer is clinically apparent, I think, maybe our understanding could evolve in that people are already metastatic. They're just latent. And those latent lesions may or may not become macromets in the future. You're talking about using medications that may not have been effective in more advanced disease. And a lot of your understanding on how these niches develop. How do you see that playing forward, clinically, given that, by a time the disease is apparent, this has already happened?

So I think that whether you have disseminated disease, even before you're ever diagnosed with cancer, is a real, true, and likely possibility. I don't have data to say one way or the other. But I think it's possible. Whether you can still have a pre-metastatic niche, I think that's also possible. Because you're having systemic changes while you were developing that cancer, in the first place. And I think, whether the tumor cell is dormant at that site, or at other sites, it's not at every site. So it's the interaction of the microenvironment with that local disseminated tumor cell, or if it's distant to that disseminated tumor cell. I think it's still applicable. We want to know about preventing that communication, that adaptation that goes on. Because these tumor cells are adapting, and the microenvironment are adapting. And the more we understand those adaptations that they have of each other, the better we can break that cycle-- whether the disseminated tumor cells are there or not, which I really truly believe they are. But there is a co-evolution, and I think Nigel showed that data very well, that different things are happening when a met is growing in the lung, versus when it's growing in the bone. And they're happening at the same time. The microenvironment component could be different. But if there were key signals that were going on between the two that were essential-- niche factors, so to speak-- then I think it would be a cool target. I mean, I personally have seen the Wnt pathway, for example, come up again, and again, and again. I go to these talks, and I keep having it come up. I don't think we have a great target for it. But the more we get into the details of that, the more we do single-cell RNA sequence of these sites, the better we're going to understand which of those factors are targetable.

Any other questions from the task force? Sir?

Yes. Yesterday, people spoke about the microbiome. And then, today, you talked about repurposing old drugs. In your research, have you found, would there be any use in the
microenvironment for antibacterials, antivirals, anything like that? Have you found that? Would that be, possibly, helpful?

So Dr. Cherukuri would be very angry if I suggested we should use antibiotics to treat metastasis because he would say that antibiotics would enhance the metastatic process by enhancing the microenvironmental response to chemotherapy. But I think that means that the microbiome has a huge role. I mean, for example, in our work, circadian rhythms play a big role. In I think we've shown there's been some data on circadian rhythm impact on bone marrow-derived cell mobilization. But there is in terms of response to chemotherapy, the timing of day that you have surgery. I think these, kind of, soft things that we don't think are important, are. And I think the microbiome can directly regulate your immune system in ways that we don't exactly know. And I think that would also be, definitely, a way that we could do it. But what drugs are you talking about? The one that comes to mind easily is metformin, for example. I see it come up again and again. I think targeted therapy, in particular, for me, is very interesting. People want targeted therapy for the mutation. We saw with lung cancer, it's fascinating, and really effective. I'm interested in those targets, because mTOR, you name it, any targeted therapy is impacting the stroma cell, too-- and maybe differently. And we need to know how that is. And maybe we use it in a different schedule, in a different dose. And we're going to see its impact on stromal cells, for example, or immune cells. And I think that's what I more mean by "repurposing." But any drug is fair game, I think. If you're really thinking outside the box, you should be having any drug on that table to be using, and modeling it as Andy Minn had suggested-- pre-clinically, in that schedule, so that we can see if there is, maybe, a scheduling difference in that way.
Advances in Imaging of Metastatic Disease

Peter L. Choyke, MD
National Cancer Institute

Dr. Choyke discussed recent advancements in the imaging of metastatic cancer, specifically with regard to metastatic prostate cancer. Highly specific, high affinity, small molecular weight PET agents and targeted radionuclide therapies are needed for the more precise diagnosis, accurate staging, and improved treatment of metastatic cancer. In his presentation, he highlighted the most important findings that can extend the lives of patients, major gaps in metastasis research, major barriers that inhibit progress, and recommended initiatives to accelerate clinical and translational research.

The five most important research findings that extend the lives of patients with metastatic cancer:

1. There have been significant advancements in cancer imaging, and particularly in the imaging of metastatic cancer, over the last decade. Vast improvements in magnetic resonance imaging (MRI), CT, ultrasound, and in particular PET/SPECT (e.g., FDG positron emission tomography with low dose computed tomography [PET/CT]) technologies have dramatically improved the field of cancer imaging.

2. PET/CTs have the highest sensitivity for the detection of cancer, and have advantages over other imaging modalities that include the ability to scan the entire body of the patient, having a somewhat quantitative readout, their availability, and the ability to be combined with CT or MRI to increase resolution. Also, the cost has dramatically decreased over time.

3. There are issues with the use of FDG, including a lack of sensitivity and false-positive readouts. The FDA has recently approved additional PET agents for the detection of cancer that include sodium fluoride, choline, FACBC, and DOTATATE.

4. DOTATATE, which binds to the somatostatin receptor and significantly improves the detection of neuroendocrine

Figure 21. Use of Ga-68 DOTATATE compared to conventional imaging methods in the staging of a patient with metastatic prostate cancer.
tumors, pheochromocytoma, thyroid, and carcinoid cancers, shows great promise in the metastatic cancer field. For instance, gallium (Ga)-68 DOTATATE improves cancer staging and the assessment of a patient’s response to treatment (Figure 21). In addition, a therapeutic radioisotope can be added to DOTATATE, such as lutetium (Lu)-177 DOTATATE, to successfully treat metastatic disease with fewer side effects. Using a therapy with such a high specificity can allow for the administration of higher doses of radiation to the cancer without damaging nearby tissues. The 2015 NETTER-1 trial investigated the use of Lu-177 DOTATATE in the treatment of metastatic neuroendocrine cancer and found that treatment reduced the risk of disease progression or death by 79 percent and improved overall patient survival (P. Ruszniewski, 2015). In addition, the ALSYMPCA trial results used radium-223 for the treatment of metastatic prostate cancer and showed for the first time that alpha particles could improve survival in these patients (Hoskin et al., 2014).

5. An additional promising PET agent is Ga-68 (used in Europe) or fluorine-18 Prostate-Specific Membrane Antigen (used in the U.S.) for the highly specific imaging of prostate cancer, which is useful for the staging of metastatic disease, the identification of sites of cancer recurrence, and the assessment of a patient’s response to treatment. In combination with targeted radionuclide therapy (e.g., Lu-177, Actinium-225), patients with metastatic cancer have been successfully treated with modest side effects as well as significant PSA reductions and scan improvements. Specifically, when used in combination with Lu-177, patients had a temporary reduction in cancer burden and an increase in lifespan. Furthermore, co-treatment with the alpha particle Ac-225 significantly improved PSA levels in patients with metastatic prostate cancer.

**Major gaps in the field of metastatic cancer research:**

1. There are a limited number of therapeutic targets that have been identified for cancers, excluding neuroendocrine and prostate cancers. Therefore, there is significant opportunity and need for the development of novel and relevant compounds for use in both imaging and therapies; however, few laboratories worldwide have the capabilities required to do such work.

2. Greater advancements are needed in the development of successful adjuvant therapies for use in combination with targeted radionuclide therapies are needed. This may be accomplished via: (1) Utilizing the patient immune response via immunotherapies, (2) employing radiation sensitizers to increase treatment potency and effectiveness, (3) The temporary expression of specific targets in tumors to increase sensitivity to killing.

- Collaborations required to meet these gaps: N/A.

**Major barriers that inhibit progress towards extending the lives of metastatic cancer patients:**

Scientific Barriers: (1) Greater access to novel targeting ligands suitable for imaging are needed as many prime candidate imaging agents are labeled as “failed drugs” that may actually be useful as high affinity agents with irreversible binding and fast elimination from the patient’s body.

Programmatic Barriers: (1) There is a lack of qualified sites able to develop and test novel
imaging agents. (2) Pharmaceutical companies are not encouraged or incentivized enough to engage in radionuclide development and production.

- **Suggested ways to overcome these barriers:** (1) Inclusion of Pharma in discussions to repurpose failed candidate drugs as potentially useful imaging agents. (2) There is a need for the increased training of radiochemists, physicians and academic scientists to conduct collaborative validation studies. (3) A potential reduction of regulatory barriers that hinder advancements in this type of science.

**Initiatives needed to accelerate clinical and translational research:** (1) The highest priority cancers in which targeted PET imaging and radionuclide therapy need to be better defined. (2) Open dialogue between both the scientific and commercial community to facilitate the identification of candidate imaging agents. (3) Improved infrastructure surrounding the production of these imaging agents.

**Question and Answer Session Transcript:**

Any questions from the task force? Sir?

Peter, you started your talk, and you mentioned several different areas where there's been advancements, technologically. And then, you focused on the PET/CT. And at the end, you were focused, again, on the PET/CT. I'm wondering if you could give some recommendations that might expand beyond that.

Into the other areas?

Yes.

Well, the reason why I did that was that, as I look back on the advancements in, say, MRI and CT scan, they've been vendor-driven. Manufacturers have really done that without the public sector's help, in large part. Perhaps, in ultrasound, there has been more involvement of R01-type grants and things. But the part of that portfolio that really has depended on public funding has been the PET part. And that's almost from the beginning. We've got to realize, this whole field, from a clinical perspective, is probably only 15 years old. FDG, although we consider it part of our armamentarium today, was only approved in 1999. So it's a new thing. And then, there was this whole point where the industry grew, very rapidly, to adapt to this. And then, it's become routine. And now, as we say, what's the next step? That also needs input from public funding, I think. Because it's too expensive. The returns on investment, for companies, are too low. Many companies that I've worked with-- GE has been in and out of it. Siemens has been in and out of this field. I predict some of the ones that are in it will be out of it, because it's very long term, and the payoff is just at the end. So I think it needs some bridging kind of support in order for it to succeed.
This is a little off your topic, but many of the presenters have talked about tumor hypoxemia, or hypoxia, as driving the metastatic process. Are there imaging modalities that will look directly at hypoxia, or surrogates like perfusion, that are on the horizon that can maybe help sort that out?

Yeah. That's a good question. There are a variety of PET agents that the chemistry is such that they stay in the tumor. They bind to hypoxic cells, but they don't bind to normoxic cells. So there are a number of those agents. Now, the PO2 that that happens that is on the order of 10 millimeters of mercury. So for a true hypoxia expert, that's not very useful. So there's a new technology that my colleague, Murali Cherukuri, is working on called electron paramagnetic resonance. And that is a more real-time imaging technique that is still in the experimental realm. It's not made it yet. And there are some structural problems. But it, basically, is a magnetic field where there is a compound that changes its bandwidth, essentially, in direct relation to the amount of PO2. So it's a direct measure of PO2. And he can get very accurate measurements, all the way down to near zero of hypoxia.

So if that can be developed forward, I think that is probably the most promising. One of the things that he's shown that's really interesting, I think, is that hypoxia is not a static state in a tumor. It's actually an oscillating state. Because he has a time resolution of about five seconds. And so, he can scan the tumor every five seconds, non-invasively. And he just shows this pattern. So it's much more complicated than we think, what the hypoxic picture really is.

All right. Time for one more.

Yes. I certainly agree when you said, nobody really knows which specialty is supposed to be doing the treating. Often, tumor board, the consultant will say, well, who do I put the consult into? And nobody really knows.

So basically, the lead into my question is, in your opinion, if the task force were going to try to target a group of clinicians, researchers, to advance this research, should it be just a, doesn't really matter the specialty-- just smart people? Or, in your experience, are there certain specialties that may be better equipped to do this?

Right now, I think it's a team sport, because no one discipline really has the coverage to do that. The sealed-source handling of radionuclides is something that the nuclear medicine physicians are comfortable with, and know how to deal with, where the radiation oncologists really understand dose symmetry. And you the medical oncologists say, wait a second, there's going to be neutropenia here, and some side effects. We need to be on this team.

So like many things in modern oncology, I don't think it neatly falls into one specialty, for now. There has to be a quarterback, and that may be site-specific. Who the champion is in a specific center may be just a matter of local expertise.
Panel Discussions

Day 1 Panel

All right, great. Thank you, sir. Here, from here on out we're going to move to the day one panel. So very quickly, this is a virtual panel. Normally we would bring the presenters up, but due to the lack of space on the stage, we're going to let everyone stay in their seats and so we'll give the opportunity for the task members to ask questions of those who have spoken before we open it up to the audience.

So please be cognizant that the task force will get to make and have those questions first before we move on. We have about 20 minutes and then I'll step up front and give a five minute warning. And then we will wrap up with administrative comments and final comments from Colonel Shriver. Thank you.

Thank you, Colin. So I'll start. If I could ask, Colin, if you could have your slide folks put up the four slide from the administrative opening comments. In other words, my slide. The one that I spoke to. Just to get us back on to complete target recognition. So again we appreciate today's 13 speakers and experts who have spoken so far. As Colin mentioned, this part of the testimony by you to us is a little bit different than a standard meeting that you go to and there is a panel and folks come up and ask questions.

What we want to do in this, in the task force, the 16 of us have been meeting every two weeks since the spring when we first were given this task. And the idea behind the panel was that we, the task force, could then adjudicate any disconnects. Talk about common themes. Sort of our last chance to grab the speakers to get anything reconciled that we need to so that we can get this into the report properly in terms of how you're really feeling about things.

And then also for the panel members to question each other. We have a lot of, obviously, all of you are experts selected and thank you for coming to do this, selected specifically for your preeminence in your fields.

So we welcome, we the task force, welcome you speaking or asking questions of your colleagues in terms of anything that you'd like to sort of have them provide additional detail on.

But let me just sort of start by mentioning what I think we've been hearing in terms of some common themes today.

And so, before I do that, again, that's the charge of the task force right there. And some of you came up here and openly asked, I wonder what I'm doing here. And believe me, you were all selected very carefully and nobody is here because we didn't know exactly what you would bring to the table.

So metastasis and survival are a very complex matter, of course. But at the end of the day, our report will have to answer this question. Clinical and translational research aimed at extending
You know, when I started chairing this task force, I reminded the task force members that this charge to us came out of Congress. This is not part of the Cancer Moonshot. That started in January 2016 with President Obama's State of the Union. This language came out on October 1st, 2015 to the DoD. So this predated anything. Cancer Moonshot has nothing to do with it. It's direct to Congress. And Congress, as I remind the task force members, does two things. They legislate and they appropriate.

So really this is a direct line to the Congress for the task force and ergo, you. So I just ask you to keep that in mind. And again, you're welcome to submit written remarks as long as you get them into us by the end of this month.

But some of the common themes I've heard today are, in fact, I wanted to ask Dr. Fisher because he went last and I don't know if you were here when this was being said, but several speakers mentioned high risk, high reward grants, including long term, greater than five-year grant cycles, multi-disciplinary, consortium grants.

Something that basically, in fact, I even asked one of the speakers who would adjudicate, who decides what high risk, high reward grants should be funded. And we had a very good response to that. Thank you.

But actually then, Dr. Fisher just mentioned, and I wrote down the quote, mechanistic rational strategies have led to the success we now have in melanoma. In fact, specifically mentioned it had nothing to do with guesswork or accidents or anything like that. So I guess my first question, I'll start with you, Dr. Fisher, and ask any of the other speakers who mentioned high risk, high reward research, how do you reconcile these two statements today? One was rational strategies. Just plodding our way to it. It got us to where we are in melanoma. And then other speakers who've mentioned high risk, high reward, which by its nature is a little bit of a gamble and not strategic thinking. So Dr. Fisher, I'll ask you to comment first on that.

Sure. I think that there are many ways of doing it, and they're all inherently problematic. But they all have, to me, some rationale behind them. And I think one way of looking at it is that the high risk is not related to just a crazy idea. It's something that has not been tested, but actually has a plausibility. There is some reason to believe that this is at a theoretical level--

Actually, I would even give an example in the melanoma field. So there was one piece in there that there was an insight, I think, which was the genomic, the dirtiness of the melanoma, of the melanoma genome, that was really considered such an annoyance. But there was an opportunity, I don't I don't know anyone who had this insight, but if somebody had that insight and said, you know, maybe these are all neoantigens. I'm not an immunologist. I'm a genomics guy and I'm a computational whatever, but maybe I'll get together with an immunologist and study whether neoepitopes could all of a sudden explain what's going on. Now that would be risky, because there was really no data. But the reward for that, you know, would be explaining why for 100 years melanoma had always had this little signal of response to various immunotherapies, vitiligo, and things of that nature.

So things that have a certain degree of plausibility, mechanistic basis behind them. So like
really intelligent high risk, high reward. As opposed to I dropped something on my lab bench and, you know, poof. You know, it has a rationale. We've had those, too, and sometimes they can be exciting. But those would be less competitive I guess I would say.

I do think, I know Joan mentioned track record of the investigator. That is really important. On the other hand, we get sort of old and stodgy and stuck in our ways. So teams of young people who will ask the tough questions. I mean if I didn't have students in my lab, I would be a completely different scientist. I need people to stick it in my side and say, you know, wait a minute. This doesn't make any sense. Or Twitter. Or use technologies that I don't really use all the time.

You need that the diversity of approach, as well. But I do think there is value in seeing people who have a track record of whatever the technology is that's needed, we'll be able to get it. And so trusting whether one can achieve the lofty goals is bolstered by people who have technology, perhaps on a team that there is a component of that. That would be at least some way of rationalizing it I think.

I think when researchers react to some conservative kinds of review, they're reacting to reviews where you need to show a lot of data. And what you're actually making, at best, is an incremental advance. And to me, high risk means actually that. That it may fail. In fact, there may be a very good chance it will fail. But if it doesn't fail, then you have something really important and really new. And I think of two callings, two groups, where they try to do high risk. One, you're going to be very familiar with. The one you may not be is venture capital. Venture capital in its original iteration, was designed to fail as much as it succeeded. But when it succeeded, they would have that occasional home run. And that that would push them forward. But they built into the original, it may have been perverted now, but the original description of venture capital was a tolerance for failure.

And the other agency that I have some familiarity, and you'll be more familiar, is DARPA. And I think that DARPA has a tolerance for failure. They do bold things. Sometimes they put a lot of money into those bold things and they don't expect all of them to succeed.

Somehow some of our health agencies haven't been able to do that as well. They're looking for assurance that what you're doing is going to succeed. So I would say, to me, that high risk is tolerance of failure for high reward.

I would like to echo that, having had that experience being an outsider to the field. I'm trained as an engineer. And I had always had trouble being accepted by cancer biologists in the beginning. Until I was appointed-- 15 years. And I think what you just heard from both of these people, what you heard from David, that bringing technology, that's the strength I had being an engineer, learning biology and being able to collaborate with people.

But the frustration we have felt, at least I have felt my whole career, is the reviewers don't want to take any chance. They don't trust that you have a great track record and yet they will ask for some piddling little question, you didn't do this, you don't have preliminary data. And that has to be taken out of the equation. Otherwise, as you've heard repeatedly, it's NIH and other agencies have turned to research reimbursement.
We have a comment. Finish the work, 90 percent of it, then come and if it's 85 percent, then they're going to ask, you don't have that extra. That mentality has to change, and the DARPA and venture capitalist have done it. Bruce brought up a great point.

We have a comment right back here.

So I think one of the problems is how we measure risk and reward. And when I evaluate grants, I don't really know what is really high risk or low risk. I think the reward is always measured by the publications. And if the PI has publications, and maybe even published the proposal, that usually is low risk, high reward. And I don't agree with this at all, because it's a little schizophrenic sometimes. Because it's published, it's considered non-innovative. And then it's not high risk.

So at some point this language has to change. And really focus on the ultimate goal, which is forwarding a field, creating technologies, creating more knowledge around something that is beyond just the rewards of, which is in our grand system, is the publications at this point. So I think it has to go beyond that. And there are places that do this. Some were mentioned. And other countries that do this. That really build and they meet with investigators and they measure outcome of the program beyond just the publications.

Colonel Shriver, I have a question. So as a follow-up to all this discussion about collaboration, it's kind of an old recommendation. I've sat on other committees where this is a recommendation back to, in a report to Congress. So one would hope that scientists are doing that anyway. But I want to ask Dr. Scher, having been one of the lay PIs for the prostate cancer clinical trial consortium that's been so successful using multiple institutions, what have been the lessons learned from making that a success? As we hear people working in silos, that didn't work that way. They were quite successful.

So one of the metrics that we, I'd say part of the reason for doing it, is it really enables everyone to advance their own research agenda. Now that the drugs are getting better, you
often have gaps in your program when you first the protocol and you're in the follow-up interval. And then, you can take on and collaborate or accrue to some other group's trials.

We were very, the DoD had very specific requirements for number of concepts to be submitted by the various sites. I think one of the most gratifying things when we did an analysis after, I think it was year five or eight, we saw, we were able to show that the PI-ship was very balanced across sites. And we put a lot of effort into young investigators. And when we were presenting to the integration panel in January, we had 42 young investigators who aren't so young anymore, who arguably would not have had the opportunity to interact with their sponsors and get the hot drugs, if you will, because they were essentially unknowns. So I can sort of hold the umbrella and most sponsors will come to the senior members of the group. I'm getting too old to do the trial myself, so I'm very happy to pass on to younger people. In fact, that's one of the ways we're judged.

Just to change the topic a little bit, the DoD has a range of grants, which in part depend on the amount or preliminary data that might be there to support the idea. I agree that there has to be some plausibility, something within reason to an idea, to a grant. But they have idea awards, which are again, less preliminary data, but rational. They also have transformative impact awards. Where you are essentially investing a serious amount of money for a collaboration between multiple centers, where it could either do really well or fail.

I think when they first presented the idea of a consortium, we had tried to do that on a few occasions, because prostate was just different than any other disease. And we were a pretty tight community ahead of time. But you could argue that that was a relatively high risk because honestly, I haven't seen anything like it. But without that infrastructure and the support for that infrastructure, we'd have trouble covering the costs to support it just from trials.

Dr. Lee.

I think one thing, without my Moonshot hat on, just NCI hat on, at best, I think I would definitely say perseverance. So the comment about beyond five years. As, Colonel Shriver, you know TCGA in its first iteration was not considered a success. That was in our shop. It was that second iteration. The first iteration of our nano program was not considered a success. Only in its third iteration is it very exciting. Likewise, our proteomics program, not to belittle Henry, but its first Phase was not as exciting as its second. So how to keep that momentum going of the high risk to when it becomes a payoff. Sitting here listening today about references to TCGA, I know that was not planned. It's very exciting to hear that, but it took us 10 years to get to this point. So that's the only thing I would submit as something for the task force to consider.

Yes, Dr. Kohn.

Just a brief follow-up on the CDMRP program. I think it might be helpful to know what the definition is used there for innovation and novel, because I know from the ovarian cancer
I'm just wondering if any of you can comment on sort of access to care in this country. Or all of the science, but how do we get the patients to be seen. Racial disparities. Because we can talk the talk, but unless we get the patients who may be in northern Wisconsin with metastatic esophageal cancer or whatever the disease is, I'm just wondering if any of you have any thoughts and ideas about how to actually get to the patients.

So I've done quite a bit of research in cancer disparities and access to care. And so I think the largest barrier is making sure that the patients are aware of the trials and the resources that are available to them. And then the next step would be to understand what is being asked of them. And to kind of take it beyond that first, will you be in this research study. Because for many individuals who don't really understand, all that they remember are the negative aspects of medical research. And so one of the things that we've done at Siteman Cancer Center is have a somewhat like a patient navigator. We kind of call them kind of our clinical trials recruitment coordinator. But they talk to the patients. They answer additional questions. They follow up with them and give them kind of extra bit of time and information that oftentimes clinicians or the recruiting nursing assistant doesn't have time to provide. But it is absolutely critical. And not just in our academic centers. We need to be recruiting in some of our more rural areas, as well. Or developing relationships with the clinicians in the community oncology clinics to work with the physicians at the academic centers where the clinical trials are being located.

I just wanted to make a comment about rare diseases then. We scholarship patients back and forth for clinical trials. But if you're Medicaid-specific, it's state-specific, and you cannot get patients on the clinical trials. And then you have Medicare, with the supplementals who do not cover certain institutions. And though pharmaceutical companies are paying for clinic visits and multiple areas of those clinical trials, there's actually double dipping going on with clinicians billing patients and only accepting patients who have that insurance. So there's a lot of breakdown in how this all takes place.

I just want to make a comment about the PCCTC and why it is successful, because I closely worked with the PCCTC. One of the main things probably today is most of the presentations were talking about bringing multi-components into the research. So PCCTC, not only the clinical research, but it's fortunately, MSK has the biomarker transmission award. So they bring that the biomarker section also into the PCCTC. They have done the clinical guidelines and then practice it. So if you bring all of this together, then you have almost like it a consortia like PCCTC.
Day 2 Panel

So let's go for a 10 minute panel. So I'll start. And, again, these panel sessions are meant to responses from all the experts including those who testified yesterday. And I think I want to ask some of the other presenters to comment on the question that I challenged Dr. Brody on. So, again, just to regroup, Dr. Brody said, "We need to take a step back and understand the disease better." Dr. Balch said, "We have lost our leadership in cancer research and treatment." Dr. Coussens said, "It's time for the system to be re-evaluated." Dr. Ghajar said, "We need to change the way we look at metastatic specimens." And so on and so forth. There's this theme emerging from you experts that something is not quite right with what we're doing in terms of metastatic cancer. And if we want to make this leap to increasing survival and all that, it's just we're missing some basic foundational elements that just have not been resourced or supported by the way the system is in research in this country. I was thinking of Dr. Balch's where he said, well, it's not that we-- these other countries give more funding. It's that they're starting afresh and so they don't have legacy science that they're funding and pay lines. And so they can take their resources, albeit less than ours, and put it towards new initiative as where we just have to keep funding so much that already has been committed to. What are peoples' thoughts and comments on this general theme, which seems to be emerging today from you?

I'd like to comment, and I apologize if we're not supposed to talk about funding, but we have to talk about funding. Out here in the real world, we've not had budgets in probably 10 years. The pay lines for most of us have absolutely plummeted. When pay lines plummet, it causes academics to have to revert to much safer science in order to keep our research programs alive to support ourselves, our postdocs, our technicians, and our students. Safe science doesn't enable us to do innovative, creative, or science, or to be able to take big leaps. It just simply doesn't because study sections simply will not fund it. Study sections want to see safe science. And so, with pay lines between 4 percent and 7 percent, you eliminate the ability to remake models, to rethink technology questions to re-engineer technology pipelines, or engage in any kind of bold thinking. And so I would say an underlying theme with all of those issues has been where we've all been for the last 10 years just trying to stay afloat.

And I just want to-- I think she's articulated it better than I did of what I meant by taking a step back because we don't have the ability to take the step back and say let's question our models, let's question our science. We have to keep moving forward and not take a break to get the next grant and to overlap.

Right. Yeah. Where we are-- in the media, we hear that the next generation of science is at risk because of where the pay lines are. Well, this is the consequence of where the pay lines are. We're stuck. And we're not going to be able to make a big push forward unless this changes.

Yes, ma'am.
I totally agree with that as well. But I think it's also not just about pay lines. I think it's also about the standard to which we're held to make the next step in our research. So you have to prove first that you know how to do whatever you're doing in order to get the next grant. And you have to have the model built before you get the money to build the model. And so it discourages—the way the system's set up, it discourages innovation because you won't have the track record that you need in order to get the grant funded, so I think that's one of the big problems. And so what that leads to is not only just incremental science, but what we're all doing just historically. We started not that long ago learning about oncogenes and tumor suppressors and the causes of cancer. We're all applying what we know about cancer to try to apply that to metastasis, but it's really a different question. So, in order to really specifically address the problem of metastasis, we can't keep using the same tools and the same knowledge. We have to jump forward, but none of us necessarily—or not all of us have a proven track record to do that different thing. That's the challenge.

So I think we have--I agree completely, but I think we have to be more specific. And I don't think we can ask the task force to ask Congress to fix funding for all cancer research and for metastasis research. I'd like to suggest two kinds of specific approaches around funding, not to dictate what they should be because I think you've heard a lot of great ideas. But one is for multi-institutional, multi-disciplinary networks, such as the tumor microenvironment network that we had through the NIH that was extremely successful. It brought together in a variety of ways, not only the grantees, but they had—at the ACR meetings, they would have tumor microenvironment groups getting together. It really built that field. It was very, very important. And then around the innovation that we've heard about, which still often comes from individuals, one of the impediments we have—my chairman asked all the people in our department to write 10 grants a year. Now, when grants are 10 to 15 pages and with all the ancillary things, it takes weeks to write a grant. But some agencies, the Prostate Cancer Foundation, for one, has five page grants. And, as a reviewer, I can really tell in five pages what's going on. And I think that we have to have an approach to innovative, perhaps, that high-risk idea, five page proposals, reviewed quickly. That's another thing that Vice President Biden has talked about is how inefficient the process is. How we write grants and we hear nine months later. And then we resubmit and hear nine months later. And, by then, the idea is completely stale. So I would advocate for short grants with rapid turnaround around innovative ideas and see if we could have—the task force could recommend a few specific areas where those would be useful.

In the back, ma'am.

So I agree with everything that's been said. I want to add that I think it's because of the work that has been done by many people in this room for a long time before this meeting that we're able to be here at this meeting and have this kind of conversation. And I think that momentum is what needs to propel the next step. I think before now I think the recognition of metastasis as a process that is ongoing all the time, even in stage IV metastatic patients, was not really recognized. And I think we weren't able to do the things that we're able to do now. And the
reason for that then is maybe part of a grant would be having sessions like this where the grantees are together discussing, and not just presenting their data, but what the challenges are to formulate the next grant plan. I don't know if that is ever possible. But if, let's say, you have a DoD grant and-- I'll give a real life example. You have a DoD grant that's looking at dormancy, and maybe my work is going well, but I've got stuck. And I know that I just need to-- I want to get a paper out for the grant and it's important. But an opportunity I know if every year, every two years, or whatever, part of that grant, I'm going to get together with other grantees and I'm supposed to present the problems I'm having, then maybe some system like that would help to continue to kick start that grant, especially if it was a longer grant. In a year or two, I'm saying my problems. And then three or four years, I come back with, oh, this is the success I had. Because I know with the wait, that it's part of the collaboration. And I could email Dr. Coussens probably if I was having a particular problem because she's nice enough to answer me and knows me, but maybe not, maybe she's busy, maybe I'd get her full brain attention if I'm presenting at a meeting like this. So if there was some way to incorporate that in the SEC-- if was like a team grant, I think it would help a lot because these challenges aren't going to go away and because we have momentum.

Dr. Ghajar?

Yeah. Just a follow-up on what Bruce said and give specific recommendations. At the end of my presentation, I said imagine a blank slate. So if you all of a sudden had resources to put into metastatic cancer research, I don't think you necessarily want to just immediately continue what has been done with different initiatives, specific research areas you're looking for, but then say we're going to go with the traditional granting mechanisms and that's what it's going to be. So Bruce brought up, and others have brought up continuing tumor microenvironment. I would also suggest that there needs to be grants that are meant to bring together people from disparate fields who wouldn't necessarily talk to each other or don't have the opportunity to talk to each other as much or work together without funding like epidemiologists and cancer biologists or like mathematicians and cancer biologists or clinicians and mathematicians to redesign treatment regimens, for instance. And, in terms of innovation and encouraging "high risk, high reward," I think one way to do that is not necessarily have defined endpoints or defined time points for these grants. Let them tell you how long it's going to take and have reviewers who can actually really critically judge that. And then have progress reports that aren't necessarily just on paper, but a discussion between the grantees and the reviewers that can-- if we propose aims one through three, and after a year, aim two started looking really bad so we started doing something else, a really experienced person is going to be able to go through that data, watch someone present the data, and say OK, yeah, I completely agree with you, you made the right choice. Or, yeah, it was going the wrong way, but you also should have done this, this, and this. And if we don't see that it in the next year, then this is going to be the consequence. And so how do you get reviewers to commit to that? By rumor I've heard-- like CPRIT in Texas, they pay the reviewers really good money for reviewers, I guess. And so they get the best of the best, the cream of the crop are going and reviewing those CPRIT grants. So is that something that needs to be done? That's maybe something that should be on the

table as well that in order to kind of energize the reviewer pool, there needs to be more at stake
Colonel Shriver?

Yeah. We're going to cut it off. Gail, did you have a final comment and then we'll step out of this?

It's a different topic. So if you'd like me to save it for the end of the day--

Yeah. So we'll have another panel this afternoon. We'll have to wrap up and have this for the panel this-- all right. Howard, you're--

[INAUDIBLE] mechanism is the conflicts issue. And, in point of fact, most of the people who are reviewing the prostate grants don't know much about prostate cancer. And you could argue that could be good because they'll be unbiased. But, in many cases, they just don't understand the issues very well. And in RS4, it was very clear in one project the reviewers were clueless, and we were fortunate to appeal that review. But, in getting to your point, the way the system is set up, the people who actually understand your field are the furthest away from your applications, which ends up working against you.

Thank you.
Closing Panel Discussion

But I'm going to ask Dr. Choyke a question, just out of my being the chair at the moment. So certainly I can see that the benefit of improved staging-- the Will Rogers effect-- for cancer, and having more specific agents. I certainly know that as a clinician.

Particularly, I've had to deal with the new sodium fluoride scans being done by nuclear medicine, which are very sensitive, and identify disease that we were not aware of on prior bone scans. Having to deal with clinicians trying to figure out how to use that information, particularly given that clinical trials, previously, had made decisions on efficacy of treatment based off a progression on bone scan, which maybe you could pick up on progression much sooner with a sodium fluoride. We all want to get the most mileage out of each treatment, so I've certainly had to deal with providers who say, don't do a sodium fluoride scan on my patients-- I only use bone scans. And I just don't know. I guess the question in all of this is you mentioned the gap in studying these new agents. But is there a gap in the uptake of these new imaging techniques to make it commercially available, either from radiology departments, or ordering providers, or even third-party payers?

Yes. So you raise a really important point. I agree with you, by the way, about sodium fluoride. Because what that scan says to you is there's either cancer, or there's nothing. But there's uptake here. And that's troubling to me, because there are many reasons why a bone is damaged and takes up an agent. And so, its non-specificity is really a problem, because it's the difference between saying somebody has metastatic disease-- based on one lesion that's hot on a sodium fluoride scan-- versus really just he hit his knee a few weeks ago. Who knows? So the new agents are better in that respect, in that they provide the specificity that, I think, we're seeking in a scan like this. And I think the future is about scans that will provide that specificity. The second part of your question is about the commercial availability. And the first thing that drives that is reimbursement. So if it's reimbursed, then I guarantee you that there will be people providing it. The infrastructure has been built in the United States already to, pretty much within a year, get any agent that's approved for reimbursement into clinics for dispersal. You may be surprised to see that it's a Ford Focus that drives up to your hospital with several curies of activity in the back trunk, but that is the current way we distribute these things. And the companies like Zevacor, and Cardinal Health, and PETNET have really done an amazing job of logistics to do this really, really complicated chemistry, reducing it down. Cardinal Health, in this area, has a place in Greenbelt, Maryland. It's in a very nondescript office park. You wouldn't know what the heck's going on inside. But inside, they have state-of-the-art cyclotrons producing curies of activity, robotic production in the state-of-the-art GMP facilities, delivering hundreds of doses across the area every day, at very reasonable prices. So I really think that it's very doable, if there's an incentive.

A follow up to Pete, and to any member of the panel. Yesterday, we heard some questions about immune resist. And then, again today, we had Dr. Rosenberg's very strong statement
that it doesn't matter-- either it gets better or it doesn't. And then, Dr. Kaplan made the
comment about stable disease. There are issues in how one designs clinical trials related to that
stable disease. But what I really wanted to get back to was the issue of pseudoprogression.
And more and more, especially, actually, in the private sector, PET/CT has become the knee-
jerking, even though it may neither be approved nor optimal for that disease. Now we have the
influx of immune oncology being used in the private sector as well. And so, comments on how
that might be misleading, or not, in interpretation, and how to approach that, especially when
it's really important to us, in the field of metastasis, to be sure that we can identify new lesions
if they truly are new for research or clinical purposes, but not go overboard.

Well, I'll get started. So FDG works on the Warburg principle. And a lot of things work on the
Warburg principle, beside cancer. Any fast-dividing cell will utilize multiple metabolic
pathways, including Warburg. So T cells, immune cells, macrophages. And certainly, the
experience is that the PET scan gets hotter after. It's almost a good sign that it gets hotter, after
immune checkpoint, in the first scan. It's almost one of these things that you don't do it, because
it really won't tell you very much. So I'm curious to hear what others think. But I share your
concern. When you have an imaging agent that can be utilized by different processes, similar to
the sodium fluoride story, you have the inherent non-specificity. And there's a certain beauty to
seeing the CT scan-- even a non-contrast CT scan-- get smaller. That seems to be much more
definitive than trying to measure SUV maxes, and that kind of thing.

I wanted to change the subject, if that's OK. So I wanted to follow up on something that
Colonel Shriver mentioned earlier. And that is the integration of survivors into some of the
research efforts. We learn from the CDMRP, we began because of that. We continue to get
funding because of survivors. And through some of our awards, we've seen great partnerships
where survivors are part of the research team. We talked a lot about collaboration in the last
two days. And we talked about scientific collaborations. But having survivors being part of
those research teams has been enormously valuable. And I've seen that in some of the large
efforts we've funded. And I think Pat Steeg is a great example. The center of excellence that
we funded on brain metastases, she has really integrated survivors into her research efforts and
program. The rapid autopsy program that started at Hopkins was because of our requirement to
include survivors into that mechanism that funded Sara Sukumar. And then, of course, we have
the example of Dr. Dennis Slamon whose trial on Herceptin really partnered with the survivor
community to really gather the efforts to accrue as many patients as were needed. So I think
that's something that needs to be part of the conversation when we talk about developing a
clean slate of types of partnerships that are needed, collaborations. Because that is part of the
culture we have. Clearly, the survivors are motivated to be part of the research process. And I
think that they just need to be part of the conversation.

I'd just like to add to that a little bit, and to just recall one of the things that was said this
morning. And that was that the patients and survivors are, many times, very interested in
participating, both in the trials, and also in providing materials like bone marrow that, normally,
might be difficult to obtain. So I think it's another benefit of having the survivors well-
integrated into the studies from the beginning, or the patients.

I think it's very valuable to use the patients. It's funny that, when you become a patient,
somehow everyone thinks you had no past life. You're a patient with no skills or experience. But most patients were professionals during the time that they were working, and stopped working when they became metastatic. And they have a lot of value to offer. And a lot of them have been through training like the project lead training, and they understand a lot about the research. We always attend the Metastasis Research Society conferences, and are partnered with them. There's a lot of skill out there that could be valuable, getting the actual patient perspective.

I had a comment about one of the themes we heard, repeatedly, through the two days was "immune therapy." And Dr. Rosenberg is here. He gave a great talk about personalized TIL therapy. We heard another talk earlier about how tumor cell damage, followed by immune checkpoint inhibitors, seemed to improve things there. I just wanted to ask Dr. Rosenberg if he had any sort of similar experience where tissue damage from another mechanism improved his TIL therapy response?

I don't have any evidence for that-- for or against. But now, it's a very approachable question, because we can use a patient's peripheral blood to look at the T cells that are recognizing unique cancer antigens. And so-- and these are some studies that are in progress-- we have, for the first time, now, the availability of techniques that can look at T cell responses, and the diversity of T cell responses against mutations, following, for example, a stereotactic radiotherapy to an individual lesion, or radiofrequency ablation to an individual lesion, to see if there is an increase in anti-tumor responses. I'm not aware that that data exists. In fact, I doubt that it does. But I think it's going to be forthcoming soon. And in any event, we have a way to ask the question now. And that is to study a patient's peripheral blood T cells, and their reactivity against neoantigens, before and after a treatment that might damage an individual lesion. Right now, the talk of abscopal effects and radiation therapy are just anecdotal. And I think there have been no trials to show that stereotactic radiosurgery, to an individual lesion, will improve the response to any maneuver. And I think those kinds of trials are necessary to decide whether or not this is just an occasional anecdote that has nothing to do with the radiation therapy, or whether or not there is a causal impact.

The speaker is no longer here. But seeing what the targeted radiation therapies were doing to some of those tumors, and then maybe incorporating checkpoint inhibitors following that, for minimal residual, kind of makes you wonder about potential.

Dr. Brody, I'll direct this to you. And the rest of the panel, as well, can certainly give their thoughts. You discussed, specifically, that this type of research is a marathon, and we should take a step back. What is the ideal time horizon, in your mind, of an award mechanism to investigate metastasis? It's certainly not a one- or two-year turnaround. But without having the time to flesh it out, specifically, what are your thoughts on that, or other essential components of such a mechanism?

So I think it depends on big picture. So for instance, I think there's some people, like Dr. Rosenberg here, he's able to present that amazing data, because he's learned from decades of experience and research to get to this point. And obviously, that's an example of a great return on investment. I think, for stuff that people younger than me, who have different ideas to go forward, to echo some of the other panelists earlier, I think it's hard to continue to develop and be innovative, but also be smartly incremental and rigorous. Because when you're thinking
about your next grant, you have to think about publishing. What's the reviewer going to think? And the end of the publication, what's the grant reviewer going to think? So I think it's a hard balance. So I was trying to say that, I think, when everyone says high-risk, high reward, I think at the same time, there has to be some diligence, that we just can't go up to the plate and try to go for the grand slam every time. It takes years of experience, and a lot of scientific rigor, to get the point that we can get outcomes like Dr. Rosenberg and others are seeing. And certainly, in pancreatic cancer, since we haven't changed, we haven't really moved the needle that much, in 40 years, in pancreatic cancer. We've got to look in the mirror, and say, yeah, we're going for it. It's important. There are some great pitches that we have right now. There are some great clinical trials. And one of them-- the one I presented-- that I'm excited about. But the reality is, maybe, in a cancer like that, we need to understand the biology a little bit better. Why doesn't the immune system work effectively, and other questions. Why don't targeted therapies, where we know we have an actionable mutation, doesn't work so effectively? But to that point, thanks for the opportunity, because I think a panel that we were both on for DoD. And I think Donna's not here-- but Donna Kimbark, who's our program leader for DoD program. It's kind of interesting, because a lot of things that were raised here, I feel like our panel addressed. And I was talking to Donna about it and I almost feel like the lesion is more difficult than just getting people to try to think out-of-the-box, transformative, collaborative science, engaging young investigators. Because our Career Development Award, all these awards that we put forth that we spoke about in our visionary settings, they had a low receipt. So maybe we even need to think further back, and not say, oh, it's just going to be funding for young investigators, and for collaborative science. But even when we put those RFAs out, we're not getting people that are actually providing grants to these mechanisms. So I'm worried that, actually, it's a state of crisis- - that there's not a lot of people out there going into science-- again, to reiterate my comment at the end, that a lot of people are either going out to Silicon Valley, or Hollywood, or Wall Street, and they're not going into science. Because they see a lot of people-- my students see me working hard, late at night, writing grants, and trying to write the next grant. And why would they go into this? You know? So I think we need to highlight more work like Dr. Rosenberg's to show that this is a marathon, so to speak, that has high-risk, high reward. But I think, unfortunately, with the media and the way the world is today we don't get to highlight those things. But I'm really worried that we need to take even a further step back. And I'd be interested in what other people think about that. Because even when we put out the RFAs, we don't get the receipt.
I have a comment along those lines, which is all these fundamental changes that are being called for with longer funding, collaborative, and high-risk that sound great, also require a really fundamental change in how we do the science because we have trainees and post-docs who need first author papers to move forward. So how are we going to do the collaborative long-term studies with this kind of workforce? So we need more staff scientists, which are much more expensive, and just an overall completely different lab culture, how we do the work in academia. And that's impossible.

I have to amend my statement, before, about the genomic data commons. We didn't have five million downloads since June, we've had 50 million downloads since June. I'm just curious as to who those 50 million people are, worldwide, that in the span of just the Vice President mentioning the genomic data commons, didn't just visit the site, but downloaded the data. So I'm also curious, because, for those of us that have heard me present this, the investigator that some of you were talking about, that you're hoping to get your programs up and running and supporting, are likely to be junior and senior undergrads, at the moment. They were born, likely, in 1997. They will have never heard a modem. And they're also born the same year that Herceptin and the Imatinib were approved. So how best to target that crowd? I know it's an NCI problem that I have, as well as a Moonshot problem. But if that's who you're targeting, they will not look at TCGA, and say, what is this? They will expect that, just like how they expect to have Wi-Fi, internet, these tools. So I just want to make sure that gets put into context, because we're certainly trying to think about that from an NCI perspective, and how to enable those 50 million, and where those 50 million people are. We're certainly going to think about them as well. So I think a good balance of that. I was just talking to Dr. Choyke about this. He was with us when our nano program first launched, and helped a lot of our junior nano-investigators that are now senior nano-investigators, that are actually conducting some of those nano trials. So some balance, and certainly, as I mentioned yesterday, persistence in leadership, would be very, very helpful. I think on this side, after that five-year or seven-year cliff, making sure that there's senior leadership continuing to vie for those programs when they're no longer popular and shiny, would be something, for the junior investigators, very helpful.

I think that's why it's really important that patients, all the other sort of support groups-- illness is an equalizer. Everyone in this room could develop cancer and die from cancer. And this younger population is so enmeshed in social media, so it really is about empowering and outreach to the masses. And it is science, it's money, it's all those things. But I think the younger generation needs to feel the impact. And a lot of that starts with dialogue, and with outreach and education. And it's the patients. And so, hopefully, through social media-- I thought that discussion was actually very interesting-- it really is how we're going to impact this country, or the world. And we're all people. We're all human. So it can really have a significant impact on all of us. And I think we have to impress that on our younger people. And it really starts with all of us here, in conversation.

I think, at least the post-docs that I've had experience working with-- and I have a really motivated one, right now, that wants to be a PI-- I think the fear of the odds that they're constantly given, all the time, from post-doc to independent PI, makes them afraid. But yet, I think, as a group, that age, they're very plastic. So I think we anticipate we're going to have more trouble changing the paradigm than, I think, that that generation does. They're used to...
things changing all the time they're used to a lot of uncertainty. So I think changing the paradigm of a grant will be more stressful to the people that have had, in this room, grants, their whole career, than my post-doc-- who would be happy to get any kind of grant she can get, whether it's collaborative or not. I think they'd be more open to that. So I think we have to keep that in mind when we're talking about young investigator rewards, or how we're going to incentivize the young investigators when they're collaborating with the Dr. Rosenbergs' and the Dr. Coussens' of the field, that are really the giants of the field, per se.

I'm wondering why they're not more seed grants, out there, for the young investigators-- small grants that allow them to get ideas off the ground. They're not a big risk, because you don't have a ton of money into it. But if they can get the idea of the ground, then they become eligible for one or two-- for the bigger grants out there. And that helps the young investigators, keep them interested, get them started. And we do it for metastatic breast cancer. We're just doing it for one kind of cancer. There could be seed grants for all sorts of different cancer issues out there.

Some of the metastasis problems, I think, with seeds grants is that, especially the generation that wants to do seq of everything-- RNA seq, DNA seq, you name it, on single cell sorting-- they want to have, in my case, lineage tracing genetically engineered mice, seed money doesn't help them. They're afraid to even apply, because they need that bar, that level that's higher. So even though it's a great idea, and it's incentivizing.

That's true. But we'll get 80 applications in a year for people wanting seed grants. I mean, there's a lot of people out there wanting them.

But they'll keep to the iterative of science that they're telling you they're doing. And they'll keep the other stuff secret, I think. They'll apply. I applied. I definitely did. Young investigators will apply. But whether that will move the science forward, I don't know.

You can always target those specific ones. We put out specific ones for liver metastasis mouse models, and that type of thing. You can do that.

Sometimes, seed money just is someone to get their skin in the game, and it really piques their interest for moving onward, even if the results of that seed money are not particularly effective. So it just gets them bought in. Dr. Hu?

Thank you, Jeremy. And I just want to make a comment regarding discussions on bioinformaticians. This, probably, is somewhat associated with the comment Dr. Jerry Lee mentioned. So many downloads, probably many bioinformaticians are analyzing the data. And after the presentation by Dr. Coussens, there was a comment made by a gentleman, there, saying, if you give the data to three young bioinformaticians-- I heard him saying "young" bioinformaticians-- you may get three different results. And then, I was thinking, "young," does that mean in training, mentoring? But then, other comments, a little bit, make me worry some. So I want to make my point. And I agree with Dr. Crawford completely, that, right now, recruiting and retaining bioinformaticians is a challenge. And his discussion with Dr. Hamilton, regarding that, is a more training. I agree completely. And then, the issue comes to this is a new field, and it requires mastering, or at least a good understanding, of computer programming, statistics, and biology, and in translational research, clinical data and diseases as well. And it's big data, new methods of biological research. And really, I believe, in my experiences, when a
question is a correctly defined, methods used correctly, analysis done correctly, results are reliable. And different people will give mostly overlapping results. Some of them completely the same, but not necessarily all completely the same. And bioinformatics works best in the team environment. A good example is TCG analysis. Data analysts work in groups composed of many bioinformaticians. They did heavy-lifting work, and pushing the paper to the top journal. We know that. So my take-home message is, if you got the impression that results from bioinformaticians are not reliable, inconsistent, please note that someone with 17 years of experience disagrees with that. If you feel that results from young bioinformaticians are inconsistent, the same person with the 17 years of experience, would agree with that. Thank you.

All right. So that's going to close our panel session. I'm going to hand it over for some administrative remarks, and then I'll do the closing remarks.
# Appendices

## Appendix A: Acronyms and Abbreviations

<table>
<thead>
<tr>
<th>Acronym</th>
<th>Definition</th>
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<tbody>
<tr>
<td>ALK</td>
<td>Anaplastic lymphoma kinase</td>
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<td>AR</td>
<td>Androgen receptor</td>
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<tr>
<td>ASCO</td>
<td>American Society of Clinical Oncology</td>
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<td>AACI</td>
<td>Association of American Cancer Institutes</td>
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<tr>
<td>BCRP</td>
<td>Department of Defense Breast Cancer Research Program</td>
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<tr>
<td>BRAF</td>
<td>V-Raf murine sarcoma viral oncogene homolog B</td>
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<tr>
<td>CAR</td>
<td>Chimeric antigen receptor</td>
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<tr>
<td>CD8⁺</td>
<td>Cluster of differentiation 8 positive</td>
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<tr>
<td>COG</td>
<td>Children’s Oncology Group</td>
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<tr>
<td>CTC</td>
<td>Circulating tumor cell</td>
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<tr>
<td>CTLA-4</td>
<td>Cytotoxic T-lymphocyte-associated protein</td>
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<tr>
<td>4 DNA</td>
<td>Deoxyribonucleic acid</td>
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<tr>
<td>DoD</td>
<td>Department of Defense</td>
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<tr>
<td>EMR</td>
<td>Electronic medical records</td>
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<tr>
<td>FDA</td>
<td>U.S. Food and Drug Administration</td>
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<tr>
<td>FDG</td>
<td>Fludeoxyglucose F 18</td>
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<tr>
<td>GI</td>
<td>Gastrointestinal</td>
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<tr>
<td>GWAS</td>
<td>Genome wide association studies</td>
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<tr>
<td>HER2</td>
<td>Human epidermal growth factor receptor 2</td>
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<tr>
<td>IACUC</td>
<td>Institutional Animal Care and Use Committee</td>
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<tr>
<td>IRB</td>
<td>Institutional Review Board</td>
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<tr>
<td>KRAS</td>
<td>Kirsten rat sarcoma viral oncogene homolog</td>
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<tr>
<td>MAPK</td>
<td>Mitogen-activated protein kinase</td>
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<tr>
<td>MetSC</td>
<td>Metastatic stem-like cancer cell</td>
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<tr>
<td>MHC</td>
<td>Major histocompatibility complex</td>
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<tr>
<td>MRI</td>
<td>Magnetic resonance imaging</td>
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<tr>
<td>mRNA</td>
<td>Messenger ribonucleic acid</td>
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<tr>
<td>NCI-MATCH</td>
<td>National Cancer Institute-Molecular Analysis for Therapy Choice</td>
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<tr>
<td>NGF</td>
<td>Nerve Growth Factor</td>
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<tr>
<td>NK</td>
<td>Natural killer</td>
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<td>NPY</td>
<td>Neuropeptide Y</td>
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<tr>
<td>PAC</td>
<td>Profiling Atlas in Cancer</td>
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<td>PC-3</td>
<td>Prostate Cancer 3 cell line</td>
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<td>PCWG2</td>
<td>Prostate Cancer Working Group</td>
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<tr>
<td>2 PD-1</td>
<td>Programmed cell death protein 1</td>
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<tr>
<td>PD-L1</td>
<td>Programmed death ligand 1</td>
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<tr>
<td>PDX</td>
<td>Patient-derived xenograft</td>
</tr>
<tr>
<td>PDO</td>
<td>Patient-derived organoid</td>
</tr>
<tr>
<td>PET</td>
<td>Positron emission tomography</td>
</tr>
<tr>
<td>PET/CT</td>
<td>Positron emission tomography with low dose computed tomography</td>
</tr>
<tr>
<td>PSA</td>
<td>Prostate-specific antigen</td>
</tr>
<tr>
<td>PTEN</td>
<td>Phosphatase and tensin homolog</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Full Form</td>
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<tr>
<td>PyMT</td>
<td>Polyoma middle-T mouse model</td>
</tr>
<tr>
<td>RECIST</td>
<td>Response Evaluation Criteria in Solid Tumors RCT</td>
</tr>
<tr>
<td>RNA</td>
<td>Ribonucleic acid</td>
</tr>
<tr>
<td>TAPUR</td>
<td>Targeted Agent and Profiling Utilization Registry</td>
</tr>
<tr>
<td>U.S.</td>
<td>United States</td>
</tr>
<tr>
<td>UV</td>
<td>Ultraviolet</td>
</tr>
<tr>
<td>VA</td>
<td>U.S. Department of Veterans Affairs</td>
</tr>
<tr>
<td>VEGF</td>
<td>Vascular endothelial growth factor</td>
</tr>
</tbody>
</table>
Appendix B: References


## Appendix C: Metastatic Cancer Operational Meeting Agenda

<table>
<thead>
<tr>
<th>Time</th>
<th>Speaker</th>
<th>Affiliation</th>
<th>Presentation Title</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Monday, December 12, 2016</strong></td>
<td></td>
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</tr>
<tr>
<td>8:00 A.M.</td>
<td>Craig D. Shriver, MD</td>
<td>Metastatic Cancer Task Force</td>
<td>Welcome and Opening Remarks</td>
</tr>
<tr>
<td>8:05 A.M.</td>
<td>Kangmin Zhu, MD, PhD</td>
<td>Division of Military Epidemiology and Population Sciences Team, Department of Defense</td>
<td>Metastasis Literature Summation</td>
</tr>
<tr>
<td>9:00 A.M.</td>
<td>Clifford Hudis, MD</td>
<td>American Society of Clinical Oncology</td>
<td>Technology to Accelerate Clinical Research</td>
</tr>
<tr>
<td>9:30 A.M.</td>
<td>Joan Massagué, PhD</td>
<td>Memorial Sloan Kettering Cancer Center</td>
<td>Metastatic Latency, Immune Evasion and Outbreak</td>
</tr>
<tr>
<td>10:00 A.M.</td>
<td><strong>Break</strong></td>
<td></td>
<td></td>
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<tr>
<td>10:15 A.M.</td>
<td>Rakesh Jain, PhD</td>
<td>Harvard Medical School and Massachusetts General Hospital</td>
<td>Reengineering the Tumor Microenvironment to Improve Survival of Metastatic Cancer Patients</td>
</tr>
<tr>
<td>10:45 A.M.</td>
<td>Klaus Pantel, MD, PhD</td>
<td>University Medical Center Hamburg-Eppendorf Center of Experimental Medicine</td>
<td>Liquid Biopsy as Diagnostic Tool to Unravel the Biology of Metastatic Cells in Cancer Patients</td>
</tr>
<tr>
<td>11:15 A.M.</td>
<td>Bruce Zetter, PhD</td>
<td>Boston Children’s Hospital and Harvard Medical</td>
<td>Why Do Cancer Patients Die and How to Stop It</td>
</tr>
<tr>
<td>11:45 A.M.</td>
<td>Danny Welch, PhD</td>
<td>University of Kansas Cancer Center</td>
<td>[No Title]</td>
</tr>
<tr>
<td>12:15 P.M.</td>
<td><strong>Lunch Break</strong></td>
<td></td>
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</tr>
<tr>
<td>1:00 P.M.</td>
<td>Peter Friedl, MD, PhD</td>
<td>University of Texas MD Anderson Cancer Center</td>
<td>Dissecting the Metastatic Cascade by Microscopy and Molecular Analysis</td>
</tr>
<tr>
<td>1:30 P.M.</td>
<td>Howard Scher, MD</td>
<td>Memorial Sloan Kettering Cancer Center</td>
<td>Integrated Drug and Biomarker Development to Improve the Lives of Prostate Cancer Patients with Metastatic Disease</td>
</tr>
<tr>
<td>2:00 P.M.</td>
<td>Bettina Drake, PhD</td>
<td>Washington University School of Medicine Alvin J. Siteman Cancer Center</td>
<td>Epidemiological Perspective on Improving Survival among Metastatic Prostate Cancer</td>
</tr>
<tr>
<td>2:30 P.M.</td>
<td>Don Dizon, MD</td>
<td>Massachusetts General Hospital Cancer Center</td>
<td>Looking Beyond Novel Targets: Social Networks and Survival</td>
</tr>
<tr>
<td>3:00 P.M.</td>
<td><strong>Break</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3:15 P.M.</td>
<td>Hensin Tsao, MD, PhD</td>
<td>Massachusetts General Hospital Cancer Center</td>
<td>State of Metastatic Cancer Research – Thoughts from a Dermatologist and Cancer Geneticist</td>
</tr>
<tr>
<td>3:45 P.M.</td>
<td>Anil Sood, MD</td>
<td>University of Texas MD Anderson Cancer Center</td>
<td>Ovarian Cancer Metastasis: Mechanisms and Therapy</td>
</tr>
<tr>
<td>Time</td>
<td>Speaker(s)</td>
<td>Institution</td>
<td>Topic</td>
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<tr>
<td>4:15 P.M.</td>
<td>David Fisher, MD, PhD</td>
<td>Massachusetts General Hospital Harvard Medical School</td>
<td>Towards Curative Approaches for Metastatic Cancer</td>
</tr>
<tr>
<td>4:45 P.M.</td>
<td>All Speakers</td>
<td>Day 1 Panel</td>
<td></td>
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<tr>
<td>5:15 P.M.</td>
<td>Craig D. Shriver, MD</td>
<td>Metastatic Cancer Task Force</td>
<td>Day 1 Closing Remarks</td>
</tr>
<tr>
<td>7:30 A.M.</td>
<td>Julio Aguirre-Ghiso, PhD</td>
<td>Tisch Cancer Institute at Mount Sinai</td>
<td>Targeting Metastatic Cell Heterogeneity to Extend Life of Stage IV Patients</td>
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<tr>
<td>8:00 A.M.</td>
<td>Sarah Goldberg, MD</td>
<td>Yale Cancer Center</td>
<td>Clinical and Transformational Research on Metastatic Lung Cancer</td>
</tr>
<tr>
<td>8:30 A.M.</td>
<td>Alfred Neugut, MD, PhD</td>
<td>Herbert Irving Comprehensive Cancer Center</td>
<td>Epidemiology of Cancer Metastasis: Risk Factors and Prevention</td>
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<tr>
<td>9:00 A.M.</td>
<td>Alana Welm, PhD</td>
<td>Huntsman Cancer Institute at University of Utah</td>
<td>Metastatic Breast Cancer Research</td>
</tr>
<tr>
<td>9:30 A.M.</td>
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<td>Break</td>
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<tr>
<td>9:45 A.M.</td>
<td>Cyrus Ghajar, PhD</td>
<td>Fred Hutchinson Research Cancer Center</td>
<td>Priorities and Unmet Needs in Metastasis Research</td>
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<tr>
<td>10:15 A.M.</td>
<td>Lisa Coussens, PhD</td>
<td>Knight Cancer Institute Oregon Health &amp; Science University</td>
<td>Tissue-specificity and Immune Response to Primary versus Metastatic Disease</td>
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<tr>
<td>10:45 A.M.</td>
<td>Charles M. Balch, MD</td>
<td>University of Texas MD Anderson Cancer Center</td>
<td>The Revolutionary Advances of Immune Therapy as a Cancer Treatment Modality</td>
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<tr>
<td>11:15 A.M.</td>
<td>Jonathan Brody, PhD</td>
<td>Jefferson Pancreatic, Biliary and Related Cancer Center Thomas Jefferson University</td>
<td>Pancreatic Cancer is a Systemic, Metastatic, and Complex Disease</td>
</tr>
<tr>
<td>11:45 A.M.</td>
<td>All Speakers</td>
<td>Day 2 Panel</td>
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<tr>
<td>12:15 P.M.</td>
<td></td>
<td>Lunch Break</td>
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<tr>
<td>1:00 P.M.</td>
<td>Andy Minn, MD, PhD</td>
<td>Abramson Family Cancer Research Institute University of Pennsylvania Perelman School of Medicine</td>
<td>Immune Checkpoint Blockade for the Treatment of Metastatic Cancer</td>
</tr>
<tr>
<td>1:30 P.M.</td>
<td>Joanna Kitlinska, PhD</td>
<td>Georgetown University</td>
<td>Metastatic Progression in Pediatric Tumors: Neuroblastoma and Ewing Sarcoma</td>
</tr>
<tr>
<td>2:00 P.M.</td>
<td>Steven A. Rosenberg, MD, PhD</td>
<td>National Institute of Health / National Cancer Institute</td>
<td>Cells as Drugs: A Personalized Immunotherapy</td>
</tr>
<tr>
<td>2:30 P.M.</td>
<td>Nigel Crawford, PhD</td>
<td>National Institute of Health / National Cancer Institute</td>
<td>Defining the Influence of Hereditary Variation on Metastasis</td>
</tr>
<tr>
<td>3:00 P.M.</td>
<td></td>
<td>Break</td>
<td></td>
</tr>
<tr>
<td>Time</td>
<td>Speaker(s)</td>
<td>Institution</td>
<td>Topic</td>
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<tr>
<td>3:15 P.M.</td>
<td>Rosandra Kaplan, MD</td>
<td>National Institute of Health / National Cancer Institute</td>
<td>Targeting the Metastatic Niche – Niche Biology in Metastasis</td>
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<tr>
<td>3:45 P.M.</td>
<td>Peter Choyke, MD</td>
<td>National Institute of Health / National Cancer Institute</td>
<td>Advances in Imaging of Metastatic Disease</td>
</tr>
<tr>
<td>4:15 P.M.</td>
<td>All Speakers</td>
<td></td>
<td>Closing Panel Discussion</td>
</tr>
<tr>
<td>4:45 P.M.</td>
<td>Craig D. Shriver, MD, Jeremy G. Perkins,</td>
<td>Metastatic Cancer Task Force</td>
<td>Day 2 Closing Remarks</td>
</tr>
<tr>
<td>5:00 P.M.</td>
<td>Adjourn</td>
<td></td>
<td></td>
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</table>