CANCER MOONSHOT
BLUE RIBBON PANEL
REPORT 2016

We are pleased to present the report of the Cancer Moonshot's Blue Ribbon Panel. The report describes a set of consequential recommendations for accelerating cancer research to achieve the ambitious goal of making a decade's worth of cancer research progress in five years and to bring the most promising science and clinical developments to all cancer patients in the near term.

The Blue Ribbon Panel and its seven working groups were given a very important charge: To assess where we are today and to imagine what *could* be done if the entire cancer community was galvanized by the support, coordination, and infusion of funding that the Cancer Moonshot has promised. It will change the course of cancer.

This is an enormous, once-in-a-lifetime opportunity for the cancer community and our nation to come together around a single disease that touches everyone. We are at an exciting time in our understanding of cancer, and the time is ripe to translate this new knowledge into new approaches to preventing, diagnosing, treating, and surviving cancer. However, we also recognize that some of our populations—such as racial/ethnic minorities and those from urban and rural areas or who are poor and medically underserved—continue to suffer disproportionately from certain cancers and have higher morbidity and mortality rates. We have an unprecedented opportunity to address disparities in cancer incidence and outcomes for all populations.

The recommendations in this report represent the merger of science, technology, advocacy, social science, and big data coming together to solve cancer's greatest challenges. Some of the recommendations involve capitalizing on existing strategies that have been proven to work but need the additional support afforded by the Cancer Moonshot to deliver them to all, especially those people who need them most and could benefit from greater access. Others are major initiatives that the cancer community has envisioned but for which resources were

lacking or the technology wasn't ready—until now. The report summarizes the recommendations, which can be found in their entirety at cancer.gov/brp.

The recommendations span the continuum of cancer research from basic to clinical to population science. Nevertheless, cross-cutting themes unify them. Those cross-cutting themes emphasize a focus on health disparities, the importance of prevention, the development of biomarkers and technologies, the need for data sharing, and predictive computational modeling. Importantly, they recognize the critical role that collaboration and partnerships will play in achieving the goals of the Cancer Moonshot. This report reflects a combined effort of government, private industry, researchers, oncologists, patients, advocates, and philanthropic organizations to identify a finite set of programs that are poised for acceleration and that could unleash new cancer breakthroughs if implemented. Our goal is to reduce the number of Americans who develop cancer each year and to prevent more of those who receive a cancer diagnosis from dying of the disease or suffering debilitating treatment-related side effects.

The Cancer Moonshot has brought the entire cancer community, industry, and patients and families together in a way that we haven't seen before. We are proud of the work generated by the Blue Ribbon Panel and its working groups and look forward to seeing these exciting and powerful recommendations implemented and putting our work in action.

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EXECUTIVE SUMMARY

In his final State of the Union address, in January 2016, President Barack Obama tasked Vice President Joe Biden with heading up a new national effort to "end cancer as we know it." Each year over 1.6 million Americans are diagnosed with cancer and almost 600,000 die from cancer. The mission of the White House Cancer Moonshot is to achieve a decade's worth of progress in preventing, diagnosing, and treating cancer in five years, ultimately striving to end cancer as we know it. Under the Vice President's leadership, a full set of recommendations for leveraging federal investments, private sector effort, patient initiatives, and more will be announced later this fall. To provide the scientific specificity for this ambitious goal, a Blue Ribbon Panel (BRP)—consisting of cancer researchers, oncologists, patient advocates, and representatives from the private sector and government agencies—was assembled to advise the National Cancer Advisory Board on the exceptional scientific opportunities that could be accelerated through this initiative.

The BRP established seven working groups to assess the state of the science in specific areas and identify major research opportunities that could uniquely benefit from the support of the Cancer Moonshot and that could lead to significant advances in our understanding of cancer and how to intervene in its initiation and progression. Like the BRP, the working groups had broad representation across the cancer community, and included researchers with subject-matter expertise as well as advocates and government and private sector representatives. The working groups concentrated on opportunities in seven areas:

- Clinical Trials

- Enhanced Data Sharing

- Cancer Immunology

- Implementation Science

- Pediatric Cancer

- Precision Prevention and Early Detection

- Tumor Evolution and Progression

Each working group was charged with nominating two or three important research opportunities that are uniquely poised for acceleration. Each recommendation was expected to define the problem in the recommended research area; the challenges or barriers for advancement; why implementing the recommendation is important; and what it will achieve. Of note, as certain recommendations from different working groups were being developed, it became clear that some could be combined into a single recommendation designed to achieve the goals of the individual recommendations. Thus, while the working groups initially proposed 13 recommendations collectively, the recommendations in the report number 10. The 13 original recommendations can be viewed at cancer.gov/brp.

The working groups were thorough and thoughtful in considering the full range of possibilities. In addition to discussions among the members of the working groups, the BRP also considered ideas—over 1,600—from the broader cancer community, submitted through a dedicated website, email, and other routes.

This report presents the BRP's recommendations of the most compelling research opportunities that should be supported through the Cancer Moonshot.

Network for direct patient engagement. Enlist direct patient engagement through a federated network where patients will be offered comprehensive tumor profiling. Many patients are eager to provide their data, and gathering this information in a linked network of databases would enable more precise knowledge about what works, in whom, and in which types of cancer. Providing their data would also "pre-register" patients for clinical trials, enabling them or their physician to be contacted if their tumor's molecular characteristics made them eligible for new clinical trials. By enabling patients to enroll directly, the network would reach a broader and more diverse patient population; efforts to reach minority and underserved populations will be a high priority.

Cancer immunotherapy translational science network. Organize a cancer immunotherapy translational science network for tumor procurement and comprehensive profiling, for both adult and pediatric cancers, that would include cancers from diverse populations that are sensitive to immunotherapy, as well as cancers that are either resistant or develop resistance to immunotherapy. The goal is to develop and

implement a national strategy to discover new immune targets and evaluate novel immune-based approaches, with the goal of increasing the cure rate in cancer patients, and eventually to develop vaccines to prevent cancers of all types.

Therapeutic target identification to overcome drug resistance. Launch interdisciplinary studies to delineate the range of genetic, molecular, cellular, and physiologic mechanisms that lead cancer cells to become resistant to previously effective treatments, with the goal of informing the development and clinical testing of new therapies to prevent or overcome drug resistance and thereby reducing deaths from recurrent disease in all populations.

A national cancer data ecosystem for sharing and analysis. Create a National Cancer Data Ecosystem to collect, share, and interconnect a broad array of large datasets so that researchers, clinicians, and patients will be able to both contribute and analyze data, facilitating discovery that will ultimately improve patient care and outcomes.

Fusion oncoproteins in pediatric cancer. Improve our understanding of the abnormal fusion proteins that result from chromosomal translocations and have been found to drive many pediatric cancers. Integral to this is a coordinated research effort that will lead to the creation of new preclinical models of these pediatric cancers, the identification of their key dependencies, and the application of this knowledge to develop novel therapeutic approaches that target their mechanisms of action.

Symptom management research. Support research necessary to accelerate the development of guidelines for routine monitoring and management of patient-reported symptoms in all care settings and in all populations, throughout the cancer continuum (from diagnosis throughout survivorship and at end-of-life) and tailored to differing patient and survivor needs. Systematically gathered patient-reported outcomes data and evidence-based symptom management for patients from diverse communities are needed to improve patients' quality of life and the likelihood that they will adhere to treatments that are effective rather than abandoning them because of intolerable side effects.

Prevention and early detection: implementation of evidence-based approaches. Conduct implementation science research to accelerate development, testing, and broader adoption of proven

strategies to significantly reduce cancer risk and health care disparities in all populations, including medically underserved groups. Research should focus on identifying effective, sustainable strategies that involve individuals, families, and caregivers, including those in underserved communities; health care providers and systems; and the greater community. High-priority areas for which much is known about effective prevention and screening modalities are human papillomavirus (HPV) vaccination, colorectal cancer screening, tobacco control, and identification of individuals with genetic predisposition to cancer.

Retrospective analysis of biospecimens from patients treated with standard of care. Analyze acquired tumor samples from thousands of patients, including those from racial/ethnic minority and underserved groups, who have received standard treatments to develop hypotheses about which tumor features predict clinical benefit, treatment resistance, and other clinical outcomes. Once these categorizations are validated in clinical trials, they can be used to develop better risk stratification of cancers and allow tailored treatments to be developed for patients who are at high risk of relapse or who likely would not benefit from standard of care alone.

Generation of human tumor atlases. Create a dynamic three-dimensional map of the evolution of human tumors of all types, pediatric and adult, by documenting the genetic lesions and cellular interactions that guide the development of each tumor as it evolves from a precancerous lesion to advanced cancer while interacting with its microenvironment (including suppressing immune system recognition) to promote tumor growth, metastasis, and development of resistance to treatment. This comprehensive picture of the events and interactions that determine cancer cell behavior will help reveal the processes that underlie cancer, make it possible to predict how cancers will develop and respond to treatment in all populations, and enable the identification of new therapies for cancer treatment and new strategies for cancer prevention.

Development of new enabling cancer technologies. Support the development of promising new technologies that will accelerate testing of therapies and characterization of tumors. These include implantable microdosing devices for testing drug effectiveness directly in tumors; new tumor models such as organoids and other patient-derived tissue models that preserve the architecture and range of cell types seen in

actual tumors; advanced imaging technologies such as single-cell mass cytometry and multidimensional fluorescence microscopy that allow proteins to be visualized within cells; new patient imaging approaches such as radiologic imaging, nuclear medicine imaging methods using new metabolic probes, and PET imaging using labeled antibodies, as well as methods that allow the results of different imaging technologies to be combined; and computational platforms that allow integration of data derived from these studies.

Conclusions

Over the next decade in the United States, over 15 million people, including over 150,000 children, will be diagnosed with cancer. Unless progress is accelerated, over a third of those diagnosed will die of their disease. The BRP recommendations outline a set of opportunities that, if implemented, will transform our understanding of cancer and result in new opportunities to more effectively prevent and treat the disease, which can reduce the burden of cancer in all Americans and the health disparities that currently exist. In particular, Cancer Moonshot funding would enable a remarkable level of coordination—especially across organizations—that will allow data from many different researchers, clinicians, and patients across the country to be assembled in new ways that will be of use to patients, doctors, and researchers. Patients will be able to contribute their data, learn about treatments, and find other relevant information, including clinical trials that may be appropriate; physicians will have access to information that better predicts treatment outcomes and helps them control symptoms and side effects; and researchers will be able to identify possible targets for the development of new treatments and preventive interventions, including immunotherapies, as well as learn more about how to avoid drug resistance. The BRP also recognized that Cancer Moonshot funds can stimulate the development of important new technologies that will themselves be of great importance in research. Importantly, primary prevention is ripe for enabling by Cancer Moonshot funds, which can be used to learn how to better implement interventions that we know are effective at reducing cancer risk in the first place.

Several working groups identified policy issues that were beyond the scope of the BRP but will need to be addressed for many of the recommendations to move forward. The policy issues have been forwarded to the Vice President's Task Force for consideration. These

policy issues include:

- **Coverage and reimbursement**

- **Privacy and consent with regard to patient data**

- **Fragmentation of the delivery of patient care in the community**

- **The need to improve the clinical trials system**

- **Incentives to encourage pediatric drug development**

- **New federal research funding models**

- **Barriers to data sharing**

- **Ensuring that racial and ethnic minorities, as well as other underserved populations, are adequately represented when implementing policy-related recommendations**

REPORT OF THE BLUE RIBBON PANEL

In January 2016, during his State of the Union address, President Obama announced the launch of a major "moonshot" initiative to accelerate progress in cancer research. This momentous effort would be "for the loved ones we've all lost, for the families that we can still save," the President said. President Obama appointed Vice President Joe Biden to lead this Cancer Moonshot with the goal of making a decade's worth of progress in preventing, diagnosing, and treating cancer in 5 years, ultimately striving to end cancer as we know it.

To identify the scientific opportunities that could be advanced by the Cancer Moonshot, a Blue Ribbon Panel (BRP) of experts from relevant scientific sectors was established as a subcommittee of the National Cancer Advisory Board. The 28 members of the BRP included cancer researchers, oncologists, patient advocates, and representatives from the private sector and government agencies. Among them were leading experts from a broad range of scientific areas, including biology, immunology, genomics, bioinformatics, drug development, clinical trials, cancer disparities, epidemiology, and public health.

The panel established a set of working groups, co-chaired by BRP members. Like the BRP, the working groups had broad representation across the cancer community, and included clinicians, researchers with subject-matter expertise, advocates, and government and private sector representatives. The working groups concentrated on opportunities in seven areas:

- **Clinical Trials**

- **Enhanced Data Sharing**

- **Cancer Immunology**

- **Implementation Science**

- **Pediatric Cancer**

- **Precision Prevention and Early Detection**

- **Tumor Evolution and Progression**

The BRP asked the working groups to recommend two to three major opportunities that could lead to significant breakthroughs in cancer research. To this end, the groups met weekly to consider where research in their topic area was now, where it needs to be in 1–5 years, what it would take to get there, and what success would look like.

To help the working groups consider the broadest possible range of ideas, the BRP also reached out to the wider cancer community—and to the public at large—to ask for suggestions. A website solicited ideas in each of the working group topic areas. Ideas were also accepted by e-mail. The panel held "listening" sessions at major cancer meetings to hear ideas from attendees and sought ideas via a Google hangout and at a meeting with NCI's Council of Research Advocates. Altogether, more than 1,600 ideas were received, all of which were forwarded weekly to the relevant working group co-chairs.

Following extensive deliberations, the working groups submitted their recommendations to the BRP. A total of 13 recommendations were approved (the complete list is available at cancer.gov/brp) and, for the purposes of this report, have been consolidated into 10 recommendations.

The 10 recommendations defined a number of areas of underlying emphasis. Among them were the importance of direct patient engagement in cancer research and of expanding clinical trials, the need to address disparities in access to cancer health care, the importance of data sharing to generate large datasets that can be analyzed to advance our understanding of cancer for better therapy, and the need for a national infrastructure to link data repositories and support data sharing and collaboration.

While diverse and broad in nature, these recommendations do not cover all areas of cancer research. Specifically, the panel prioritized those areas of basic, clinical, and population science research that could be most rapidly applied to patient care.

Network for Direct Patient Engagement

D evelop a federated, large-scale patient participation network through which patients will be offered comprehensive tumor profiling. Gathering information about tumor profiles and treatment outcomes in a linked network of databases would enable more precise knowledge about what works, in whom, and in which types of cancer. Moreover, this network should include patients who usually do not participate in clinical trials, such as racial and ethnic minorities and other underserved populations, enabling us to learn more about cancer in all populations. This network would also allow patients to "pre-register" for clinical trials, enabling them or their physicians to be contacted if their tumor's molecular characteristics made them eligible for clinical trials that match their cancer profile. By enabling patients to enroll directly, the network would reach a broader and more diverse patient population.

What is the problem?

Molecular characterization, including detailed genomic profiling, of tumors has demonstrated the heterogeneity of cancer and has identified genetic alterations that may allow selection of targeted therapeutic interventions based on the unique profile of a patient's tumor. However, routine incorporation of detailed molecular characterization of tumors to guide patient therapy from the inception of therapy has been extremely challenging across the full range of cancer types. In addition, patients from underrepresented racial/ethnic minority groups and other underserved populations are not well represented in these past efforts, leading to lack of information on all types of cancers in all populations.

The avenues for patients to register their interest in or enter clinical trials are very limited. The vast majority of Americans do not have easy access to precision cancer testing since oncology clinical trials are offered mainly at large academic cancer centers and not at community cancer centers where most cancer patients receive their treatments. This has resulted in broad segments of the cancer patient population being excluded from clinical trials. Today, only about 5% of all cancer patients are enrolled in clinical trials, with even lower representation of racial and ethnic minorities and those from low-income or rural areas. In addition, we are potentially missing important patterns that could inform better patient care today if we could match up certain tumor molecular profiles with benefit (or even lack of benefit) from specific therapies for cancer.

What are the challenges?

Although comprehensive genomic profiling is technically feasible, its current application in clinical practice has been fragmented and inefficient, limited by cost, lack of standardization of genomic profiling panels and tumor collection, insufficient evidence of broad-based clinical utility, and barriers to data sharing among the research community. The infrastructure for clinical trials designed to evaluate targeted therapies based on tumor profiling requires

significant expansion to ensure that all patients treated in the community as well as at academic centers can participate.

When patients pre-register and provide their cancer tissue, it would be necessary to safeguard their privacy and ensure the genetic and clinical information provided to the network is secure and protected. Patients would sign a consent form, with the understanding that they would later receive personalized information about their health and disease—a comprehensive tumor profile including the genomics of the tumor, as well as characterization of the immune cells and microenvironment. Patients would need to believe that the information they receive about their health throughout the process is useful. This could be facilitated by providing information and incentives for community oncologists to educate their patients about the potential benefits of participating in clinical trials and the network. Education directed to patients would need to explain that a modern definition of cancer relies on tumor profiling and that their contribution may benefit not only them but also future generations. As active participants in the network, patients would feel more truly engaged and benefit from access to information tailored to their own health and cancer status.

Why is this important?

A Network for direct patient engagement would provide comprehensive tumor profiling for a large-scale cohort of cancer patients by linking and leveraging a number of existing pilot programs across the nation that use next-generation genomic sequencing, such as the American Association of Cancer Research Project Genomics, Evidence, Neoplasia, Information, Exchange (GENIE); Oncology Research Information Exchange Network (ORIEN); and Precision Medicine Exchange Consortium (PMEC); as well as other laboratories (academic and commercial) accepting certain standardized operating procedures and quality controls to match participating patients to biomarker-driven clinical trials and collect treatment and outcome data for those who do not go onto trials. A linked model would allow the participation of many labs across the country rather than a single central lab, which would have limited capacity and be cumbersome to access. The opportunity would also exist to combine these genomic profiling data (cancer mutation panels and whole-exome, whole-genome, and RNA sequencing) with immunological profiling data in one network for easier accessibility, sharing of information and deep analysis.

In addition, if patients are willing and able to provide serial biopsies at clinical inflection points (pre-treatment, during treatment, at time of clinical recurrence or progression) throughout their care, this profiling could help us gain a better understanding of how resistance to targeted therapies develops and can be overcome. Through this "big data" collection, more precise knowledge about what works, in whom, and in which types of cancer would be generated to ensure that cancer treatment is based on solid evidence and the best current scientific principles. Data sharing from this network could also be tied to the enhancements

in the recommendation for a National Cancer Data Ecosystem for Sharing and Analysis (Recommendation D).

What will it achieve?

This is an unparalleled opportunity to expand access to advanced tumor testing to improve the precision and categorization of cancers, and then to engage a diverse patient population who would consent to share their clinical data in order to create a matched set of scientific data and clinical outcomes from which new patterns could emerge in a shared analytic framework. Patients are increasingly willing to contribute their own efforts to a national cancer research effort and share their stories and their clinical data so that such patterns can be analyzed for the public good and to improve medical care. A national patient participation network with broad reach and inclusivity that provides comprehensive genomic profiling and immunotyping information would accelerate the enrollment of a diverse set of patients into clinical trials. Patients and/or their physicians would be contacted if their profile revealed a molecular match to new precision oncology therapies, enhancing access to clinical trials at the right time in the course of their cancer treatment. The proposed expanded network would open doors to all patients, including those with limited socioeconomic means, rural populations, and other medically disadvantaged groups who otherwise might never have access to comprehensive cancer testing and novel treatment.

Greater accessibility would translate into greater diversity in the data pool, providing a truer representation of the American population and improved therapy options for all people. Generation of diverse data from this network would accelerate drug development in rare adult cancers, rare subsets of common cancers, and pediatric cancers.

Conducted at the proposed national scale and scope, which could only be done with an infusion of Cancer Moonshot funding, this network would bring an unparalleled opportunity to expand access of all patients to advanced tumor testing, improve the precision and categorization of cancers, and accelerate the pace of our learning about matching treatments to the genetic characteristics of tumors. In short, it would have a transformative impact on cancer research and care, potentially leading to precision oncology being integrated into everyday care in doctors' offices for all patients.

Cancer Immunotherapy Translational Science Network

Organize a Cancer Immunotherapy Translational Science Network that will develop and implement a national strategy to discover and evaluate novel immune-based approaches to treat and prevent both adult and pediatric cancers. The overarching goals are 1) to activate and/or redirect our own immune systems to attack and kill all cancers, including those that develop in racial and ethnic minorities and other underserved patient populations, and 2) to develop preventive immunotherapies as potent as current polio, diphtheria, and rubella vaccines that will protect future generations from developing cancer.

What is the problem?

Our immune system has the intrinsic potential to recognize cancer cells as "foreign" and kill them. The key cell that mediates immune surveillance against cancer, called a T lymphocyte or "effector T cell," kills cancer cells by recognizing specific mutated proteins (referred to as tumor antigens or neoantigens) or misexpressed or abnormally modified non-mutated proteins on cancer cells that distinguish them from their normal counterparts. Many exciting advances in immunotherapy have been reported in the last decade. However, several barriers need to be addressed if we are to improve the effectiveness of immunotherapy. Cancer prognosis is correlated with the presence of effector T cells in tumor sites.

Hence, an important goal is getting activated effector T cells that recognize unique cancer neoantigens, which occur on adult cancer cells, into the tumor to maximize anticancer T cell activity. Because most pediatric cancers express few neoantigens, novel targets need to be identified that are abundantly expressed on pediatric tumors but not on normal tissues and that can serve as the basis for the development of new immunotherapies. T cells can also be redirected to recognize and kill cancer cells by genetically engineering them to express receptor molecules that bind tumor antigens. These "engineered T cells," when transferred back to patients, have been highly successful in treating certain blood cancers. However, for most cancers we know little about what tumor antigens can be safely and effectively targeted to discriminate cancers from normal tissues. To improve engineered T cell therapies, we will need to identify antigens or antigen combinations that are unique to cancer, develop T cell receptors and linked circuits that specifically target these antigens, and improve our ability to optimize the efficacy and safety of these engineered cellular therapeutics.

Another barrier to effective T cell immunotherapy is that tumors generate a disabling immunosuppressive tumor microenvironment that limits the ability of the immune system to act against the cancer. Thus, the extended application of immunotherapy to treat a broad range of cancers will require not only identifying novel tumor antigens and targeting T cells to recognize these antigens, but also developing strategies to disrupt the immunosuppressive properties of the tumor microenvironment.

The immune system can also be "educated" to prevent cancer. To achieve this goal, we will need to identify antigens that arise from the earliest genetic changes that initiate cancers

and develop novel vaccine approaches that can produce effector T cells that recognize these antigens. We will also need to learn how to identify early signals indicating that developing tumors are acquiring resistance to effector T cell function at precancer sites so that we can design strategies to overcome this barrier.

Hence, this recommendation is focused on two key actionable goals that must be rapidly advanced in order to ensure maximal progress against all cancers in all individuals. The first goal is to develop robust cancer immunotherapies that target relevant tumor antigens in cancers and their premalignant lesions, and develop approaches to overcome an obstructive, immune-suppressive tumor environment in both children and adults. In short, we must learn how to both strengthen T cell immunity—either through immunization or engineering—and concurrently discover how to disrupt a hostile tumor microenvironment that prevents T cell activation and infiltration into premalignant or cancerous tissue. A second long-term goal is to develop vaccines and other immunotherapies that will prevent most forms of cancer in all populations.

What are the challenges?

The therapeutic potential of the immune system has not been exploited effectively due to two major barriers that only recently have been appreciated with the advent of the recent immunotherapies: first, that we have so far identified few unique tumor antigens that can be targeted by T cells; and second, the presence of an underlying immune-suppressive environment that surrounds the tumor and begins forming as early as the first premalignant change. We are in an extraordinary period of opportunity, with the development of more relevant preclinical models and unique technologies, including imaging, genomics, proteomics, and the ability to manipulate and analyze large datasets, that can change the way that clinical interventions are conducted and evaluated.

Why is this important?

The success rates of first-generation cancer immunotherapies, such as checkpoint inhibitors, genetically engineered T cells, and new immune activators have improved remarkably over the last 10 years, resulting in durable, long-term survival—and, in some cases cures—for a subset of patients with advanced cancers such as melanoma, blood, and lung cancers. However, only 10-20% of patients with these cancers have long-term responses to current immunotherapies. Rates may be lower among minority and underserved populations. We must learn why some patients who have melanoma (such as President Carter) or lung cancer respond to checkpoint blockade immunotherapy, whereas patients with many other types of adult cancers, including ovarian, breast, pancreatic, brain, and prostate cancer—as well as most pediatric cancers—have brief responses or do not respond at all. Success will depend

on understanding, at the most basic level, each tumor's unique microenvironment, consisting of many interacting cell types, cancer proteins and immune-suppressive pathways, as well as efficient and effective translation of preclinical studies into adult and pediatric patients. The challenge is to increase efficacy, in terms of the percentages of patients, diversity of patients, and the types of cancer, that derive a benefit from immunotherapy.

What will it achieve?

Current immunotherapy treatments represent only the tip of the iceberg of what is possible, and human studies using newly developed, cutting-edge technologies are key to further advances. The combined use of ever-improving genetic tools, synthetic biology tools, and stem cell biology may enable the manipulation of the immune system to eliminate diverse types of cancer. For pediatric cancers, a distinct approach is needed that focuses on identifying cancer-specific antigens that can serve as the basis for both antibody- and cell-based immunotherapies.

A Cancer Immunotherapy Translational Science Network is needed to coordinate all these efforts and to achieve the advances in immunotherapy encouraged under the Cancer Moonshot. This Network would provide a national infrastructure to take advantage of a standardized baseline protocol (including drug treatments and prevention strategies for high-risk individuals, tissue acquisition, and biomarker interrogation) embedded in the broader community (both academic and industry) to test novel immunotherapies efficiently and with a deep understanding of fundamental obstacles to success. The Network should include explicit efforts in both pediatric and adult cancers. Initially, a subset of immune-responsive cancers, such as lung cancer, renal cancer, and melanoma, and their premalignant lesions will be targeted, as well as a subset of cancers where immunotherapies have yet to be routinely successful, such as prostate, ovarian, brain, and pancreatic cancers, and their premalignant lesions.

Success will be recognized by the development of new immunotherapy treatments, including combinations, that increase the efficacy of current immunotherapies in more patients, across many different cancers and population groups, and that lead to therapeutic cures. Lastly, the elimination of cancers "before" they develop and become malignant is an important and exciting goal. Vaccination against high-risk HPV types has been shown to prevent cervical cancer and other cancers caused by HPV. Thus, the development of preventive cancer vaccines against a broad spectrum of cancers—including, importantly, those without a viral etiological agent—could transform society by reducing the burden of cancer on future generations.

PEDIATRIC IMMUNOTHERAPY TRANSLATIONAL SCIENCE NETWORK

Therapies that stimulate the immune system to attack tumors, known as immunotherapies, have recently become a foundational treatment for several cancer types, including melanoma and lung cancer. These therapies can rapidly shrink tumors, and in some patients these treatment responses last for years.

Immunotherapeutic approaches have proven efficacy in a limited number of childhood cancers, including inducing sustained complete responses in children with advanced leukemia treated in clinical trials with genetically engineered immune system cells and improved survival for children with high-risk neuroblastoma.

It is estimated that each year, 16,000 children 0-19 years of age will be diagnosed with cancer; almost 4,000 will die. Yet, for most childhood cancers there are no effective immunotherapies. This is a consequence of a lack of molecular targets in childhood cancers that can stimulate the immune system to attack tumors and a poor understanding of how the microenvironment around tumors in children stymies immune system attack.

In addition, mounting evidence indicates that immune-based therapies, such as immune checkpoint inhibitors, are most effective in patients whose tumors have many genetic mutations. But childhood cancers typically have relatively low mutation burdens, and thus are much less likely to express neoantigens and to be susceptible to immune checkpoint blockade therapies.

This is also true of the majority of malignancies that afflict adolescents and young adults, which are typically driven by oncogenic fusion events with few (if any) additional driver mutations.

Second, most immunotherapeutic strategies in the pipeline are being developed for adult malignancies, and the expression pattern for the target has not been fully considered in childhood cancers, especially with regard to

> **Through this network, researchers would focus on identifying new targets for immunotherapies and testing new treatment approaches, including cancer vaccines, cellular therapy, and combinations of immunotherapy and other forms of therapy.**

expression in normal developing tissues in children from birth through adolescence.

The opportunity now exists to identify optimal immunotherapeutic targets for childhood cancer, define the biological mechanisms by which pediatric tumors evade the immune system, develop novel treatment regimens that target both the tumor and elements in its microenvironment that suppress the immune response, and design clinical trials in which to test these new approaches.

To enhance the speed with which new immunotherapies can be tested in children, the BRP recommendations call for the establishment of a nationwide pediatric translational science network that can support existing childhood cancer clinical trial groups. This translational science network would facilitate the testing of new immunotherapy approaches in childhood cancer and establish a robust research pipeline to help further advance this field of study. Through this network, researchers would focus on identifying new targets for immunotherapies and testing new treatment approaches, including cancer vaccines, cellular therapy, and combinations of immunotherapy and other forms of therapy.

The panel believes that, with immunotherapy, we have uncovered only the tip of the iceberg, and that focused research using cutting-edge technologies and research tools will allow researchers to develop new immune-based therapies capable of eliminating diverse types of childhood cancer and reducing the number of children afflicted each year.

Therapeutic Target Identification to Overcome Drug Resistance

L aunch an interdisciplinary initiative to determine points of cancer cell weakness, known as vulnerabilities, that can be used as targets for the development of new therapies that prevent or overcome a tumor's ability to resist or become non-responsive to cancer therapies. This national effort should integrate the molecular characterization of clinical samples obtained before and after treatment and at disease relapse with experimental data derived from innovative model systems that best mimic what happens in human primary and metastatic cancers as they become drug resistant. To benefit as many patients as possible, this collaborative project should include exemplary pediatric and adult tumor types, including those from minority and underserved populations, and involve conventional chemotherapy, radiation therapy, targeted therapies, and immunotherapies.

What is the problem?

One of the major causes of cancer death is that treatments, that may be effective initially, lose their effectiveness at controlling the cancer. With the loss of drug effectiveness, the cancer regrows unabated and is deemed drug resistant. A second treatment with a different drug or regimen may be temporarily effective, but often the cancer again develops resistance. Drug resistant cancers emerge in both pediatric and adult patients. Whether the mechanisms by which drug resistance develops in pediatric patients are similar to those mechanisms that operate in adult cancers is unclear. It is also unclear whether the mechanisms differ in different populations. It is important to know because currently it is not possible to predict in whom or when drug resistance will develop. Indeed, our understanding of how cancers become drug resistant and what can be done to prevent or overcome drug resistance is incomplete. Being able to accurately predict when a patient may develop drug resistance, and potentially who is at higher risk, could have profound implications for selecting appropriate cancer therapies for individual patients.

Understanding how drug resistance develops is complicated. Some cancers have an intrinsic or innate ability to resist the effects of cancer therapy, whereas others have to adapt to acquire such an ability. The mechanisms responsible for these differences are poorly understood, although it is now well recognized that there are numerous mechanisms, and that these can differ among cancers and from patient to patient and among different racial/ethnic groups. In addition, an individual patient may have multiple different resistance mechanisms at work within the same tumor or within the same cancer cell due to the cancer cell's ability to rewire or reprogram itself to be refractory to the therapy. Resistance mechanisms may be activated by changes that occur within the cancer cells themselves or changes that occur in cells and soluble mediators present in the microenvironment associated with the tumor mass. Resistance mechanisms appear to evolve and change over time, providing the cancer with a constant survival advantage. Despite multiple mechanisms underlying the development of drug resistance, recent studies have suggested that many individual resistance mechanisms may converge onto common drug-resistant cell states. By

understanding the underlying biology of this convergence researchers may be able to identify points of weakness that they can use to design therapies that are able to circumvent the challenge of drug resistance.

What are the challenges?

Despite progress in understanding cancer cell drug resistance over the last decade, knowledge gaps remain regarding the underlying biology associated with the development of drug resistance, and in our ability to identify the relevant cancer cell vulnerabilities associated with resistance to specific therapies in appropriate models that mimic what happens in patients. Until recently, we lacked tools to rapidly identify or systematically assess multiple vulnerabilities or how their inhibition would affect different therapies in patients. These limitations are compounded by the paucity of technologies with sufficient sensitivity to assess the emergence of drug-resistant cancers in patients, particularly in a non-invasive way, and by limited access to appropriate paired clinical samples collected before and after treatment and at the time of drug-resistant disease recurrence because the infrastructure and coordination required to collect, process, and analyze paired tissue biopsies, particularly from those with drug-resistant disease does not currently exist.

This project will require an interdisciplinary effort to comprehensively characterize cancer cell vulnerabilities from serial clinical specimens obtained from patients before and during treatment and upon relapse, and to undertake complementary systematic experimental studies that fully assess and validate potential targets in appropriate preclinical models. Samples should be obtained from pediatric and adult patients receiving conventional chemotherapy, immunotherapy, or targeted therapy—ensuring adequate representation from racial/ethnic minority groups and other underserved populations—and analyzed to generate a map of all available cancer cell vulnerabilities. Priority should be given to studies of pediatric patients with cancers that have a low probability of cure (e.g., tumors of the central nervous system, acute myeloid leukemia, or high-risk subsets of acute lymphoblastic leukemia) and of adult patients with cancers with a high probability of becoming drug resistant.

In addition, the initiative should dedicate efforts to develop non-invasive tests for markers, such as circulating free DNA or tumor cells, to accelerate our ability to detect the emergence of drug-resistant disease in pediatric and adult patients; and develop core capabilities across the nation to accommodate all elements of the project, such as scalable research biopsy and data generation programs, computational analysis, and large-scale screening activities that include ex vivo growth, manipulation, and target validation assessments. Systematic experimental studies should be undertaken in appropriate model systems for pediatric and adult cancers to comprehensively define all mechanisms and vulnerabilities that are linked to a cancer cell being drug resistant. These studies should, to the greatest extent possible,

involve new models and technologies that mimic a clinical environment and what happens in a patient; involve large scale, accurate, rapid screening methods to assess cell responses to multiple small molecules or drugs that interfere with how cancer cells survive; permit modifying genes and proteins expressed by cancer cells to assess their function in unique and common resistance mechanisms and their role after the development of drug resistance; and allow for specific investigations into the role of the cancer microenvironment and different cell populations. Whenever possible, primary tumor tissue should be used to assess drug-resistance mechanisms and efforts should be made to correlate clinical and experimental data.

Why is this important?

The development of drug resistance accounts for most cancer recurrence and for significant cancer-associated mortality. Despite progress made in treating pediatric cancers, intrinsic and acquired resistance are primarily responsible for cancer continuing to be the leading cause of death from disease in children. We are currently unable to predict in which patients and when drug-resistant disease will develop. Developing a map of associated mechanisms and identifying all critical vulnerabilities associated with the development of drug resistance will permit development of new predictive models and therapies to prevent or overcome drug resistance and reduce deaths from recurrent disease.

What will it achieve?

This project, applied to representative tumor and therapeutic contexts in diverse adult and pediatric cancers, would produce new insights into the biology of drug resistance in cancer that directly inform the development and clinical testing of novel therapeutic combinations. Enabled by the Cancer Moonshot's emphasis on interdisciplinary collaboration, the project will make it possible to develop methods to non-invasively detect and molecularly characterize cancer recurrences at the earliest possible time point so that appropriate alternative therapy can be initiated before the tumor burden becomes excessive, and before the cancer has changed its genetic makeup. Furthermore, the national scale of this project should enable researchers to identify targets to which drugs can be developed and provided to patients to avoid drug resistance or alter the cancer cells so that they become sensitive to particular drugs.

A National Cancer Data Ecosystem for Sharing and Analysis

Create a national infrastructure for sharing and processing cancer data. Our ability to accelerate progress against cancer demands that researchers, clinicians, and patients across the country collaborate in sharing their collective data and knowledge about the disease. This recommendation proposes the development of a National Cancer Data Ecosystem that will enable all participants in cancer research and care communities to contribute, access, combine, and analyze diverse and inclusive data sets related to cancer. This broad infrastructure will enable researchers to more effectively mine cancer-related data to develop new strategies to prevent, diagnose, and treat cancers as well as to understand the fundamental nature of the disease. It will also empower patients to take an active role in their care by providing useful knowledge about treatment options and appropriate clinical trials.

What is the problem?

Advances in biomedical research that inform our understanding of cancer and influence decisions on how to treat or prevent it are increasingly reliant on large, diverse data sets and complex analyses by research teams, aided by emerging computational and other technologies. Many powerful sources of data are being rapidly generated in the research and clinical communities. However, these are currently not being fully leveraged, due to the pace at which data are accruing, the lack of a coordinated effort to assemble the data in readily-accessible fashion, and the inability to effectively process the data in an inter-operative fashion. It is now well recognized that these data are critical for identifying and utilizing associations between molecular information (e.g., genomic data from patient samples or model systems) and clinical outcomes in patients (e.g., progression or response or resistance to therapy), but the ability to take full advantage of this opportunity is hindered by the current challenges in the storage, accessibility, and processing of these data.

Limitations in data access affect cancer patients directly. Even with the advent of electronic medical records, cancer patients know all too well the difficulties of accessing their own medical history, transferring their records from one provider to another, or integrating information among providers, for example between a primary health care provider and an oncologist. Patients are often highly motivated and interested in sharing their personal health information and accompanying insights and observations to advance research. However, while patient portals and forums exist, there is no single national infrastructure to enable straightforward contribution of data from patients or the receipt of personal health data. Underserved patients are often not aware of these opportunities and thus are not included in these efforts.

A National Cancer Data Ecosystem will both host and encourage the development of the necessary computational tools and infrastructure to enable optimal cancer data sharing and utilization among researchers, clinicians, patients, and the public. It will also help establish

an ethos of data sharing that addresses the necessary motivations and expectations to allow the ecosystem to flourish, thus accelerating progress in cancer research, treatment and prevention.

What are the challenges?

While there have been localized efforts to achieve the envisioned National Cancer Data Ecosystem, coordination is needed at a national level to address the challenges of connecting these disparate efforts and including all populations. The Cancer Moonshot provides the opportunity to drive a nationally coordinated effort and to bring together partners in the public and private sectors, including academia, patient advocacy organizations, and information technology companies. In addition, important technological advances and societal shifts in attitudes toward data sharing have occurred, such as advances in cloud computing and machine learning, the data revolution, rapid generation of patient health data via wearable devices and other tools, and overall general acceptance of sharing personal data, all of which combine to make this an opportune time to initiate the infrastructure of a national cancer data sharing ecosystem.

Why is this important?

The enormous volume of data being generated by cancer researchers, clinicians and patients today requires a national infrastructure to share, combine and analyze those data in an easy-to-access format. The National Cancer Data Ecosystem will allow both public and private information resources to be readily accessed, discovered and connected through the use of a common information architecture. The need for such an infrastructure is underscored by several of the companion recommendations in this report that require large-scale data collection and integration across many sources, including the Cancer Immunotherapy Translational Science Network (Recommendation B), a Network for Direct Patient Engagement (Recommendation A), Therapeutic Target Identification to Overcome Drug Resistance (Recommendation C), and Generation of Human Tumor Atlases (Recommendation I). Implementing and unifying these new repositories through the underlying data science infrastructure of the National Cancer Data Ecosystem will ensure they can be linked with one another and with future information resources that adopt this common platform.

A central tenet of the National Cancer Data Ecosystem is enabling the public, including all cancer patients and others, to directly contribute their data, or to request a health care provider do so on their behalf, for scientific research. A Network for Direct Patient Engagement encourages patients and providers to directly share cancer outcome information and would serve as one of the initial pilots of the National Cancer Data Ecosystem along with other initiatives in the private and public sectors that enable patient-directed contribution of data. The National Cancer Data Ecosystem will provide appropriate levels of protection

of patient privacy, based on informed patient preference and understanding of risk, while allowing the public to benefit from the fruits of scientific and medical advances and the experience of individual cancer patients and survivors.

What will it achieve?

Implementation of the National Cancer Data Ecosystem has the potential to transform our collective understanding of cancer through the availability of shared patient information and other data derived from diverse cancer research efforts. Encouraged by the Cancer Moonshot, this national cancer information infrastructure will connect currently siloed data sources and serve as the foundation for developing powerful new integrative analyses, visualization methods, and portals that will not only enable new insights into cancer initiation, progression, and metastasis, but also inform new cancer treatments and help initiate new clinical trials. The National Cancer Data Ecosystem is expected to improve the overall quality of care for cancer patients and encourage individuals to directly participate in and derive immediate value from their interactions and contributions. It will provide patients, including those from racial/ethnic minority groups and other underserved populations, with useful knowledge, community, and options as they move through their cancer journey. Over time, the National Cancer Data Ecosystem will vastly improve the efficiency and effectiveness of the nation's cancer research efforts by bringing powerful computational methods and vast amounts of data in an organized fashion in order to enable progress in cancer treatment and prevention.

Laurie Glimcher and Dinah Singer at a Blue Ribbon Panel meeting

Fusion Oncoproteins in Childhood Cancers

I mprove our understanding of the molecular and biochemical mechanisms of transformation driven by fusion oncoproteins. Oncoproteins are critical drivers of many childhood cancers and transform developmentally restricted cells of origin. They are found in both primary and relapsed tumors; few drugs target oncoproteins. With a better understanding of oncoproteins, we can develop faithful models of these pediatric cancers to identify their key dependencies and use this information to develop novel therapeutic approaches that target these mechanisms.

What is the problem?

Each year, more than 40,000 children undergo cancer treatment; each year nearly 4,000 die. Despite significant progress made in the treatment of children with cancer, in the United States cancer remains the leading cause of death from disease among children, with significant short- and long-term toxicity of treatment continuing to affect the majority of children with cancer.

Specific recurrent genetic changes known as translocations are a hallmark of childhood cancer. They are often uniquely defining features of pediatric cancer types (e.g., EWS-FLI1 in Ewing Sarcoma, PAX-FOXO in alveolar rhabdomyosarcoma, and C11orf95-RELA in supratentorial ependymoma). These translocations generate fusions of normal proteins that become oncogenic, targeting developmental programs critical for transformation of the unique cell of origin for each cancer. Fusion oncoproteins are well-defined cancer drivers that are often found in cancers with few other genetic lesions. Therefore, they represent highly credentialed targets for potential therapeutic development.

Recent studies suggest that many fusion proteins work via deregulation of protein complexes that control gene expression or chromatin state, which could provide a path toward mechanistic understanding. However, a much deeper understanding of the protein complexes required to drive cancer-associated gene expression is needed to make further progress against cancer.

What are the challenges?

The number of preclinical models of fusion oncoprotein-driven pediatric cancers is limited. Often in childhood cancers, there is a marked paucity of models for studying the basic molecular mechanisms of the disease as well as therapeutic approaches. A systematic characterization of the genomic and epigenomic characteristics of fusion-driven pediatric cancer models is also lacking.

To date, there has been no systematic attempt to determine the key dependencies generated by the unique fusion oncogene/cell of origin combinations. Recent developments in focused gene editing, such as CRISPR-Cas9-associated screening, will allow detailed assessment

of genes required for specific fusion oncoprotein-associated tumors and the definition of specific functional domains within each fusion protein that are of critical importance.

Although individual research groups are screening for therapeutic targets, the identification of key dependencies broadly across fusion-driven childhood cancers will require a collaborative, systematic approach to cell line collection/generation, data generation and storage, and analyses. Ideally, this approach should include detailed assessment of dependencies on proteins present in complexes with the fusion protein, as well as novel synthetic lethal dependencies in the presence of the fusion protein. Rare cancers can be difficult to study. The ability to progress from structure–function data to biological insight to small-molecule inhibitor to therapeutic testing requires a highly dynamic and collaborative network of investigators with unique perspectives and expertise. Such groups with overlapping/complementary interests in specific pediatric cancers are rarely found within one laboratory or institution. Cancer Moonshot funding would provide the opportunity to coordinate a network of collaborating investigators with expertise in proteomics/structural biology, genomics/epigenomics, chemistry, experimental therapeutics, and disease-specific biology to do the following:

- Develop a comprehensive collection of genomically characterized cell line, mouse, and induced pluripotent stem cell models of fusion-driven pediatric cancers. Currently existing models are limited and inadequate.

- Advance our understanding of the mechanisms of action of each of the common fusion oncoproteins in childhood cancers

- Determine the key vulnerabilities in these fusion-driven pediatric cancers through functional genomic screening, and generate a map of the key functional domains for each fusion oncoprotein. Establish a pipeline for performing systematic screening, such as CRISPR/Cas9 and shRNA screening, of potential vulnerabilities.

- Determine the key protein members of each fusion oncoprotein protein complex and their key functional domains

- Develop a pipeline for small-molecule screening and the validation of lead small molecules in cell line and mouse models of fusion-driven cancers

Why is this important?

A collaborative effort is essential to advance our understanding of the mechanisms of action of each of the common fusion oncoproteins in childhood cancers and would be spurred by targeted efforts to develop therapies for specific childhood cancers. Understanding these in pediatric cancers will also inform adult cancers with similar fusion oncoproteins (e.g., TMPRSS2-ERG in prostate cancer). Development of systematic approaches to target fusion oncoproteins

will serve as a paradigm for targeting diseases driven by other "undruggable" proteins.

What will it achieve?

This proposal will provide insight into childhood cancer development and potentially uncover new therapeutic opportunities. Fusion oncoproteins are well-defined pediatric cancer drivers for which focused experimentation could rapidly drive the field forward. The work described here would lead to a better understanding of the biology and mechanisms of action of these proteins that are a common hallmark of childhood cancer. Bringing together groups with expertise across the cell biology, epigenomic, proteomic, and drug development spectrum would lead to the development of novel small-molecule probe compounds and, potentially, drugs. This will galvanize continued drug development in biotechnology and pharmaceutical companies by lowering the barriers to successful drug development for pediatric cancers. Given that most of the fusion oncoproteins subsume normal developmental and gene regulatory pathways, it is likely that the drug development performed here will have utility in a number of other cancers that span the pediatric–adult cancer divide.

Recent drug development efforts suggest that small-molecule approaches that target gene regulatory mechanisms may have therapeutic efficacy in patients; however, these approaches have been developed to target only a small number of the potential therapeutic opportunities within each cancer. Indeed, very little therapeutic development has focused specifically on fusion protein-driven pediatric cancers in spite of the fact that the fusion proteins are common cancer drivers and often found in cancers with few other genetic lesions. Detailed functional studies will likely point to new opportunities for small molecule development.

Symptom Management Research

Accelerate research that can identify approaches to monitor and manage patient reported symptoms, and integrate the information to revise and update national guidelines for symptom control and support. There is a compelling need to improve symptom care for cancer patients and cancer survivors, including survivorship in racial/ethnic minorities and other underserved populations. Symptom management is key not only for improving quality of life but also for ensuring patient adherence to treatment that will lead to improved therapeutic response and extended survival. This is a unique opportunity to improve the quality of patients' lives, in particular pediatric patients who deal with significant long-term side effects of cancer treatments well into adulthood.

What is the problem?

Every year, 650,000 cancer patients are treated with chemotherapy and 470,000 receive radiation alone or in combination with chemotherapy. Both disease and treatment cause deleterious symptoms and side effects that occur during the course of treatment or appear long after treatment is completed. While all patients experience unpleasant side effects, nearly a third report three or more co-occurring moderate-to-severe symptoms during treatment. These symptoms contribute to lower functional status and quality of life, lead to multiple costly visits to emergency departments, and can cause treatment delays and discontinuation of therapy. Treatment delays and nonadherence to treatment due to symptoms are particularly concerning because they decrease treatment effectiveness and increase the risk for recurrence and death. When symptoms are poorly controlled, cancer treatment adherence is particularly challenging for the medically underserved and those with low health literacy. Furthermore, poorly controlled symptoms have also been shown to increase the likelihood of patients leaving the workforce and not returning to work, even after becoming disease free. Unfortunately, patients from racial/ethnic minority groups, older patients, and those from underserved populations often have significant delays in treatment, experience worse side effects, are more likely to be nonadherent to treatment, and have less access to remedies to control their side effects.

What are the challenges?

Great strides have been made in dissemination and implementation research in the area of cancer symptom management. Validated patient-reported outcome (PRO) tools, such as those available through the NIH-supported PROMIS and PRO-CTCAE initiatives, have led to advances in the systematic collection of patient-reported symptoms and functional status data. With the addition of Cancer Moonshot funding, implementation science research on how to deploy these PRO measurement technologies to all cancer patients, including those from minority and underserved populations, could be dramatically accelerated, which would rapidly remove the current communication barrier between cancer care providers and their patients and family caregivers, and provide a mechanism to report poorly controlled symptoms whenever and wherever they are present. This funding would also foster

needed research on ways to integrate these systems into overall care delivery (including the electronic health record), on the most effective strategies for the cancer care team (and primary care providers involved in the care of survivors) to act upon the PRO data and intensify symptom care, on means of optimizing use in diverse patient populations, on ways to expand their use with patient self-management strategies and e-Health applications, and on strategies to evaluate their potential to bridge supportive and palliative care access issues including outreach to underserved, rural, and frontier communities. In short, the gap between current and more effective supportive care and palliative care provisions is poised to rapidly close, making management of cancer symptoms a priority area for accelerated funding. This has become even more urgent given the increasing number of people surviving cancer. Currently, there are approximately 15.5 million people in the United States who are cancer survivors.

Why is this important?

Implementation of this recommendation would accelerate the development of systems for the routine monitoring and management of patient-reported symptoms across the cancer continuum (from diagnosis throughout survivorship and at end-of-life) as the standard of care for cancer patients in all care settings. These systems would rapidly link the cancer patient/survivor/family caregiver with knowledgeable and prepared health care providers as needed and with timely self-management resources that effectively and efficiently control adverse symptoms, thus optimizing patient quality of life. Symptom management programs can be tailored to differing patient and survivor needs, including the needs of diverse communities and rural populations that live at a distance from their cancer treatment facility. Reduction in the deleterious symptoms of cancer and its treatment will encourage patients to continue with and benefit from recommended therapy and clinical trials, maintain optimal well-being, and stay engaged in family and societal roles. Furthermore, reduction in moderate-to-severe symptoms will lead to marked decrease in cancer care costs related to emergency department visits, urgent care, and unplanned hospitalizations and readmissions.

What will it achieve?

Implementation of this recommendation will accelerate the development of systems that collect patient self-reported symptom data as an integral element of all national cancer databases. A database of symptoms could be used to:

- Revise and update evidence-based guidelines on symptom management

- Track patient-reported outcomes

- Make comparisons, share best practices, and encourage the attainment of a high standard for symptom control and supportive care nationally

- Identify gaps and new scientific questions that could be addressed through symptom management science

Prevention and Early Detection: Implementation of Evidence-Based Approaches

Sponsor initiatives to improve the current state of early detection, genetic testing, genetic counseling, and knowledge landscape of the mechanisms and biomarkers associated with cancer development and conduct implementation science research to accelerate development, testing, and broader adoption of proven strategies to significantly reduce cancer risk and address cancer health disparities in these areas. Research should focus on identifying effective, sustainable strategies that involve individuals, families and caregivers, health care providers and systems, and/or the greater community. High-priority areas for which much is known about effective prevention and screening modalities are colorectal cancer (CRC) screening, HPV vaccination, tobacco control, and identification of individuals with genetic predisposition to cancer. Given that we already know several effective approaches for preventing many cancers, advances in implementation procedures would prevent additional cancer cases and unnecessary deaths in the general population, populations that experience persistent cancer disparities (e.g., low-income, minority, rural, and other underserved populations), as well as populations with familial cancer risk attributable to known gene mutations, including those underlying Lynch syndrome (LS) or Hereditary Breast and Ovarian Cancer (HBOC).

What is the problem?

There are a number of cancers that are preventable, but evidence-based strategies to prevent them are not currently accessible to all individuals or are being adopted by too few people, leaving millions of Americans at high risk for preventable, yet deadly cancers. On the other hand, if we understood better the reasons these proven cancer prevention strategies are not being widely used, especially among underserved populations, and how we could increase uptake of these strategies, we could reduce deaths due to cervical cancer by 90%, CRC by up to 70%, and lung cancer by as much as 95%.

Hereditary cancer testing in appropriate populations is a cancer prevention strategy that is currently underused, leading to unnecessarily lost lives and diminished quality of life. There are more than 50 known hereditary cancer syndromes, each characterized by inherited genetic mutations that increase the risk of cancer. Currently, there is a need for nationwide efforts to identify individuals with hereditary cancer syndromes, and to determine and implement optimal intervention strategies, such as earlier cancer screenings, that would reduce the risk of developing malignant disease. For example, in the case of LS, which leads to increased risk of colorectal and endometrial cancers as well as other malignancies, tumor testing is recommended for all individuals with CRC; however, fewer than 5% receive this screening, representing a missed opportunity to identify individuals and family members who may have inherited a substantially higher cancer risk. It is estimated that in the United States, up to 1 million people live with LS, but many are unaware of it. Similarly, about 250,000–400,000 women live with HBOC syndrome, a predisposition to breast and ovarian cancer beyond BRCA1 and BRCA2. Screening women with breast and ovarian cancer for HBOC syndrome would identify cases where a cancer diagnosis is linked to an underlying predisposition that is likely shared with family members.

More than 30,000 HPV-related cancers (cervical cancers and many vulvar, vaginal, penile, anal, and oropharyngeal cancers) are diagnosed each year in the United States. HPV vaccines are effective in blocking persistent viral infections and ultimately preventing HPV-related cancers. However, the rates of vaccination with the recommended three doses of HPV vaccine are only 40% among girls and 22% among boys in the United States. In the case of CRC, about 1 in 3 adults between 50 and 75 years old do not go for regular screenings. Populations with documented low screening rates include Hispanics, American Indians/Alaska Natives, Asians, rural populations, foreign born, and those with lower education and income.

Eliminating tobacco use is another important strategy for reducing largely preventable cancer deaths, since 40 million adults in the United States smoke and it is estimated that 50–65% of all smokers will die from a tobacco-related disease. In 2015, about 30% of cancer deaths were from lung cancer.

What are the challenges?

Substantial progress has been made in identifying interventions that are effective for CRC screening, HPV vaccination, and tobacco control; however, barriers to large-scale implementation of these strategies exist that have prevented their wider adoption. Implementation research is needed to accelerate the development and testing of effective strategies to achieve wider adoption of these evidence-based approaches, especially among populations that suffer the disproportionate burden of these cancers.

Technological advances in genome science have enabled rapid identification of individuals with an inherited risk of cancer by direct DNA sequencing. However, until recently, the cost of genetic testing was considered too high for routine clinical practice. With existing and anticipated improvements in genomic technologies, these costs have fallen and will continue to fall. As a result, health care providers should be able to order DNA-based tests for their patients. Public- and private-sector national investment in cancer genetics/genomics, tumor registries, and tumor genotyping has built a knowledge base that can now be leveraged to identify individuals with increased risk of cancer development and early-onset cancer, allowing coordination of patient care as well as research pertaining to individuals with inherited predisposition to cancer. Efforts to reach racial/ethnic minority and underserved populations with these advances are also needed.

In the case of the HPV vaccine, gaps in communication tools and approaches have prevented the general population from gaining the appropriate knowledge about the HPV vaccine and its effectiveness in preventing cervical cancer. Parental misconceptions about the relationship between HPV vaccination and promiscuity, and fears of possible side effects have compounded the problem and lowered the rate of vaccine uptake. Furthermore, misunderstanding of the risk of infection in boys continues to result in their lower uptake of the vaccine. The parallel effort for wider implementation of CRC screening has faced barriers

such as the lack of identification by electronic health records of those needing CRC screening and the insufficient consideration of new, less-invasive screening tools. Tobacco control is limited by lack of knowledge about how to implement and sustain comprehensive tobacco control through the existing health-related infrastructure and in a range of situations, particularly among populations in which tobacco use and tobacco-related disparities are high. We have much to learn yet about effective interventions to bring down rates of lung cancer. In addition, we need a better understanding of effective strategies for tobacco cessation among patients already living with lung cancer.

Why is this important?

The identification of individuals with hereditary cancer syndromes would allow delivery of evidence-based genetic counseling, preventive and early detection services, and on-going surveillance through public health programs, leading to improved health outcomes for patients. Research initiatives based on cohorts with increased genetic risk of cancer would promote better understanding of biological mechanisms that drive tumor development and progression, the identification of novel biomarkers and improved risk modeling. It would also allow smaller, faster trials of preventive intervention in germline mutation cases. It is expected that many of these findings could be translated to the general population.

Increased implementation science research is particularly needed to find effective ways of improving rates of uptake of cancer prevention and screening programs in populations with greatest need, such as those experiencing cancer health disparities.

What will it achieve?

It is well established that early cancer detection and intervention reduces cancer mortality. Success in increasing HPV vaccination rates, increasing CRC screening and follow-up, and reducing tobacco use will greatly lower the incidence of and mortality from these preventable cancers, preventing nearly 400,000 cancer cases and more than 300,000 cancer deaths annually. In addition, if we implement widespread genetic testing, we would have the opportunity to identify families and individuals affected by hereditary cancer syndromes. These individuals can directly benefit from cancer prevention and early detection strategies, empowering them to make informed cancer-preventing health decisions that will lead to improved outcomes. Cancer Moonshot funding would help to emphasize the focus on prevention and allow us to carry out an evidence-based demonstration project on LS, to garner data of the benefit of genetic testing for hereditary cancer syndromes. Advances in implementation science directed at the full integration of current evidence-based cancer prevention and screening interventions in the areas of HPV vaccination, CRC screening, and tobacco control would dramatically accelerate progress in diminishing the cancer burden in the United States, especially if coupled with identification of populations with high hereditary cancer risk. It is estimated that over half of all cancer deaths could be prevented in these four areas alone.

ADVANCING CANCER PREVENTION: LYNCH SYNDROME DEMONSTRATION PROJECT

Some cancers run in families due to an inherited predisposition to cancer development. Included among this group are people with a condition known as Lynch syndrome. This condition is marked by the presence of inherited mutations in a group of specific genes that increase their risk of developing a number of cancers at an early age, including colorectal and endometrial cancer and, to a lesser extent, stomach, ovarian, pancreatic and several other cancers. It is estimated that 1,000,000 people in the United States have Lynch syndrome; less than 5% are aware of it. About 135,000 new cases of colorectal cancer are diagnosed each year, up to 7,000 of which are caused by Lynch syndrome.

Because of the widespread availability of genetic testing, we now have the opportunity to successfully identify families in which Lynch syndrome is often found and individual members of these families with these cancer-predisposing genetic mutations, which impair a type of DNA repair known as mismatch repair. Because early detection and prevention can also decrease the risk of dying from cancer in people with an inherited predisposition to cancer, these individuals are an important target population for cancer prevention and early detection strategies.

In fact, professional medical groups recommend that all people diagnosed with colorectal cancer and women diagnosed with endometrial cancer be tested to see if they have Lynch syndrome.

Not only can this inform their own care but it means that other members of their family may have Lynch syndrome and should be tested for it. Unfortunately, studies have shown that only a small portion of people diagnosed with colorectal and endometrial cancer are actually screened for Lynch syndrome.

This project would establish a new national network of individuals and families with Lynch syndrome. It would facilitate enrollment of patients with Lynch syndrome cancers into existing and new clinical trials and help to expand genetic counseling capabilities and access to genetic counseling services to areas where they have traditionally been lacking.

In response, the Blue Ribbon Panel recommendations call for a nationwide demonstration project to systematically screen all people diagnosed with colorectal and endometrial cancer for Lynch syndrome. This demonstration project could be carried out via NCI's established research network, including NCI-designated Cancer Centers, hospitals that are part of the NCI's National Community Oncology Research Program, and other centers.

Under this demonstration project, patients diagnosed with these cancers would undergo an initial screen for mismatch repair deficiency using standard tests. Those found to be potential Lynch syndrome carriers would then undergo targeted sequencing to validate the presence of the specific genetic mutations associated with Lynch syndrome.

First-degree relatives of these patients would then be given the opportunity to be screened and provided with appropriate genetic counseling to educate them about what screening entails and what it means, and what actions they can take related to their own health should they be found to have Lynch syndrome.

The primary goals of this project will be to improve preventive care for individuals with Lynch syndrome and to develop models for cancer risk assessment and prevention. These models, as well as the infrastructure developed for integrating data on those with Lynch syndrome, will be applicable to cancer care and research in other high-risk populations as well as the general population.

This project would establish a new national network of individuals and families with Lynch syndrome. It would facilitate enrollment of patients with Lynch syndrome cancers into existing and new clinical trials and help to expand genetic counseling capabilities and access to genetic counseling services to areas where they have traditionally been lacking.

In addition, because cancers develop earlier and more rapidly in people with inherited cancer risk, this project will allow researchers to study cancer development over a shorter timeline, and identify novel biomarkers and preventive interventions much sooner than would be possible if studying a cohort of patients with non-inherited, or sporadic, cancers.

Also, because the cancer risks are higher and progression to cancer more rapid in those with Lynch syndrome, clinical trials testing new treatments in these patients may be smaller, shorter, and more efficient. This demonstration project will also permit researchers to identify families with Lynch syndrome who could be invited to participate in an array of more intensive early detection and prevention research studies, including those that focus on lifestyle risk factors, identification and optimization of biomarkers for early detection, and testing innovative prevention strategies.

Recommendation H:

Retrospective Analysis of Biospecimens from Patients Treated with Standard of Care

Conduct retrospective analyses of archival tumor samples from cancer patients treated with standard of care and whose outcomes are known in order to better understand and target the mechanisms driving individual tumor types. The Cancer Moonshot provides a unique opportunity for the cancer research and clinical trials communities to apply state-of-the-art technologies to analyze the tissues already collected from cancer patients for molecular, genetic, and cellular clues to explain why some patients respond well to standard of care while many others do not. The ability to identify and analyze the complex network of genes, proteins, inflammatory/immune signatures, and biochemical pathways regulating different cell types within tumors from patients with known treatment outcomes will help refine criteria on how to optimally classify tumors and to assess whether standard of care is likely to be beneficial and the potential benefit of experimental therapies based on their molecular, genetic, inflammatory/immune, and cellular signatures.

Analysis of tumors from thousands of treated patients, including those from racial/ethnic minority groups and underserved populations, whose outcomes are known would allow for rapid development of hypotheses to be validated prospectively in clinical trials. This includes efforts for linking pathology reports to specimens to create valuable clinically annotated and diverse biospecimen collections.

What is the problem?

Many thousands of patients have been treated with similar standard of care regimens. Some have had outstanding responses with substantial prolongation of life or even a cure, whereas others did not respond at all. Some patients with early outstanding responses have ultimately relapsed or become resistant to continued therapy with the same agents and eventually succumbed to their disease. In some cases, patients resistant to standard chemotherapy who undergo immunotherapy subsequently respond to prior chemotherapies to which they had been resistant. The underlying molecular, genetic, inflammatory/immune, and cellular mechanisms that may distinguish these groups of patients—even if they initially fall within the same disease classification—remains poorly understood. There is now an appreciation of the complexities of the tumor and its surrounding tissue microenvironment, in terms of its cellular, genetic, inflammatory/immune, and molecular heterogeneity. However, how each of these components drives either sensitivity or resistance to therapy, and how these features evolve over time or in response to therapy, have been difficult to address due to the lack of appropriate technologies and biological platforms required to study them effectively. Ultimately, while development of new drugs is supported by the pharmaceutical industry, fewer resources are devoted to distinguishing which patients are most and least likely to respond to a given drug, including identification of which patients will respond best to different therapeutic approaches. This remains understudied and ill defined, and is a roadblock to developing more successful cancer therapies.

What are the challenges?

Several limitations, ranging from technological and infrastructural to educational and financial, have made it difficult to carry out large-scale retrospective analyses of tumor samples. For instance, the technologies and high-throughput capabilities needed to visualize and analyze large numbers of tumor cells and tissues and determine their genetic and molecular makeup have only recently attained the degree of sophistication necessary to answer questions about tumor heterogeneity and evolution over time and after treatment. Next-generation sequencing technologies are now available to quickly sequence and identify gene mutations and to identify changes in global gene expression that are associated with different tumor types and stages of disease. Other complementary high-throughput technologies involving mass cytometry and multidimensional fluorescence microscopy are now accessible as well, with capabilities to study multiple simultaneous parameters associated with cancer cell physiology at the single-cell level. This includes the ability not only to characterize the composition of cells in tumor masses, but also to simultaneously monitor dozens of proteins and enzymes involved in regulatory pathways commonly altered in cancers and their surrounding supportive cells.

Additional barriers to obtaining the samples necessary for these analyses reflect issues with clinical infrastructure, medical oncologist reimbursement, and reluctance of patients, especially those from racial/ethnic minority and underrepresented groups, to enroll in trials. Recent implementation of the NCI's National Clinical Trials Network (NCTN) has helped pave the way for these issues to be addressed head-on. While barriers exist, over 2000 institutions, consortia, and practices participate in the NCTN and meet the enrollment criteria for continued membership. This mechanism should be pursued in ongoing clinical research efforts, including better development of quality metrics, reimbursement of time, and inclusion of contractual and regulatory structures that are well established, functional, and inexpensive. The strengths of the system are the willingness of oncologists and patients to engage in clinical trials, the use of standard treatments as appropriate, uniform management of cancer care, agreed-upon standards, and tissue availability for research and diagnostic use. NCTN has also focused on centralizing tissue banks, technology cores, and data management centers to facilitate access to clinical details on the research end and educational/informational resources to patients and community health centers alike—which helps inform ongoing trials and on best practices for common and rare cancer types. NCTN may, therefore, set an exemplary framework for other groups to expand upon in the implementation of this recommendation.

An alarming limitation that affects the research and clinical communities across the board is the fact that only 5% of all cancer patients enroll in clinical trials, with even lower representation of racial/ethnic minorities and underserved populations. Many oncologists do not have the bandwidth to recruit more patients, limiting the diversity of patients in trials.

Challenges also result from potential inconsistencies in the collection of tumor specimens from treated patients, difficulties in sample preparation, and issues with shipping to central labs and conducting tumor assays. Without more-coordinated efforts, the ability to successfully implement this recommendation and obtain meaningful large-scale information will remain a challenge.

Why is this important?

The reasons why cancer patients with similar disease and disease stage may end up with very different outcomes despite receiving the same standard of care remains an enigma. This gap in our understanding costs lives and drains scarce resources. A thorough analysis of archival samples to determine the underlying cellular, genetic, inflammatory/immune, and molecular events that drive a tumor's response or resistance to therapy will help refine patient sub-classification at the molecular level. It will also provide invaluable information on which patients are likely to benefit from standard of care and which patients require additional or novel interventions. Equally important, a retrospective analysis may also identify patient subgroups that may not need therapeutic intervention at all—patients who currently fall victim to "overdiagnosis" and are thus receiving the standard of care without significant benefit. A comparison of archived successes and failures will also set the framework to help inform ongoing and future clinical trials being carried out in pursuit of more effective treatments.

What will it achieve?

Implementation of this recommendation will establish expanded networks of cancer researchers and clinicians, similar to NCI's NCTN, that can only be accomplished efficiently and effectively at this large scale through the coordination afforded by the Cancer Moonshot. It will develop better risk stratification of cancers and allow tailored treatments to be developed for patients who are at high risk for relapse and would not likely benefit from standard of care alone. Having a trove of cellular, genetic, inflammatory/immune, and molecular parameters available will enable the clinical oncology community to define a patient's risk category for therapeutic response and in so doing, enhance the cure rate for locally advanced cancers and anticipate how individual advanced-stage patients will respond to distinct therapies. Finally, this recommendation will help identify efficient ways to conduct faster and smaller precision-based trials on patients with the appropriate biological parameters.

Generation of Human Tumor Atlases

D evelop human tumor atlases for adult and pediatric cancers that map the evolution of human tumors by documenting the genetic lesions, molecular pathways, and cellular interactions that guide tumor development from pre-malignant tissue to primary cancer, progression to metastasis, response to therapy and acquisition of resistance. These atlases would include lesions from diverse populations and would integrate new or existing datasets to comprehensively describe the molecular, cellular, and physiological events associated with each cancer and changes that occur over time within individual cancer cells, the cancer mass itself, the tissue of origin, and sites of metastases. By providing high-resolution maps of the dynamic three-dimensional architecture of individual tumors over time, the atlases would enable a better understanding of the complex interactions that determine cancer evolution, behavior and responses to therapies and environmental changes. This recommendation extends the type of analysis that is envisioned in Recommendation C (Therapeutic Target Identification to Overcome Drug Resistance), as it focuses on the tumor as a whole, not just the malignant cells of the tumor. Once the atlases are built, and predictive modeling is enabled, researchers and physicians would be able to consult the atlases to determine whether an individual patient's tumor is likely to progress or not, and to refine therapeutic choices for that individual.

What is the problem?

While researchers have learned great deal about the evolution of cancer from patient material and from animal models of the disease, there are major gaps in our understanding of the complete architecture of tumors as they arise, progress, and respond to therapy. Without such information, it remains challenging to accurately predict the prognosis of individual tumors or to determine appropriate therapies, including immune-based therapies. The numerous and complex interactions that occur between malignant and non-malignant cells, including immune cells, that reside within or are recruited into a tumor are collectively responsible for the eventual pathogenesis of the disease, but these remain incompletely understood at present. In particular, we know little about how the composition, characteristics, and interactions within a tumor change over time and in response to therapy.

During tumor growth, from the earliest detected lesion to the development of a primary tumor to the dissemination of disease in the process of metastasis, the microenvironment changes from one that can restrain cancer growth to one that supports and promotes tumor growth. These changes occur alongside those that occur in the cancer cells, which over time become increasingly more malignant.

However, studies of cancer processes typically focus on relationships among a limited set of variables, at a single point in time, and are at best an oversimplification of the true dynamics occurring within a tumor. Thus, we need to develop and implement methods to examine multiple spatial, molecular, cellular, and physiological parameters together to achieve a

comprehensive understanding of all components within a tumor, how these change over time, and how these components influence responses to therapies. Similarly, following the fate of the earliest stages of tumor development in individuals with genetic predisposition to cancer will afford insights into the molecular underpinnings of the disease. Understanding these processes would allow us to predict how a tumor will progress, and allow us to develop new strategies to prevent and intervene in cancer at earlier and earlier stages.

Early cancers can be eliminated or controlled by the immune system, whereas cancers that acquire the ability to suppress antitumor immunity can progress. A critical component to fully understanding how tumors grow, persist, respond to therapy, metastasize, and recur requires an understanding of the changes that occur to the immunological profile of a tumor. This profile defines all the molecular, cellular, and soluble components that can influence the immune response to cancer that can be positive (i.e., eliminate the cancer) or negative (i.e., ignore or promote the cancer).

What are the challenges?

Until recently, our ability to identify and characterize unique cell populations from individual cancers was limited by our lack of knowledge of appropriate specific markers to tag such populations and by the limitations of available technologies to distinguish individual cells among a mixed population and to perform such analysis in three dimensions. We now have tools that can deeply probe tumors, their microenvironments, and their architectures at a single-cell resolution across time. Additional analytical tools will be developed for this purpose in the future. Because of the magnitude of the data generated, the computational methods needed to process the data and to aid in the interpretation of the data have been and remain a limitation. In addition to these technological limitations, the infrastructure and coordination required to collect, process, and analyze tissue biopsies from patients with cancer, particularly from those with metastatic or recurrent disease or those undergoing treatment, and the capacity to make these data readily available to the scientific community, do not currently exist.

Constructing human tumor atlases that trace tumor cell populations over time in adult and childhood cancers will require an interdisciplinary effort that involves the collection, annotation, and careful analysis of biopsies taken from paired primary and metastatic cancers or metastases from a single primary cancer to different anatomical sites, and of tissue biopsies taken before, during, and after treatment, with specimens that represent the diversity of the population. In addition, it may be advisable to collect liquid biopsies (i.e., samples of body fluids) with paired tissue biopsies to provide information from complementary cancer-derived materials (such as circulating tumor cells, cell-free DNA, exosomes, etc.). Tissue and liquid biopsy data should be integrated with demographic and clinical data. Given the magnitude of this effort, there should be an initial focus on exemplary

pediatric and adult cancers, including at least one adult cancer in which immunotherapy has proved efficacious and one in which immunotherapy responses have been poor. The human tumor atlases should have specific subdirectories that focus on the clinically relevant areas associated with metastasis, drug resistance and recurrent disease, and the immunological profile.

Why is this important?

Generation of human tumor atlases is critical to develop a complete map of the life of pediatric and adult cancers. The atlases will provide insights into the development and establishment of the structure of a tumor, its makeup, and how it functions. Importantly, human tumor atlases would provide insights into how cancer cells are influenced over time by different microenvironments, immune factors, and therapies, as well as insights into how rapidly cancer cells can adapt to changes in their environment.

The comprehensive nature of the atlases will allow an assessment of potential biological consequences that may occur in response to conventional chemotherapies, targeted therapies, or immunotherapies before treating patients in the clinic. This information is expected to improve our ability to provide prognostic information, thus avoiding unnecessary treatments in some cases and making it possible to intervene in the disease process at earlier stages.

What will it achieve?

With additional funding and coordination provided by the Cancer Moonshot, the human tumor atlases would provide, for the first time, a comprehensive view into the diversity of how cancers work, how they develop, how they are influenced by different microenvironmental and immune factors, and how they change over time, in response to treatment, and in diverse populations. A better understanding of the programs that operate within a cancer cell, on a cancer cell, and of microenvironmental programs that drive tumor development, metastasis and drug resistance would yield new insights into how to improve cancer therapies and eventually prevent cancers from initiating or to intervene in their progression. Such knowledge may yield new insights into targeted therapies and immunotherapies that could be applied at any point during the evolution of the tumor (e.g., at the premalignant stage, during treatment of primary tumors, or at the time of metastatic cancer) to interrupt this lethal process.

Development of New Enabling Cancer Technologies

Develop innovative new technologies in the areas of imaging, instrumentation (e.g., multidimensional single cell imaging and molecular analysis technologies and intra-tumoral microdosing devices), biological models (e.g., patient-derived tissues and 3-dimensional organlike cultures and humanized mouse models), and computational platforms (e.g., integrated multiscale data systems) that interconnect molecular, cellular, tissue, and patient-derived information. Development of these new technologies would greatly enable researchers and physicians to develop and select effective, individualized therapy strategies for a diverse set of patients, including racial and ethnic minorities and other underserved populations.

What is the problem?

A long-standing challenge in translational cancer research is the lack of dependable instrumentational, biological, and computational platforms on which to test anticancer agents and accurately predict success in patients. Recent technological advances have made it possible to test multiple combinations of therapeutics in a variety of systems that more closely mimic the complexity of tumors at different stages of disease progression. These advances have the potential to more accurately predict clinical outcomes when combined with powerful high-throughput genomics, proteomics, and imaging technologies.

Testing and prioritization of drug candidates at the preclinical and early clinical stages are typically conducted in cancer cell lines (i.e., cells grown in culture flasks or engrafted onto immune-compromised host mice) or genetically engineered mouse models that focus on individual or narrow groupings of tumor-associated genetic mutations. While these pre-clinical models have been extremely informative about basic cancer biology, they generally do not recapitulate all aspects of disease progression or the heterogeneity of cell types that form the tumor mass and its surrounding tissues. Consequently, these models have limitations in their potential for testing therapeutics, despite significant progress in expanding the number of human cancer cell lines and mouse models of human disease. Many cancer patients develop resistance or relapse to standard of care for unknown reasons. Establishment of preclinical cancer models that better recapitulate the complexities of tumor biology, including the immune components, and highly lethal metastatic programs would facilitate the development of more effective therapies.

Adding to the challenges, computational complexities in informatics have hampered efforts to integrate large biomedical data sets containing genomic (e.g., The Cancer Genome Atlas), proteomic (e.g., Human Protein Atlas), histological (at the cellular/tissue level), and clinical (patient) information. Multiscale integration of data collected using different mouse and cell line repositories, drug libraries, and analytical tools is equally challenging. Collectively, this has created significant roadblocks for basic researchers and clinicians in their efforts to deposit, retrieve, combine, and analyze cancer-relevant data derived from humans

and laboratory systems that would make it possible to accurately model and predict the effectiveness of different treatment regimens. This has also slowed down the translational pipeline of turning different drug combinations into clinically available therapies.

What are the challenges?

Tumors are highly heterogeneous at the cellular, molecular, and genetic levels; however, sophisticated technologies for characterizing this heterogeneity and for testing drug combinations have simply not been available. The same holds true in biomedical informatics, where the diverse nature of the data and methods used to generate them has made it difficult to harmonize and consolidate data into functional, interoperable units that are readily accessible to basic and translational researchers.

Nevertheless, the field has matured significantly in recent years, and new technologies offer hope for circumventing these problems. For example, newly engineered devices designed to dispense "micro" doses of drugs directly into an intact tumor (either separately or in varying combinations) are now emerging and have been tested successfully in animal models. These technologies, if widely implemented, could revolutionize the way drug combinations are tested and tailored for each individual patient. Other technologies have been developed to target cancer drugs more selectively to cancer cells or to deliver new forms of cancer therapies (e.g. inhibitory RNAs) to tumors.

Parallel advances in patient-derived organoid and tissue-slice platforms have enabled the development of companion 3-dimensional systems that recapitulate the original architectural and molecular diversity found in different subtypes of cancers and are therefore suitable for fast and efficient pharmacologic screening. Breakthroughs in the design of mouse models that have been engrafted with patient-derived tumors and/or functional human immune systems also hold potential to enable basic and translational researchers to include important cancer-related architectural complexities and cellular heterogeneity in their testing systems.

Furthermore, improved high-throughput multiplexed imaging technologies, like single-cell mass cytometry and multidimensional fluorescence microscopy, now allow for more than 30 to 100 different proteins to be monitored simultaneously at subcellular resolution. These systems can be used to determine the location of cells (and proteins within the cell) relative to its neighbors in the same tissue, and to elucidate how these cellular and molecular configurations influence its functional characteristics. Similarly, these high-throughput technologies are useful for the isolation and characterization of DNA and RNA from individual cells—and with them the power to profile in great depth thousands of single cells simultaneously. Continued development of these powerful technologies will expand our ability to visualize tumor architecture.

Beyond these, new technologies need to be developed for patient imaging, such as target-

specific radiologic imaging, nuclear medicine imaging methods using new metabolic probes, and immunoPET. It will be important to develop methods that allow different imaging methods to be combined, such as histology, immunohistochemistry, and molecular analyses of fixed tissues. Collectively, these and many other technological advances in the bioinformatics and meta-data analysis sectors will, once they become standard use, further enhance the translational potential of medicines for personalized treatment of patients.

Why is this important?

The broad implementation of emerging technologies that mimic the complexities of tumors will enable the basic and clinical oncology communities to make more informed and predictive decisions on how to successfully treat each individual patient, regardless of the cancer type or stage at the time of diagnosis. Cancer, by definition, is a highly heterogeneous disease—even for tumor types that may fall under the same classification. Unfortunately, this heterogeneity leads to standard of care therapies that benefit some but not all patients. This inherent complexity of cancers is exacerbated by the fact that not only are tumor cells within a single tumor mass likely to be genetically heterogeneous, but they also interact with multiple cell types, such as fibroblasts, endothelial cells, and immune cells, that increase the diversity of the tumor biology and response to therapy. Having the capabilities to tap into integrated biomedical informatics platforms is critically important, as the combined data can better guide researchers and clinicians into productive research and therapeutic directions. Similarly, access to technologies that enable the isolation of cancer cells directly from patients for 3-dimensional organoid development and/or allow the testing of drug combinations directly on patients' tumors with microdosing devices can accelerate progress in cancer therapeutics by focusing on systems that preserve tumor integrity and complexity.

What will it achieve?

Under the Cancer Moonshot, implementation of this recommendation will create an incentive for biomedical manufacturers and researchers to develop powerful new technologies that help researchers and physicians deliver smarter, more effective therapies tailored to patients' individual tumors. Access to these emerging technologies will also accelerate the discovery and translational pipelines of drug development and galvanize the pharmaceutical, biotechnology, technology, and government sectors in an effort to establish a centralized and comprehensive data sharing system conducive to the exchange of information and resources within virtual communities.

EMERGENT TECHNOLOGIES FOR INTRA- AND EXTRA-TUMOR PHARMACOTYPING DEMONSTRATION PROJECT

Determining the best treatment for each cancer patient can be a difficult task. To make that decision, clinicians rely on information such as the tumor type and stage, the presence of certain prognostic markers, and specific genetic characteristics of the tumor. Nevertheless, it is not always possible to determine if a patient will be responsive to a specific therapeutic agent, and in some cases, several rounds of varied treatment strategies are required to find one that is effective in a given patient.

An emerging possibility to more efficiently determine the most effective therapeutic agent is to use the patient's own tumor to safely and simultaneously test several candidate drugs. A major advantage of this strategy is that it has the potential to be completely personalized to each individual patient. A number of new technologies have advanced this strategy, and more early research on the potential uses of

these innovative technologies needs to be conducted.

Patient-derived organoids are one new technology that could allow for rapid, individualized therapeutic testing. Organoids are spheres of cells grown in a three-dimensional format in the laboratory. They can be developed from pieces of healthy or tumor tissue obtained from patients, for example, during a routine biopsy. Early research shows that results from laboratory tests with patient-derived organoids closely mirror the patient's actual clinical response. Therefore, it will be important to determine whether organoids can be rapidly developed from patients and used to test candidate therapies.

Developing organoids for every cancer patient may not be feasible, but it should be possible to establish an organoid resource in which every possible tumor type would be represented.

This resource could also play a major role in the preclinical development of new therapeutics. The panel additionally endorses more research on the possibility of incorporating other types of cells, like immune cells, into the organoid culture, so as to better represent the tumor environment.

This resource could also play a major role in the preclinical development of new therapeutics. The panel additionally endorses more research on the possibility of incorporating other types of cells, like immune cells, into the organoid culture, so as to better represent the tumor environment.

Another new technology with vast potential is the use of small devices that are surgically implanted in a patient's living tumor—that is, while it is still in the patient's body—to evaluate the effectiveness of several drugs simultaneously. Such devices contain tiny wells that are filled with a small dose of a single drug or combination of drugs. The ability of the drug or drugs in each well to kill the tumor cells immediately surrounding the well can be determined rapidly.

These "microdosing" devices have the advantage of testing drug responses in the living tumor, with the surrounding environment and immune system intact. However, more research is needed to determine how well the test results represent true clinical responses. In addition, the panel supports development of similar microdosing technologies that do not require surgery for delivery.

While implantable devices and organoids are only just emerging, the panel recognizes their potential to rapidly advance cancer care. Further studies will be needed to determine if these technologies are safe, effective at predicting clinical responses, and feasible to use in a clinical setting.

Conclusions and Next Steps

Collectively, these recommendations outline a way to spur transformative advances in cancer. They recognize and build on the remarkable developments that have brought us to where we are today: technological advances that allow us to map cancer cells and the tumor environment in great detail, to examine the effects of precisely perturbing gene function, and to investigate the genomic, biochemical, and molecular basis for cancer with ever-greater resolution; computational advances that allow us to assemble and analyze enormous data sets; and societal advances that have set the stage for greater involvement of patients in research and for extensive collaborations across organizations and industry.

The BRP concludes that these recommendations will help advance science that will benefit patients most quickly, whether by making it easier to find the most relevant clinical trials, by allowing researchers to see patterns across data that will help them rapidly zero in on key processes in cancer, or by speeding advances in technology that will enable acceleration overall.

Indeed, a number of the recommendations focus on different aspects of the issue of generating detailed tumor atlases. These include characterizing the tumor, its microenvironment and the immune milieu, along with clinical data, and assembling that information in such a way that it can be used both by doctors—to help them select treatments that may be best for a given patient—and researchers—to help them identify drug targets and gain insight into such basic cancer processes as metastasis and the origins of drug resistance.

The recommendations highlight the value and importance of involving patients in the research process. As Americans conduct more and more of their day-to-day transactions online—shopping, banking, communicating with their doctors—it will be increasingly natural for them to participate in online platforms that enable them to contribute their data, to educate themselves and their families about the implications of their data, and also to search for treatments and trials that are most appropriate for them.

Finally, the recommendations attest to the great willingness of the cancer research community to approach research in a new way, through new collaborative efforts among groups that traditionally have not worked together. In this way, we can bring existing data and research together

with new data and approaches to truly accelerate our understanding of cancer.

A number of cross-cutting themes unify the recommendations. Among them are the need to address health disparities, the importance of prevention, the development of biomarkers and technologies, the need for data sharing, and predictive computational modeling. Importantly, they recognize the critical role that collaboration and partnerships will play in achieving the goals of the Cancer Moonshot.

Several policy issues emerged during the BRP's deliberations, including medical coverage and reimbursement, privacy and consent with regard to patient data, fragmentation of the delivery of patient care in the community, the need to improve the clinical trials system, incentives to encourage pediatric drug development, new federal research funding models, and barriers to data sharing. The BRP recommends that these issues be brought to the Vice President's Task Force as well as non-governmental entities committed to changing the face of cancer as we know it.

BLUE RIBBON PANEL MEMBERS

The Blue Ribbon Panel is composed of leading experts from a broad range of scientific areas, including biology, immunology, genomics, diagnostics, bioinformatics, and cancer prevention and treatment. Members also include investigators with expertise in clinical trials and cancer health disparities, as well as representatives of cancer advocacy groups and pharmaceutical and biotechnology companies.

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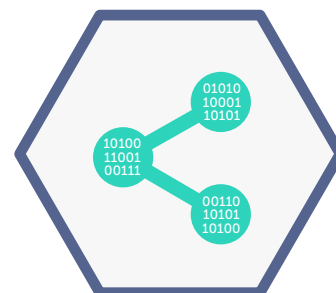
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