Research Opportunities for the Vice President's Cancer "Moonshot"

Recommendations of the Blue Ribbon Panel

Index

A Systematic Study of Cancer Metastasis
Tumor Evolution and Progression Working Group

What is the recommendation (1-3 sentences)?

Launch a multi-disciplinary effort to elucidate the metastatic lesion and its vulnerabilities from the earliest to most advanced stages of cancer in both pediatric and adult populations, with a focus on exemplary tumor types and anatomic sites.

Where are we are now (2-3 paragraphs)?

Metastatic cancer accounts for most cancer-associated morbidity and mortality. Evidence in patients and experimental models has demonstrated that metastatic dissemination of cancer cells from primary tumors may occur early (in some tumor types even before progression to invasive stages), yet most disseminated cancer cells will not develop into "macro-metastatic" lesions. Rather, they remain dormant (sometimes for many years) as individual cells or small clusters. Thus, the outgrowth of metastatic lesions likely requires additional factors such as non-cell-autonomous effects provided by the microenvironment (e.g., tissue injury-related inflammatory signals or signals from the cells of the metastatic niche) or by cooperating cancer cells (i.e., due to clusters of cancer cells disseminating together or subsequent self-seeding). At the same time, evasion from the immune system undoubtedly contributes, but this too may occur at earlier stages—possibly even at the time that invasive disease first develops in situ. However, our understanding of the genesis and maintenance of metastatic states remains fragmentary.

Until recently, we lacked the ability to model and perturb the metastatic process using patient-derived tumor cells. Although mouse models yielded valuable insights into mechanisms governing metastasis, high-order genetic manipulation remained time- and labor-intensive. Similarly, our ability to query the salient heterogeneity of malignant and microenvironmental cells and how these might promote the metastatic niche was under-developed. However, recent technological advances such as genome editing and high-resolution analysis offer the promise of overcoming these barriers, thereby bringing a new understanding of metastatic states and how they are maintained in patients.

Where do we need to be (in 1-5 years)?

<u>Priority 1.</u> Gain a comprehensive understanding of the dependencies operant in metastatic states.

New experimental methodologies such as genome editing make it possible to identify genes and pathways that are essential to tumor cells in various contexts. Such approaches could be leveraged to characterize genes or pathways that are required for survival in various metastatic states. This may involve querying the malignant cells directly or probing effectors from the microenvironment that may provide key inputs into metastatic programs.

Approaches of interest may include (but are not limited to) functional interrogation of patient-derived models; systematic or mechanistic studies of genetically engineered mouse models that reflect critical aspects of metastasis (and dependencies therein); new technologies that may

assess cancer dependencies in primary tumor material directly; and tractable systems that model specific metastatic challenges (e.g., brain or bone metastases).

Priority 2. Construct "3-dimensional" and "4-dimensional" cancer cell atlases of paired primary and metastatic cancers, or metastases to different anatomic sites.

Emerging technologies are making it possible to produce high-resolution and even single-cell characterization of all major cell types (malignant, microenvironment, and immune) in tumor tissues. Leveraging such technologies, it would be of interest to perform utra-high (e.g., single-cell) resolution analyses of biopsies or resections obtained from individual cancer patients throughout the course of disease and treatment, including the advent of drug resistance. In addition, new *in situ* technologies that read out cell/tissue topology could be used to ascertain the cellular adjacencies that may influence particular functional states. Atlases generated by this approach should ideally be linked to model systems that allow experimental testing of the hypotheses generated (see Priority 3, below).

Such atlases could provide, for the first time, a view into the heterogeneity of salient programs and states operant in metastatic foci, how they are influenced by different microenvironmental and immune factors, and how they evolve over time or during treatment.

Priority 3. Develop and characterize new cancer model systems designed to fill key gaps in existing studies of metastasis.

For many cancer types, we still lack appropriate experimental model systems that would allow us to study the salient tumorigenic programs governing metastasis, and to discover new therapeutic targets. Recent years have witnessed advances that could enable a dramatic expansion in various types of models, including patient-derived xenografts, and the possibility of generating tumor-bearing mice with "humanized" immune systems. These advances could be leveraged to generate new models of key metastatic sites (e.g., brain metastases) that are less well represented at present, and use these models to characterize states and dependencies operant therein.

- Rationale for investing (Why is this priority ripe for accelerating?)
    - Opportunity brought about by recent development in science, technology, practice: New technologies for high-resolution tumor characterization (e.g., single-cell analysis, multiplexed molecular imaging, and other approaches) and perturbation (e.g., genome editing) together with advanced and emerging model systems offer considerable new opportunities for studies of metastasis.
    - Does it address an unmet need or important gap in knowledge or practice? *Yes:* knowledge of metastatic states and vulnerabilities therein remains a crucial unmet need in many cancers.
- What would be needed for success?
    - New or expanded resources: support for sampling of tumor tissue and blood over the course of disease/metastasis and from specific anatomic sites (including autopsy specimens, if appropriate); deployment of technologies and analytical capabilities for high-resolution characterization of these tumors; implementation

of experimental approaches to perturb appropriate metastasis models *in vivo*; tools for sharing and analysis of omic and experimental data that emerge.

- Barriers/roadblocks eliminated or reduced: support scaling of existing experimental efforts, augment existing infrastructures for biopsies and blood collection to ensure collections of all sizes are supported; support for quality data generation efforts; establishment of new computational teams focused on deconvolving the biology linked to metastatic states
- New or enhanced technologies: scalable functional/editing studies; studies of heterogeneity; single-cell analysis, high-content tissue topographic analysis, model system dissemination

Strategy: What will it take to get there?

We recommend that the NCI develop a coordinated research effort to study all aspects of the metastatic program from the earliest stages of dissemination through overt metastasis at the molecular and biological levels. This effort may involve a particular focus on selected exemplary tumor types. This effort will require access to historical patient specimens (presumably early lesions) and paired metastatic and primary tumor specimens from more advanced cases. Another component would involve pairing the tissue collection efforts with the development of relevant functional models that both inform dissemination and metastasis and allow for functional analyses of metastatic programs operant in various anatomic sites (liver, bone, brain, etc.). Rapid autopsy programs may also be useful for assessing the molecular evolution of multiple metastatic lesions from the same individual.

These priorities will also require:

1. Scalable research biopsy and data generation programs. These initiatives will require fresh and/or serial biopsies of metastatic and drug-resistant specimens for deep tumor/microenvironmental characterizations and generation of ex new vivo models. Thus, the cancer moonshot should support collaborative efforts to procure these biopsies at scale and link them to state-of-the-art technologies for data generation and analysis. Liquid biopsy protocols should be paired with tissue biopsy efforts to provide complementary cancer-derived materials (circulating tumor cells/DNA, exosomes, etc.). Collecting liquid (blood) biopsies between collections of tissue samples would help to build a model for better characterization. Furthermore, bridging data garnered from liquid biopsies and imaging studies would facilitate translation activities; deep characterization of the tissue and liquid biopsies together with imaging data on a low number of patients might yield information generalizable to a larger number of patients. Materials obtained from these research biopsies should be seamlessly integrated with workflows capable of generating a wide range of data types.

2. Computational analysis capabilities. A critical need exists to develop algorithms that integrate and extract therapeutic meaning from data generated from metastatic biopsies using the latest technologies. New algorithms will help to identify relevant variations in heterogeneous tumors. Thus, we envision the establishment of collaborative efforts whose mission to design and implement such tools.

3. *Ex vivo* cultivation, perturbation, or target validation activities. Expansion of cancer models in vitro and in vivo would be aided by increased capacity for handling, distributing, and propagating cancer cell line and patient-derived xenograft models. Focused efforts to optimize approaches for generating and maintaining these models, building robust collections, and perhaps hosting research on these models done by individual investigators or moonshot teams should be considered.

What does success look like?

Successful completion of this project would yield new insights into the specific cell-autonomous, non-cell autonomous, soluble, and microenvironmental programs and effectors that drive the metastatic process, and how these intersect with related challenges such as drug resistance. Such knowledge may yield new insights into therapies that could be applied either at the time of metastatic cancer or earlier in disease (e.g., during treatment of primary tumors) to interrupt this lethal process.

New Therapeutic Targets to Overcome Cancer Drug Resistance
(Joint Recommendation from Pediatric Cancers and Tumor Evolution)

What is the recommendation (1-3 sentences)?

Launch multi-disciplinary studies to identify new drug targets elaborated by cancer drug resistant states. Such studies will include approaches to overcome drug resistance in exemplary pediatric and adult tumor types and therapeutic contexts.

Where are we are now (2-3 paragraphs)?

- Summary of the current state of the science/practice

  Most cancer patients die because their tumors exhibit intrinsic resistance or develop acquired resistance to available therapies. However, our knowledge of the spectrum and mechanistic underpinnings of drug-resistant cell states remains incomplete. It has become well-recognized that resistance can be highly multifactorial and heterogeneous, with multiple independent resistance mechanisms operant in the same patient, tumor focus, or even the same tumor cell. Furthermore, some drug resistance programs may be non-cell autonomous and may overlap significantly with programs that drive metastasis and overall tumor survival/maintenance.

- Identify barriers to progress and/or emerging opportunities

  Barriers to progress in understanding cancer cell resistance exist on genetic, molecular, cellular, and physiological levels. Understanding why, when, and how resistance develops is complicated by gaps in understanding regarding, but not limited to, tumor cellular heterogeneity; cell plasticity among potential cancer stem cell/tumor initiating cell populations; rewired and/or reprogrammed signaling pathways; compensatory signaling mechanisms; positive/negative signaling feedback loops; contributions of genetic polymorphisms (SNPs, CNVs); and the contribution of non-cancer cell components within the tumor microenvironment. Moreover, this multifactorial and heterogeneous nature of resistance means that multiple mechanisms can be operant in the same patient and even the same cell. That said, a growing body of evidence suggests that many individual resistance mechanisms may converge onto certain drug-resistant cell states, the understanding of which may provide new opportunities for combination therapies capable of circumventing this challenge.

Where do we need to be (in 1-5 years)?

1. Apply systematic experimental studies in appropriate model systems to define spectra of resistance mechanisms and dependencies linked to drug-resistant states.

New genome editing (e.g. CRISPR) and unbiased small molecule screening to systematically discover their vulnerabilities and make it possible to identify genes and pathways that are essential to tumor cells that harbor specific genetic or molecular alterations. Specifically, it is paramount that there is a focus on pediatric cancers with a low probability of cure (metastatic solid tumors, select CNS tumors, AML, certain high risk subsets of ALL, and all refractory and recurrent cancers). These approaches may be leveraged to discover individual resistance

mechanisms, common resistant cell states onto which they may converge, and genes/pathways that become essential after evolution to drug resistance. The interrogation of translocation-based tumors and identification of ways to expand the view of signal transduction pathways, particularly those involved in metastatic disease, is important. This effort should yield many new insights into tumor pathways and molecular contexts underpinning drug resistance that could be exploited using existing or future therapeutic regimens.

Priority should be given to efforts that approximate the clinical environment linked to drug resistance as closely as possible. Examples include diverse models (e.g., organoids, patient-derived xenografts, co-cultures in physiologic/"hypoxic" conditions, genetically engineered mouse (GEM) models, etc.), and assessment of drug-resistant states in addition to "steady-state" 2-D cell culture. Patient-derived models will be of particular interest but mouse models capable of interrogating aspects of tumor evolution as they relate to drug resistance are also important, particularly as they allow investigators to address these processes in the context of an intact immune system. New technologies that assess drug resistance mechanisms in primary tumor material directly will be a plus. In addition, model systems that assess non-cell autonomous effectors of cancer drug resistance (e.g., derived from the microenvironment or immune cells) would also be of interest.

2. Comprehensive characterization of drug-resistant clinical specimens, including 3-dimensional and 4-dimensional cancer cell atlases linked to drug-resistant states.

Emerging single-cell technologies are making it possible to produce high-resolution characterization of all major cell types (malignant, microenvironment, and immune) in tumor tissues. Both this recommendation and the accompanying recommendation on metastasis could include single-cell and/or multiplexed in situ cellular analysis of biopsies obtained from individual cancer patients throughout the course of disease and treatment, including the advent of drug resistance. Single-cell analysis will ideally be combined with new *in situ* technologies that read out cell/tissue topology to ascertain the cellular adjacencies that may influence particular functional states. Moreover, the atlases generated by this approach should be linked to model systems that allow experimental testing of the hypotheses generated. Such information could bring forth major new insights into tumor biology and heterogeneity, as well as cell states that identify new therapeutic targets and predict treatment response in metastasis and drug resistance.

3. Develop a collection of drug-resistant cancer models designed to fill key gaps and emphasize areas of unmet medical need.

For many cancer types, we still lack appropriate experimental model systems that would allow us to study the salient tumorigenic programs linked to drug resistance and to discover new therapeutic targets. Recent years have witnessed advances that could enable a dramatic expansion in various types of models, including cell culture systems (e.g., organoids and tissue slice cultures where cells are in their unperturbed environment), patient-derived xenografts, genetically engineered mouse models, and the possibility of generating tumor-bearing mice with "humanized" immune systems. Thus, the above recommendations may include new cancer model generation that is most representative of clinical areas of unmet medical need.

Rationale for investing (Why is this priority ripe for accelerating?)—see above

Opportunity brought about by recent development in science, technology, practice: The advent of new tools to perturb cancer cells (e.g., through systematic gain- and loss-of-function studies), to culture such cells ex vivo or in PDX settings, and to conduct serial sampling of tumor cells throughout the course of treatment offer unprecedented opportunities

Does it address an unmet need or important gap in knowledge or practice?

The development of drug resistance underlies cancer recurrence and accounts for significant cancer-associated mortality. Notably, despite significant progress made in the treatment of children with cancer, in the U.S. cancer remains the leading cause of death from disease in children, with intrinsic and acquired resistance being central to mortality. With no current means to predict who will develop resistance, or when resistance will arise, there is a substantive gap in knowledge and a clinically unmet need.

What would be needed for success? *For example*:

- New or expanded resources: support for serial collection of tumor tissue and blood during treatment and upon frank drug resistance; deployment of technologies and analytical capabilities for high-resolution characterization of these tumor cells prior to treatment, during treatment, and upon resistance; implementation of experimental approaches to perturb appropriate models ex vivo, in vitro, or in vivo;
- Barriers/roadblocks eliminated or reduced: support scaling of existing experimental efforts, augment existing infrastructures for biopsies and blood collection; support for data generation efforts; establishment of new computational teams focused on deconvolving the biology linked to resistance
- New or enhanced technologies: scalable functional studies (gain-of-function studies, loss of function studies, genome editing efforts); single-cell analysis, high-content tissue topographic analysis, etc.

Strategy: What will it take to get there?

- Concrete actions to take in the next 1-5 years

  We recommend that the cancer moonshot effort pursue a multi-disciplinary effort that consists of both systematic experimental studies and comprehensive characterization of clinical specimens obtained prior to treatment and upon relapse to exemplary cancer therapeutics in selected tumor contexts (targeted therapy, immunotherapy, and/or chemo-radiotherapy). Collaborative efforts dedicated to the study of childhood cancers, which could include establishment of centers of excellence, in addition to separate studies of adult cancers should include: 1) adult and pediatric dependency screening; 2) pediatric and adult cancer model generation; 3) preclinical therapeutic testing. In addition, there should be a dedicated effort to develop and test circulating free DNA (cfDNA) methods in pediatric and adult cancers. This effort will incorporate technologies such as single-cell sequencing as well as tissue-based characterization, which may allow specific investigations into the roles of microenvironmental cells and specific patterns of heterogeneity in the overall tumor drug-resistant state. In parallel, both systematic and in-depth functional studies of drug resistance will be conducted using appropriate tumor model systems so that correlative features

observed in clinical specimens could be characterized mechanistically (and conversely, resistance mechanisms identified in vitro could be queried using the clinical data).

Similar to the "Metastasis" recommendation, these priorities may also require:

1. Scalable research biopsy and data generation programs. These initiatives will require fresh and/or serial biopsies of metastatic and drug-resistant specimens for deep tumor/microenvironmental characterizations and generation of ex new vivo models. Thus, the cancer moonshot should support collaborative efforts, such as the establishment and maintenance of centers of excellence, to procure these biopsies at scale and link them to state-of-the-art technologies for data generation and analysis (below Liquid biopsy protocols should be paired with tissue biopsy efforts to provide complementary cancer-derived materials (circulating tumor cells/DNA, exosomes, etc.). Materials obtained from these research biopsies should be seamlessly integrated with workflows capable of generating a wide range of data types.

2. Computational analysis capabilities. A critical need exists to develop algorithms that integrate and extract therapeutic meaning from data generated from metastatic biopsies using the latest technologies. Thus, we envision the establishment of collaborative efforts whose mission to design and implement such tools.

3. *Ex vivo* cultivation, perturbation, or target validation activities. Expansion of cancer models in vitro and in vivo would be aided by increased capacity for handling, distributing, and propagating cancer cell line and patient-derived xenograft models. Focused efforts to optimize approaches for generating and maintaining these models, building robust collections, and perhaps hosting research on these models done by individual investigators or moonshot teams should be considered.

What does success look like?

A cancer drug resistance landscape project, applied to representative tumor and therapeutic contexts (e.g., specific targeted therapy, immunotherapy, and chemo-radiotherapy regimens) in adult and pediatric cancers, should produce new information about the biology of drug-resistant states that directly informs the development and clinical testing of novel therapeutic combinations. The initiatives should make it possible to non-invasively detect and molecularly characterize recurrences at the earliest possible time point so that salvage therapy can be initiated at a point of minimal tumor burden, with minimal molecular diversity. By the end of five years, several of these might emerge that could be administered up-front in cancer patients and circumvent prevalent drug-resistant states (or even "push" cells into drug-sensitive states).

Clinical Trials - Science BRP Working Group Report

What is the recommendation (1-3 sentences)?

Many thousands of cancer patients have been treated with similar standard of care regimens. Some have had outstanding responses with substantial prolongation of life or cure. Some had early outstanding responses but with relapse and resistance to continued therapy with the same agents and ultimate death. Some have had minimal or no response with no prolongation of life. Many thousands of formalin-fixed, paraffin-embedded tumor samples from patients that have received standard of care—that is, care provided in the clinical trial setting—are available for molecular analysis to determine what parameters correlate with an outstanding versus dismal response. By *fully analyzing samples already available* from thousands of patients receiving standard of care, it will be readily possible to develop hypothesis as to which patients will benefit and which patients will not benefit and thus which patients will need to receive experimental therapies early on.

Analysis of tumors from thousands of patients already treated with known outcomes, will allow for rapid development of hypotheses to be *validated prospectively in clinical trials*. Identification of categories of patients destined to not benefit from standard of care will also lead to a better explanation as to why adaptive resistance occurs and should accelerate studies to find regimens to circumvent adaptive resistance. The result will be less treatment for some patients, reclassification of others into a new set of risk criteria, and the ability to focus therapies and therapeutic research on the patients with the highest risk cancers.

Where are we are now?

Summary of the current state of the science/practice

Assumptions:

- By generating and analyzing extensive molecular and microenvironment assessment of tumors from patients already treated by standard of care, parameters that correlate with success or failure can be derived within several years. Prospective collection of samples is imperative, but assessment of tumors already in hand from patients already treated will provide substantial information in a much shorter time.
- Opportunity will likely define what patients are likely to benefit from standard therapy, what patients are unlikely to benefit and require additional or novel interventions.
- Complementary to the other areas of focus in this Planning Committee – response prediction, genomics – research can be designed to change the standard of care.
- We propose five (could be 6) clinical disease stratifications in which research questions could be explored, and suggest that tumors from 1,000 patients in each category be fully analyzed and patient records be used to annotate the outcomes:
    - Cancers surgically resected with high (80% or more) likelihood of cure
    - Resected cancers with high risk of relapse, generally treated with adjuvant therapy if applicable (maybe = MRD in leukemias)
    - Cancers that are localized but unable to be resected
    - Previously untreated metastatic disease

- Metastatic disease with acquired (or primary) resistance.

Each of these subsets span cancer types, and for each a subset of scientific questions might be addressed, with examples as follows:

Stage	Opportunity	Sample Trials
Resected, high likelihood of cure	Define characteristics of favorable outcome.	Poor-risk genomic phenotype in ostensibly good-risk category: test: more intensive treatment
Resected, needs additional therapy	Analyze characteristics of cancers of relapsers versus cures. Define genomic classification complementary to current (usually morphologic) risk definition. Better definition of high risk patients, and identification of targets for treatment.	1. Good-risk genomic phenotype after surgery for a higher risk tumor: trial of adjuvant versus no additional therapy 2. Poor-risk genomic phenotype even with adjuvant therapy: use findings to suggest different therapy, immunotherapy. 3. Studies in breast cancer (Tailorx 10,300 patients, MINDACT 6700, Clalit 2000) show feasibility
Locally-advanced unresectable	Identify characteristics of those who respond (generally higher response rates than with metastatic disease), and those who don't. The nonresponders can be considered for novel treatment proposals in which some of these patients can be cured.	1. Data mining of poorly responsive locally advanced malignancies in which new approaches can be employed 2. Clinical trials directed at subsets of patients based on DNA or RNA mechanisms of action 3. Opportunity here especially for immunological approaches, and perhaps resectability at a later stage would be adjuvant to the systemic therapy.
1st line metastatic	Define biological basis for variable response, and targets that evolve and prevent cure. Encourage proposals that would define sensitivity and resistance using bioinformatic analyses to adduce information.	1. Few impactful studies exist in this arena; evolving technology may now permit more insightful analyses. 2. Chemotherapy response rates are rarely > 50%. Identify non-responders as early as possible, and identify their biological characteristics to identify targets for novel investigative approaches.
Recurrent/resistant metastatic	Primary resistant tumors may be highly informative for biological informants of drug-independent resistant behavior. Relapsed tumors following initial therapy are likely to have a limited number of resistance strategies, most of which for standard therapies are poorly defined.	Secondary (adaptive) resistance tumors could be examined for genomic changes over time, correlates of adaptive resistance, and identification of mechanisms of resistance and mechanisms to overcome resistance..

- Identification of good- and poor-risk characteristics across disease stages will suggest testable models of tumor progression. Tumor biology will drive clinical trials in cancer therapeutics.
- Cross-cutting genetic and genomic themes will help to address tumor microenvironment, immunophenotypes, stem cell remnants, heterogeneity, and DNA damage response/signaling.

- Several groups (e.g., Children's Hospital of Philadelphia) are engaged in retrospective analysis of biorepository samples, and others (e.g., members of the NCI Clinical Trials Network [NCTN]) are interested but have limited resources. Partnerships could be formed to share outcomes data and other data.

What are the clinical trials? Specific examples:

Good Prognosis Adjuvant Setting:

- Genomic analysis of 1000 patients in four diseases. These tissues may be available with outcomes in existing banks. Define profiles of risk, high and low. Example in colon cancer: E5202 has about 1900 patients with Stage II disease. Risk of relapse in this stage is about 20%, and standard treatment is no therapy in the absence of adverse risk factors. Develop high vs low risk profile.
  - *Sample trial: Colon Cancer Stage II.* Patients selected by MSI status and p53. About 75% received chemo +/- avastin. Results not yet available. Proposal would be to subject the samples from the non-MSI patients to whole exome sequencing (at a minimum), and gene expression profiling. miRNA and limited proteomics also possible. Here we want to find markers of patients who do poorly (we would expect relapse in 15-20%), and identify that profile. The clinical trial would then apply that profile (having validated it internally in the study first, and later in another trial population), and use it to conduct trials of promising interventions looking for big effects.
- In low risk, a *single arm observational study of NO TREATMENT* would target a 5-year recurrence rate of less than, say, 2-4%. This trial would be part of the difficult goal of proving *utility* of the test. This would need to be a simple test conducted in the community, with various design issues to guarantee integrity of the intended approach.

The following table gives the 95% confidence intervals on the 5-year recurrence rate for different observed recurrence rates and sample sizes.

Observed Rate	n=500	n=1000	n=2000
2%	(1.0%, 3.6%)	(1.2%, 3.1%)	(1.4%, 2.7%)
3%	(1.7%, 4.9%)	(2.0%, 4.3%)	(2.3%, 3.8%)
4%	(2.5%, 6.1%)	(2.9%, 5.4%)	(3.2%, 5.0%)

For a test, if the null hypothesis is taken to be the smallest unacceptable recurrence rate, and we want to have good power (say 85%) to reject the null rate in favor of a smaller recurrence rate when the true rate is 2% smaller (ie 6% vs. 4%; 5% vs. 3%; or 4% vs. 2%), then the sample sizes needed for a one-sided 2.5% test are 1091 for 6% vs. 4%, 874 for 5% vs. 3%, and 676 for 4% vs. 2%. Actual sample sizes would be larger, depending on assumptions about drop out, etc.

Good-risk genomic phenotype after surgery for a higher risk tumor:

- Genomic analysis of 1000 patients in four diseases. Again, for some of these tissues are already available to begin analysis in year 1. Here we want to identify patients who do well.
- Again example in colon cancer, tissues are available.

Sample trials:

I. Genomically-Defined Good-risk Patients: Phase III trial of therapy versus no therapy – this is well-established as a feasible design (TAILORx in breast cancer for example). The goal would be equivalence, defined here as an advantage (in 5-year DFS) of less than 3-5% for treatment. TAILORx was powered to detect a decrease of 3% in 5-year DFS (from 90% to 87%). In this noninferiority setting, if the null hypothesis of no difference is used (that is, the null is equivalence), then it is conventional to use larger type I errors and higher power than in superiority tests. With 10% one-sided type I error and about 95% power (conventional for this design), to detect 90% vs. 85%, 232 events would be needed; for 90% vs. 86% 323 would be; and for 90% vs. 87% 515 would be. If one plans on 10% of the cases having events at the time of final analysis, this would give sample sizes about 10 times as large as the number of events.

II. Genomically-Defined Poor-Risk Patients: An unselected population that receives chemotherapy has a 30% chance of relapse in 5 years. The genomically-defined population would likely identify those with say a 60-70% risk. Here we would anticipate that small trials should yield strong effects, and that the treatments tested would themselves be guided by the genomic testing, and would include immunologic therapies. Trials here would target big effects (Hazard Ratios of 0.6 or less), and could be accomplished in studies of 300-600 patients per study.

Locally advanced, non-resectable tumors

- Genomic analysis of 500-1000 patients in specific diseases in which this stage of disease is relevant – examples include lung, esophageal, H/N, breast, pancreatic, sarcomas, cervical, rectal. Pick 4-6, and conduct an observational study in the real world. The endpoints here are in real time – tumor shrinkage, or rendered operable, yes/no. In the non-responsive group, the biology of that class would ideally drive the next set of interventions. For example, if the resistant patients have a mesenchymal profile, that group might be targeted with EMT-directed interventions. Since radiation is a part of many of the treatments of these diseases, insight into radiation resistance would emerge from these studies. These trials would be smaller studies with intensive tissue sampling and/or imaging, designed to elucidate biological processes underlying both response and resistance.
- 1st line metastatic – exploration of newer and more effective therapies in subpopulations
- The landscape for targeted drugs is well-covered, but not for the more standard chemotherapy drugs that are still an important part of therapy
- Potential to fund studies of tumors receiving standard therapies, potentially to complement, in many diseases, the adjuvant trials described above

- Resistant disease – exploration of mechanisms of resistance, trials directed to target common mechanisms of resistance with a goal to delay onset of resistance.
- Trials of standard therapies in several tumors – for example rituxan in lymphoma, using pre/post biopsies in sufficient numbers of patients – perhaps 250-500.
- Studies are most relevant for highly effective therapies, chemo/targeted/IO
- Goal should be to consider tumor/TME/immune responses

Identify barriers to progress and/or emerging opportunities

- New drug studies are well-resourced, and have the power of pharma funding to ensure completion. However, the bulk of drug-based cancer therapy is already established, but the basis of success, the definition of who should be treated, and the approaches that might make them better, remain relatively unstudied
- Only 5% of all patients enroll in a clinical trial. Barriers including clinic infrastructure, medical oncologist reimbursement, and patient reluctance to enroll in trials should be considered.
- While barriers exist, over 2000 institutions/consortia/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 willingness of oncologists and patients (800 pats screened on MATCH trial in 3 months) to engage in clinical trials, use of standard treatments as appropriate, uniform management of cancer care, agreed standards, and available tissue for research and diagnostic use.
- Missing from this system are: (1) Appropriate bandwidth for oncologists to recruit patients, lack of nursing and research team resources to recruit patients, provide informed consent, and organize sample acquisition, which could be solved with research reimbursement for patient accrual. (2) Ability to consistently collect tumor specimens from treated patients, lack of sample preparation/block selection (need pathology support), challenges of shipping to central labs and conduct tumor assays (central support).
- The Cancer Genome Atlas (TCGA) database may not have the clinical data necessary to support the retrospective studies. For example, imaging data were never captured in TCGA. Careful consideration should be given to determining whether genotyping is feasible and logical as part of standard of-care in clinical trials, and whether the quality of the data generated will be acceptable for other applications, such as RNA-seq.
- Challenges related to sample quality and performance need to be overcome. A pilot study or demonstration project could test the quality of biorepository samples.
- The recommendation provides opportunities to: (1) discover new molecular targets of response using well-annotated samples from patients who were treated with traditional chemotherapy and radiation (results from the NCI's Exceptional Responders Initiative

would be useful); (2) better stratify patients into various treatment arms in trials; and (3) determine patient response to treatment in many contexts.

Where do we need to be (in 1-5 years)?

- In depth analysis of existing resources from clinical trials in various stages, with a 2-year delivery time
- Fast-track analysis of clinical trials based on these profiles to challenge current therapeutic strategies: 1 year development, 2-3 years accrual.

Rationale for investing (Why is this priority ripe for accelerating?)

Opportunity brought about by recent development in science, technology, practice

- Emergent and established technologies bring together clinical priorities
- Bringing SOA omic/other technology have the promise of redefining cancers in a targeted fashion, which parenthetically define the utility of these technologies themselves
- Clinical research projects can dovetail with other proposed priorities

Does it address an unmet need or important gap in knowledge or practice?

- One major need is to understand treatments currently administered. For example, with adjuvant therapy, 100% of patients with a particular disease stage receive treatment, yet only 10-20% benefit. Of the 80%, many are already cured and may not require treatment, while some are going to relapse regardless and should receive different treatment.

What would be needed for success?

- New or expanded resources – Leveraging the existing system to reimburse current work and further expansion of clinical trials.
- Barriers/roadblocks eliminated or reduced – The shortage of committed medical oncologists and lack of reimbursement are major barriers. An interdisciplinary team approach is essential with appropriate reimbursement mechanisms in place.
- Workforce training – Current structures exist, but further education is needed regarding genetic and genomic implications of cancer treatment and clinical trial development. Team communications, interactive patient education to facilitate consent, and engagement of diverse populations will expand clinical trials to this novel platform.
- New or enhanced technologies –omics is/are the key. The MATCH trial provides a model for trials with genetic and genomic assay analysis, with extensive validation across sites to assure reliability.
- New scientific approaches – the plan integrates new scientific approaches throughout.
- Structural/behavioral/societal changes – expansion from current methods is the springboard for change.

Strategy: What will it take to get there?

Issues to consider

- Nature of genomic characterization. What depth – Hotspots, WES, WGS, DNA methylation, Expression profiling, miRNA, proteomics? Does it need to be uniform across proposals? Cost?
- Envisage research platform conversion to commercial test (learn from Oncotype-DX)
- Number of patients needed for characterization to power initial tests of treatment strategies?
- Distribution of tumor types? How not to get overwhelmed with the four common cancers?
- Will RFP/RFA's ask for tumor type focus, or breadth across cancers?
- What is the order of magnitude of patients accrued for observational endpoints?
- What will be the timing, size and scope of the clinical trials?

Concrete actions to take in the next 1-5 years

- A one-year embarkation will ensue – negotiations, decisions about the new risk stratification categories and related clinical trials.
- Real world patient accrual, set up of central resources (study structures, data elements, database, registration procedures, sample acquisition procedures, nucleic acid and protein extraction, pre-analytics, assay validation, ongoing communications with patient and oncologists, among many), tumor testing, documentation of treatment, and early outcome data for some categories yrs 1-3 of funding.
- Trials in patients with advanced/resistant disease can begin year 1.
- Trials in locally-advanced disease depending on strength of evidence could also begin early, year 1 or 2.
- Trials in the adjuvant setting would rely in part on information obtained as part of the set of observational studies. Technology could be applied to the well-curated specimen banks that exist in the legacy cooperative groups of the NCTN. These would provide the fastest route to the initiation of trials addressed to adjuvant strategies in newly-defined sub-populations. Feasibility of this approach has already been established (as in the MINDACT breast cancer trial, which addressed risk categories on clinical versus genomic grounds).

What does success look like?

1. Better risk stratification of cancers– allows treatment to be tailored on those who at highest risk for relapse
2. Better definition of poor-risk versus good-risk at a biological level will indicate potentially useful therapeutic directions and allow smaller trials to evaluate them.
3. Greater success in curing locally-advanced cancers.
4. Better understanding of response in advanced cancer.

BRP "Clinical Trials" Working Group Proposal
A Network for Direct Patient Engagement

The recommendation (in 1-3 sentences)? Develop a simple mechanism to provide comprehensive tumor profiling (genomics, immune cells and microenvironment) for all high risk and advanced stage cancer patients for a period of 5 years; the profiling would be implemented in a federated model that could link many labs accepting certain standard operating characteristics and quality controls, as well as data glossaries to ensure data compatibility. Through profiling, patients could be contacted to allow matching to new "smart therapy" options, as through a pre-registration system to accelerate clearance into the right trials for the right patients at the right time.

This would be linked to a novel, simple and straightforward national consent to allow patients to "donate their data" on clinical outcomes so that profiling and clinical characteristics could be linked.

Enlist direct engagement by cancer patients through multiple existing and new channels, both on and off conventional "intervention clinical trials," to volunteer for this nationally federated and shared database to collect genomic data as well as conventional pathology and other descriptors, along with the ability to track and match clinical inflection points and outcomes. To avoid patient selection bias, develop educational tools and incentives to more fully engage community oncologists in clinical trials. Develop composite profiling of tumor with genomics as well as microenvironment descriptors (including tumor immunoprofiles and infiltrates).

For patients willing and able to provide serial biopsies at clinical inflection points (pre-Rx/on Rx/at progression), this "multidimensional molecular/cellular/tissue profile" could inform research on various classes of therapeutic agents. Use "recognition" technology to match patterns to specific cancers, similar to "big data" projects used in defense/anti-terrorism/astrophysics to develop a new ontogeny of clinically relevant cancer groupings by pathways and profiles. To further increase the value of patient profiling data and provide compelling efficacy data, identify actionable items early, such as pairing profiling data with new cancer drugs.

Summary of the current state of the science/practice:

Since genomic profiling of tumor has demonstrated importance for understanding tumor heterogeneity and identification of genetic alterations that may allow for precision medicine therapeutics, expansion of the diagnostic pathology report to include advanced molecular profiling of the cancers in all patients will be a transformational endeavor. Matched drug availabilities and combined modality protocols could be accessed by the treating oncologists. This system will allow for potential therapeutic interventions earlier in a patient's cancer journey, rather than late in the process. This is most definitely not a monolithic "top down" model that we propose, but rather a flexible, interactive and federated system of tumor profiling linked to clinical data repositories to link molecular data with associated clinical outcomes for patients.

Genomic profiling (limited panels, larger panels, Whole Exome Sequencing, Whole Genome Sequencing) is already technically feasible but limited to patients who can pay, or in clinical trials which rarely share data across centers and sponsors. This is all technically feasible with appropriate engineering at social, economic and organizational levels. Multiple platforms for tumor genomic profiling are available; however, no standardized approach is universally accepted. Also, there is no standard accepted quality assurance methodology nor accepted Information technology standards that allow for federated databases to talk with one another and cross-reference data. A standardized next-generation sequencing panel for profiling patients that includes validated tumor and germline gene panels as well as panels to investigate the immunogenome would be useful.

Identify barriers to progress and/or emerging opportunities:
Cost of obtaining tissues and obtaining quality tissue samples for genotyping needs to be addressed. Consent issues need to be addressed as simply and straightforwardly as possible, with a consent that is "one and done" for tumor analyses, future research and data collection and use. Patients can be engaged without necessarily requiring physicians to serve as the sole portal of entry to this large open-sourced study with appropriately mechanisms to support important operational details of tissue collection, processing and data transfer. There is no standardization of the platforms, tumor collection, processing, utility or data warehousing. However, NCI clinical trials network groups (ECOG/ACRIN in the NCI MATCH trial) have developed some processes for obtaining tumor tissue, shipping to analytic centers, and providing genomic results to the treating physicians with a turnaround time of approximately 2 weeks. This experience shows that this is a feasible operational, and the reception by patients and community oncologists has been very positive to date with rapid accrual. The committee is proposing a federated effort with defined operating principles to allow many labs and centers to perform such profiling and data collection, with quality and data-dictionary standards, so that the whole will be greater than the sum of any component parts. This will also overcome capacity bottlenecks which would be inherent if only one large site were to perform all tissue analyses for the country.

The opportunity exists to collaborate with other groups doing similar work to consolidate useful clinical information. Many repositories are not equipped to handle clinical data. The data systems could be linked to the NCI Genomics Data Commons or other new Cancer Moonshot initiatives such as the patient-focused volunteer CancerBridge database system. Other initiatives such as the GENIE project also work to enhance sharing of clinical data.

Challenges exist regarding the interpretation of clinical trial treatment and outcome data for patients, providers, and other stakeholders. Existing initiatives, such as the American Society of Clinical Oncology's CancerLinQ and Flatiron Health's platforms on oncology, could serve as models to improve interpretation.

Decision support is needed to provide real-world evidence. Having such evidence would provide the opportunity to develop innovative tools that could facilitate the gathering of

data (e.g., using patients' digital devices to provide a continuous flow of patient-reported outcome (PRO) data).

Where do we need to be in 1-5 years?

Key research priorities:

1. Nationally federated database built from standardized and interoperable components of cancer profiles and patient phenotypes (outcomes).
2. Matching to clinical trials at national scale, with definitions of go/no-go milestones to ensure success continues and marginal utility testing is stopped.
3. Public-private federated model for tumor profiling, matching to relevant trials and identifying with precision the full scope of anticancer activities across cancers at a national scale.

Rationale for investing: Why this is the best opportunity to invest at this time!

- Opportunity brought about by recent development in science, technology, practice: Although profiling is already feasible and in limited deployment, a shared national effort with aligned goals to maximize current opportunities will avoid slow pace and poorly organized, hit-or-miss individual center/individual sponsor research efforts. There is also the fairness argument in favor of doing this at national scale, since offering a national program of tumor profiling and data sharing will be more fair to disadvantaged patient groups and those with limited socioeconomic means.

- Does it address an unmet need or important gap in knowledge or practice? Absolutely yes. Pre-registration of profiles will create a "pre-check" mechanism for cancer therapies and cancer clinical trials for defined subsets of patients that will allow us to tell our patients more about expected risks/benefits. Pre-certifying patients on any level will improve our understanding of unselected trials, and will facilitate finding the rare but "low hanging fruit" in which single mutations could be targeted with life-improving impact for patients. This will also allow machine learning to identify patterns important for rational combinations and synthetic lethal opportunities with new agents and strategic orthogonal targeting. We would also be able to assess where such profiling adds no value, and stop such subsets from proceeding wastefully with ongoing analyses of the data over a 5 year period in relatively "real time."

What would be needed for success? *For example*:

- New or expanded resources: national scale with CMS coverage and infrastructure to move quickly to expand what is considered a "standard" diagnostic work-up. "*Move beyond the microscope and tell me more about MY cancer*" can be the battle cry for our volunteer army of patients who want to contribute to a national charting of the cancer landscape towards precision cancer diagnoses and the best possible options for care. The rapid accrual to the NCI MATCH clinical trial in the

community already attests to the untapped demand for this testing, and the opportunity to accelerate knowledge creation and help patients faster through a coordinated national federated effort. This proposal also aims to be a responsible steward of resources by focusing on developing analytics to assess in which clinical settings such profiling is having positive impact, as well as to stop profiling efforts if there is no demonstrable impact.

- Barriers/roadblocks eliminated or reduced: only the privileged can currently access molecular tumor profiling. This is inefficient, unfair, and scientifically unjustifiable. A national effort is efficient, fair, and maximizes the chances of successful outcomes and data collection with analytics in 5 years.
- Workforce and public trained: genomic education is necessary for the workforce as well as the public. Patients need to be educated that a modern definition of cancer includes these important aspects so that we can together define these diseases with more precision, and their own outcomes may change. They are also part of the team building this important "data railroad" for cancer across the country to improve the way we transmit information and learn about cancer. Training "on the cancer journey" is most effective, and this effort will accomplish this.
- New or enhanced technologies: new incentives to merge with data sharing and other groups, as well as new incentives to improve technology of tumor processing and profiling (as in the High Tech Sector) from this national initiative.
- New scientific approaches: epigenomic profiling will take off soon, and this can build upon the genomics foundation. Efforts to use genomics to assess immune infiltration and T cell repertoire are similarly in development and being done on a smaller scale. The wealth of information from a broadly annotated population is an opportunity we cannot miss.
- Structural/behavioral/societal changes: closer interactions will evolve between patient/advocacy groups as well as academics, community oncology practices, governmental researchers, regulators (with a focus on quality "real world evidence") and resources, as well as the biopharma/industrial sectors and IT sectors.

Strategy: What will it take to get there?

Concrete actions to take in the next 1-5 years: Develop processes to standardize technology, tumor handling, expand treatment protocols and implementation for accessibility, and create Health IT to manage data and simplify transfer.

Develop a mechanism to cover the costs (not charges) for profiling as a "standard cost of doing business" in cancer care. Insurers benefit from research – consider adding a line item for a research fund contribution as a mandated cost of providing insurance products in this country (this concept will be put into our committee's policy recommendation as

well). From a policy standpoint, it is also important to link this to a delay in implementing any new restrictions on the Common Rule for Research on Human Participants. There are important unintended negative consequences.

What does success look like? Success measures include a clinical report that includes individual patient tumor genomics and other cancer characteristics with a defined standardized data terminology and a shared database, federated amongst interoperable components, to allow analyses and linkages between patient and tumor characteristics and clinical outcomes (benefits and toxicities).

A national database, several new drug successes, and much information about what does and does not work in trials as well as in the "real world" of practice. Additionally, this resource will allow researchers to probe mechanistically WHY certain treatments are succeeding or failing in profiled patients. Patients will have a reservoir of data against which to compare their personal profile and understand their own disease, and their family profiles as well. Faster development of new agents with a robust biopharma sector contributing new agents at affordable prices (decreased cost to approvals) while maintaining healthy profit margins and attracting new investments in cancer research and development. Rare subsets can be grouped effectively into robust markets to encourage drug development for pediatrics and parsed subsets of common diseases (even rationally-defined mechanistic subsets of triple negative breast cancer, brain tumors, or gastrointestinal cancers, for example).

Impact on patients: Done at the national scale and scope, this would be profound and potentially game-changing for cancer care and research, as above. Better engagement, better understanding, better outcomes.

Why is this not "Business As Usual"? This is much different than the current unfair, fragmented, inefficient system in place that limits access to technology and only gleans a small subset of data from the massive heterogeneity of cancer patients in the USA. And – with coordination and a series of public/private partnerships, this is perhaps not all that much more costly to execute than the current fragmented and limited systems duplicated across many cancer centers in the US at this time!

Appendix:
Demonstration Project to Develop New Technologies

What is the recommendation (1-3 sentences)?

Implement innovative scientific approaches, particularly through the development of new technologies, that rapidly prioritize the selection of effective therapies for individual patients, based upon the empiric response of that patient's tumor to therapeutics. Recent exemplars include intra-tumoral microdosing devices that are briefly implanted in a patient's tumor prior to surgical resection, and patient-derived organoids to simultaneously screen many drugs in vitro.

Where are we are now (2-3 paragraphs)?

- Summary of the current state of the science/practice
    - Prioritization of drug candidates during preclinical and early clinical development is typically based on activity profiles across cell lines, xenograft and PDX models, often focused on a specific genomic context (e.g. driver mutation) that forms the basis for the drug target. Although there have been many successes with this approach (most approved targeted therapies), it is limited by the availability of models that are "validated," i.e. predictive of clinical benefit in patients represented by that set of models. Large swaths of human cancer are not currently modeled by existing cell lines and xenografts, despite significant efforts to expand the number of cancer cell lines (e.g. cancer cell line encyclopedia, etc).
    - In vivo multipore drug dispensers have been fabricated and evaluated in preclinical models. The devices are capable of dispensing small amounts of drugs separately and in combination, such that a small number of cancer cells near the pore are exposed to drugs. Surgical removal of the device after several days, and co-registration with the nearby drug depot, identifies active therapies that promote cell death.
    - Patient-derived tissue models can be rapidly derived from normal tissues and carcinomas such that molecular and simultaneous multiplex therapeutic profiling can ensue. For example, early results from colon cancer organoids and conditionally reprogrammed cells in feeder culture suggest that therapeutic response of patient-derived tissue models to standard cytotoxic agents is predictive of the patient's clinical response.
- Identify barriers to progress and/or emerging opportunities
    - The microdosing implantable devices are only beginning clinical feasibility assessment, and such devices could also be used to evaluate biologics including immune modifiers. Since surgery is not always possible in sick cancer patients, the fabrication of such devices and alternative approaches to capture the same

information when surgery is not possible represent technology development opportunities (e.g. microscale CTC capture, cell-free nucleic acid, nanosensors).

- Patient-derived cultures have not been established from all human cancers to date. For example, organoids have not been established from all human cancers to date (e.g.: GBM, primary prostate), and they currently do not include elements of the tumor stroma that may impact therapeutic efficacy. Current 2D co-culture and 3D organoid protocols can take weeks to months to generate enough samples to do deep molecular and therapeutic assessment, representing opportunities for technology development. Patient-derived cultures represent model systems to evaluate personalized immune-oncology approaches, such as the identification of neoepitopes and Adoptive Cell therapies. Finally, as normal tissues such as liver, heart and intestine are being grown in microscale formats for predictive toxicology, both efficacy and toxicity platforms could be used synergistically to personalize a therapeutic index.
- Expanding the recommendation to include a Phase 0/Phase 1 platform would further advance pharmacology efforts. A novel technology that would indicate the benefit of a clinically administered dose would be transformational; a device that could obtain profiles (e.g., cytokine profile) at metastatic sites in a tumor would greatly accelerate the drug qualification process. Insight into effective combination therapies for patients would be critical for developing new predictive models and could serve as an interface between technology and drug development.

Where do we need to be (in 1-5 years)?

- Key research priorities (pick 2-3)
    - Clinical trials to evaluate the safety and predictive ability of intratumoral microdosing/monitoring devices to pick effective therapies for patients.
    - Clinical trials to demonstrate the feasibility of organoids to choose drugs prospectively for cancer patients.
    - Clinical trials to evaluate the ability of implantable devices and organoids to address therapeutic resistance/dormancy in patients.
    - Preclinical studies to explore broader application of patient-derived cultures including technology, shifting the focus to short-term drug sensitivity readouts using high-throughput and high-content imaging, flow cytometry, CyTOF (versus waiting for establishment of a serially passaged organoid lines) and the inclusion of stroma and immune infiltrates (versus pure epithelial cell cultures) to evaluate drugs targeting the microenvironment.
- Rationale for investing (Why is this priority ripe for accelerating?)

- Opportunity brought about by recent development in science, technology, practice
    - Emergent technologies
    - Microdosing implantable devices recently developed.
    - Organoids are a very recent breakthrough to robustly culture human normal tissues and neoplasms.
- Does it address an unmet need or important gap in knowledge or practice?
    - Yes.

- What would be needed for success? *For example*:
    - New or expanded resources
    - Barriers/roadblocks eliminated or reduced
    - Workforce trained
    - New or enhanced technologies
    - New scientific approaches
    - Structural/behavioral/societal changes

All of the above are needed, but first scientific evidence is needed in early phase trials.

Strategy: What will it take to get there?

- Concrete actions to take in the next 1-5 years
    - RFAs to motivate the invention and testing of microdosing and monitoring devices (SBIR, etc), including the funding of Phase 0 neoadjuvant trials.
    - RFAs to evaluate organoids and other in vitro models (CTCs, CRCs) in a series of clinical trials.
    - RFAs for preclinical optimization of patient-derived cultures including organoids and other in vitro models for short-term drug sensitivity readouts and inclusion of stroma and immune cell infiltrates in culture conditions.
    - RFAs to 'platformize' patient-derived cultures and other in vitro models across large panels representing all types of cancer and including specific molecular subtypes, such that pre-screening of therapies can be done on a broad scale.
    - White paper on above that outlines the current limitations and opportunities.

What does success look like?

"Pharmaco-typing" our patient's tumors will complement the current genotyping efforts to understand and treat cancer patients. The ability to initially choose the most active therapies for cancer patients should optimize their care, and bring us closer to the treatment of bacterial infections. Furthermore, such approaches can be subsequently applied to address innate and acquired resistance to original therapies. In addition, databases populated with genotype and pharmacotype results from large numbers of patients can be mined for further predictions of of drug and drug combo sensitivity. Although not a primary goal, this effort could also expand the availability of preclinical organoid models for earlier stage screening of drug candidates.

Milestones per above:

1. Demonstrate that implantable microdosing/sensing devices can be safely tested in tumors in a Phase 0 neoadjuvant setting.
2. Determine whether tumor heterogeneity within a single tumor or between multiple tumors in a patient has the same sensitivity to therapeutics in a microdosing early phase trial.
3. Determine whether the most active therapies identified with implanted microdosing devices are predictive of patient clinical efficacy.
4. Demonstrate that organoids and other patient derived tissue models can be robustly generated from patients and genotyped and pharmacotyped in time frame that can influence prospective clinical management.
5. Determine whether organoids and other patient derived tissue models predict active therapies for patients.
6. Determine whether serial biopsies and organoid cultures can predict cancer heterogeneity, disease evolution, and therapeutic sensitivity and resistance.
7. Design clinical trials that can triage patients into treatment arms based upon the early results of a Phase 0 microdosing and organoid trials.

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Precision Prevention and Early Detection Working Group Recommendation

Cancer Prevention and Early Detection in Individuals at High Risk for Cancer

What is the recommendation?

To realize the potential of cancer prevention and early detection in our nation, NCI should sponsor an initiative to improve the current state of early detection, genetic testing, genetic counseling, and knowledge landscape of the mechanisms and biomarkers associated with cancer development. This initiative should include demonstration projects that will show how cancer screening programs can simultaneously save lives, improve quality of life, and reduce healthcare costs.

Background and Significance

It is estimated that more than half of all cancer deaths could be prevented, and it is well established that early detection of cancer improves cancer mortality. Thus, an enhanced focus on early detection and prevention should be a priority to reduce the burden of cancer. It is now appreciated that some cancers run in families due to an inherited predisposition to cancer development. Due to the widespread availability of genetic testing, we now have the opportunity to successfully identify these families and the affected individuals. Because early detection and prevention can also improve mortality in individuals with an inherited predisposition to cancer, these individuals are an important target population for cancer prevention and early detection strategies. With appropriate attention to implementation, identification of at-risk individuals may empower them to make and act upon informed, cancer-preventing health decisions.

We propose an initiative to focus research on the highest risk individuals. This research should employ cutting-edge technologies to identify early markers of disease and facilitate detection of precancerous lesions or stage cancers for improved cancer outcomes and prevention. This recommendation seeks, by risk stratification, to capitalize on the recent and emerging foundation of knowledge in cancer genomics to transform early detection and to optimize cancer prevention for those who are most in need. In addition, it will facilitate the development of approaches that can be expanded in the future to include individuals at high risk for other cancers. The expanded identification and characterization of high-risk populations would enable advancements in research, care, and survivorship for individuals with precancerous lesions and early cancers and will facilitate elucidation of cancer-relevant gene–environment interactions and behavioral modifiers of disease risk and progression. Further, because this initiative will focus on a cohort of individuals with an increased likelihood of cancer development and early-onset cancers, it will promote the development cancer detection and prevention strategies on an accelerated timeline. We anticipate that many of these advances will be applicable to the general population.

Strategy Outline

To fully implement the proposed recommendation, we suggest a strategy comprising the following steps:

1. Case ascertainment – Increase ascertainment of individuals with germline mutations;
2. Delivery of evidence-based services – Deliver evidence-based genetic counseling, preventive and early detection services, and on-going surveillance of identified individuals with germline mutations through high-quality and broad-reach public health genomics programs; any work in identifying germline mutations should include a plan for future treatment;
3. Pre-Cancer Genome Atlas (PCGA) initiative in germline mutation carriers – Establish a research initiative, the Pre-Cancer Genome Atlas (PCGA) in Germline Mutation Carriers, to better understand the molecular underpinnings and fate of the earliest stages of neoplastic development in these high-risk individuals;
4. Tools to promote data sharing – Develop the informatics tools to support a data-sharing initiative that will aggregate and link clinical-grade cancer genomic data with clinical outcomes from individuals across the country and that will support a network of at-risk individuals, research investigators, and research studies;
5. Functional analysis of "variants of uncertain significance" – Evaluate "variants of uncertain significance" identified through sequencing of germline DNA;
6. Translation of PCGA insights into novel biomarkers and improved risk modeling –Translate findings from PCGA into novel markers and models of risk and/or outcomes;
7. Smaller, faster interventional trials – Conduct small, short-term, biomarker-driven interventional trials of preventive interventions in germline cases;
8. Extending success to somatic cancers in the general population – Identify and contribute sporadic pre-cancer cases to the PCGA to facilitate translation of the findings in high-risk individuals to segments of the general population;
9. Best practices that ensure participation across populations – Ensure access to genetic testing and counseling, translational research opportunities, and best practice screening, prevention, and early intervention strategies as well as plan(s) for future treatment across the spectrum of our nation's population, including urban poor, rural and other underserved populations.

Initial Demonstration Projects

We recommend a set of demonstration projects that focuses on individuals—across the full spectrum of the population—with hereditary cancer risk attributable to known genes, including those underlying Lynch Syndrome (LS) and Hereditary Breast and Ovarian Cancer (HBOC). Individuals with LS have an increased likelihood of developing colorectal, endometrial, and other cancers such as gastric and ovarian cancers. Individuals with HBOC associated with *BRCA1* and *BRCA2* genetic alterations have an increased likelihood of the development of breast and ovarian cancers as well as other cancers such as aggressive prostate cancer (in affected men) and pancreatic cancer. The primary goals of these projects will be to improve preventive care for these individuals and to develop models for cancer risk assessment and prevention. We anticipate that these models as well as the infrastructure developed for data integration, will be applicable to cancer care and research in other high-risk populations as well as the general

population, which may develop sporadic cancers not associated with an inherited risk gene. An overview and detailed strategy for detection and ascertainment of individuals at risk for LS as well as a cost estimate are attached (Appendix). A similar pathway analysis–based strategy is applicable for detection and ascertainment of individuals at risk for HBOC and has been drafted as well and included in the Appendix.

Where are we now?

The current state of affairs is summarized according to each of the nine strategic areas outlined above:

1. Case ascertainment – Underuse of germline cancer testing in appropriate populations is leading to unnecessarily lost lives and diminished quality of life (PMCID: PMC4301704). Although some states have fledgling public health genomics programs that are helping to reach people at risk for cancer, there is not currently a nationwide initiative to identify those at highest risk due to germline carrier status and to determine and implement optimal intervention strategies that would reduce the risk of developing malignant disease in these individuals. A 2013 study illustrates the need for coordinated, rational, nationwide screening for hereditary cancers: the study reported that fewer than 5% of individuals with colorectal cancer received Lynch syndrome screening of their tumors, despite the fact that this is a recommended standard-of-care practice by the Evaluation of Genomic Applications in Practice and Prevention (EGAPP) Working Group (http://www.egappreviews.org/recommendations/index.htm), the American College of Gastroenterology, and the American Medical Association. This represents a tremendous missed opportunity, which will be addressed by the recommended demonstration project, to identify individuals and family members who are at substantially elevated risk for HBOC- and LS-related cancers.
2. Delivery of evidence-based services – There is lack of public education about genetic testing and counseling, thus the population is not well aware that there is potential for inherited cancer risk that merits intervention. It is estimated that a public health genomics program–mediated intervention is likely to be relevant for at least 5–10 percent of all people with cancer and broadly inform molecularly targeted, rational preventive actions (PMID:26510020). In addition, more research is needed in the area of genetic risk communication, with particular attention to the issue of effective messaging of complex and uncertain genomic information and the impact of such information for patients and providers.
3. Pre-Cancer Genome Atlas (PCGA) initiative in germline mutation carriers – While the ClinVar resource catalogs relationships between germline mutations and clinical phenotypes, including at the case level, it has not benefited from a concerted effort to record individuals with germline cancer mutations or phenotypes of families who share the mutations.
4. Tools to promote data sharing – Somatic mutation testing of tumors and cancer genetics programs are increasingly identifying individuals and family members with germline mutations that place them at high risk for early-onset and multiple cancers. However, this information is not being shared or leveraged in a systematic way. Thus, there are

tremendous opportunities to mine tumor profiling data generated in healthcare organizations throughout the U.S. and to conduct studies to evaluate the prevalence of tumor mutations originating in germline DNA.

5. Functional analysis of "variants of uncertain significance" – As the genomic analysis of patient tumors increases, more and more mutations in known cancer-causing genes, such as the mismatch repair genes, *BRCA1*, *BRCA2*, *APC*, and others, are being identified. Many of the genetic changes fall into the category of "variants of uncertain significance" (VUS). Specifically, VUS are mutations found in a gene that is known to be associated with cancer development when mutated, but the particular variant has not been demonstrated to be either pathogenic or non-pathogenic. VUS findings lead to difficult clinical decisions for physicians and patients. An important scientific opportunity is therefore to develop assays and conduct functional genomic studies to establish if a VUS has pathogenic potential.
6. Translation of PCGA insights into novel biomarkers and improved risk modeling –In contrast to cardiovascular disease, where pre-disease conditions such as hypertension and high cholesterol can be readily identified and the risk mitigated by lifestyle or drug interventions, cancer is often detected after the onset of symptoms, when it already reached an advanced stage and is difficult to treat. In cases such as colorectal cancer, in which asymptomatic precancerous lesions (i.e., polyps) can be detected by screening colonoscopy, the polyp can be endoscopically removed to prevent tumor development, providing a compelling rationale for screening as a strategy to reduce the burden of cancer. Precancerous lesions have been observed in breast, pancreas, and most other organ sites. However, non-invasive strategies to detect their development at an early stage have not been developed as broadly.
7. Smaller, faster interventional trials – Currently, the process of identifying a new biomarker or potential therapeutic through to verification of its clinical utility via large-scale interventional trials is lengthy. Because carriers of germline mutations of cancer risk tend to be diagnosed with cancer at an earlier age and are more likely to be diagnosed with cancer, there is a unique opportunity to work with this population to conduct faster, more efficient interventional trials of prevention and early detection strategies.
8. Extending success to somatic cancers in the general population – As the cancer community learns more about which genes are involved in hereditary cancers, they are discovering these genes are also frequently altered in sporadic cancer (PMID: 1528264). In addition, tumor profiling is also increasingly leading to the identification of mutations in known cancer-risk genes, which are then shown to be actionable germline lesions (PMCID: PMC4843184, PMID: 26822237, PMCID: PMC4636487). Thus, there is a growing convergence of germline and somatic knowledge. Recently developed non-invasive or minimally invasive technologies to detect biomarkers of precancerous lesions or early cancers, for example imaging biomarkers or "liquid biopsies," provide investigational opportunities to improve screening and early detection in populations at highest risk. If designed correctly, there is an opportunity to extend strategies developed for early diagnosis, cancer prevention, therapy, and detection in high-risk cancer populations to the general population.

9. Best practices that ensure participation across populations – Data suggest that there is differential access to and use of genetic testing, counseling and preventive care among underserved racial and ethnic minorities compared to white populations leading to important health care disparities (PMID: 16682739). This initiative proposes increasing the genetic testing, counseling, and surveillance capabilities of the nation, and the opportunity to do this in a way that minimizes health disparities should be seized.

Where do we need to be (in 1-5 years)?

Within approximately five years, the U.S. should have:

1. Case ascertainment – An established national public health genomics initiative that provides access to genetic evaluation across the population, and a system in place to link high-risk individuals with research and care programs focused on early detection, specimen collection, and risk-reduction interventions. This will ensure that individuals at highest risk for early-onset cancer due to germline mutations can be identified.
2. Delivery of evidence-based services – Implemented early detection screening strategies in those at highest risk followed by access to best practice preventive care prior to cancer diagnosis (synergy with Implementation Working Group); new models of genetic education and counseling in place to enhance access to genetic information across the population; and on-going surveillance of identified individuals through high-quality and broad-reach public health genomics programs.
3. Pre-Cancer Genome Atlas (PCGA) initiative in germline mutation carriers – Established the PCGA resource, which should include all consenting individuals tested in this initiative's demonstration projects as well as any other germline mutation carriers willing to contribute their data.
4. Tools to promote data sharing – An established national data-sharing initiative to aid research efforts that will leverage the significant benefits of high-risk cohorts for studying the pre-cancer genome and epigenome, novel preventive interventions, early detection approaches, and biomarkers (synergy with Data Sharing and Clinical Trials Working Groups). This initiative will facilitate connections between at-risk individuals, research investigators and potential research opportunities. Such an initiative could significantly enhance and accelerate prevention research and further drive investment in this area.
5. Functional analysis of "variants of uncertain significance" – A comprehensive national research program to inventory genetic VUS and conduct functional genomic and epidemiological studies to assess their potential relevance for cancer initiation and progression.
6. Translation of PCGA insights into novel biomarkers and improved risk modeling – Facilitated use of PCGA for biomarker discovery, development of new prevention strategies, and development of new early detection methods.
7. Smaller, faster interventional trials – More rapid translation of biomarker findings into a range of novel preventive interventions (e.g. targeted drugs, immuno-preventive agents, and lifestyle alterations) after the conclusion small, short-term, biomarker-driven trials of preventive interventions in germline cases.

8. Extending success to somatic cancers in the general population – Translation of biomarker findings from individuals with germline mutations of cancer risk to the general population with risk for cancers driven by somatic aberrations.
9. Best practices that ensure participation across populations – A mechanism to engage the full spectrum of the U.S. population in assessment of inherited cancer risk and access to best practice genetic counseling and clinical care for cancer prevention and early detection; additionally, biobanks and databases enhanced to reflect the full spectrum of the population across demographics (e.g., race/ethnicity, age, geographic location and zipcode). This will facilitate exploration of germline mutations across the population such that it may be a model of inclusive representation that reduces rather than exacerbates health disparities.

Rationale for investing NOW: Why is this priority ripe for acceleration?

Due to prior public- and private-sector national investment in cancer genetics/genomics, tumor registries, and tumor genotyping, past research and development can be leveraged in a meaningful way to achieve the goals of this initiative on a rapid timeline. This rapid timeline is facilitated by the choice of a cohort of individuals who have increased risk of cancer development and early-onset cancer. Further, this population—up to one million individuals in the US with LS and HBOC alone—is currently underserved in terms of receiving appropriate genetic testing, genetic counseling, and preventive care, despite existing requisite technologies and established guidelines for cancer prevention, screening, and care in these syndromes. This state of affairs has come about due to lack of infrastructure for coordinated care and research surrounding individuals with inherited predispositions to cancer. This initiative aims to establish an adaptive infrastructure by capitalizing on existing resources; this infrastructure will address an immediate need of these underserved individuals and will be broadly applicable to individuals in other high-risk populations as well as the general population at risk for somatic cancer development.

<u>Proofs-of-concept based on existing infrastructure</u>

- Novel technologies and non-invasive approaches (e.g., liquid biopsies, novel imaging strategies) to detect cancer biomarkers are undergoing rapid advances. These techniques, in combination with parallel standard-of-care imaging, provide unique opportunities for early detection. Improved early detection is especially important for germline mutation–associated tumors for which early detection is not yet practical, particularly ovarian and pancreatic cancers, which are part of both LS and HBOC.
- Genetic understanding of inherited cancer risk has led to advances in both chemoprevention (e.g., NSAIDS in colon cancer) and therapeutic interventions (e.g., drugs targeting DNA repair in ovarian and breast cancer, now also pancreatic and castration-resistant prostate cancer, and immunotherapies in Lynch syndrome).
- The success of The Cancer Genome Atlas and the associated explosive progress in technology development laid the groundwork for a successful effort for timely completion of the "Pre-Cancer Genome Atlas" (PCGA). Lessons and results from work supported by other organizations (e.g., the Cancer Global Alliance's *BRCA* challenge

includes germline variant alleles for breast cancer) also should be considered in the implementation of the PCGA.

- The field of oncology is leading the way in precision medicine. Numerous cancer treatments are already targeted to cancers harboring particular biomarkers. It is possible that any findings or lessons learned with regard to this proposed project will be relevant to other areas of medicine outside oncology care.

Rationale for investing in the population with hereditary cancer predisposition

As discussed above, more than half of cancer deaths could be prevented, and early detection of cancer improves cancer mortality and quality of life. Prior public- and private-sector national investment in cancer genetics/genomics, tumor registries, and tumor genotyping has led to the accumulation of new knowledge that can now be used to 1) identify those individuals at highest cancer risk to offer them best practice preventive care, and 2) facilitate the development of novel early detection approaches.

Because cancers develop earlier and more rapidly in those with germline risk, the recommended stratification approach will allow investigators to study cancer development over a shorter timeline, and thus realize potential benefits in the form of novel biomarkers and preventive interventions much sooner than would be possible if studying a cohort of patients with sporadic cancers. Further, because the cancer risks are higher and evolution to cancer more rapid, trials may be smaller, shorter and more efficient. In addition to directly affecting individual lives, this recommendation will permit investigators to identify large numbers of high-risk mutation carriers for possible participation in an array of more intensive early detection and prevention research studies, including studies on lifestyle risk factors, identification and optimization of biomarkers for early detection, and innovative, genetically-informed chemo-prevention strategies. The results of this work will allow accelerated translation of new knowledge to individuals and populations at highest risk. Further, we expect many of the discoveries, techniques, and infrastructure developed as part of this initiative to be applicable to other high-risk populations as well as the general population.

Rationale for the proposed demonstration projects in LS and HBOC

There is a strong rationale for the proposed initial focus on LS and HBOC. The Centers for Disease Control and Prevention (CDC) estimates that approximately one million Americans are at risk for early-onset cancer due to Lynch syndrome (LS) and Hereditary Breast and Ovarian Cancer (HBOC) syndrome. Individuals with Lynch syndrome have a higher likelihood of developing colorectal, endometrial, and other cancers (e.g., gastric and ovarian).

The EGAPP Working Group and others (e.g., NCCN, ACG, USPSTF) recommend tumor testing to screen for Lynch syndrome among all individuals with colorectal cancer, since this can facilitate the identification of healthy, at-risk relatives with Lynch syndrome for whom enhanced colorectal cancer screening can significantly reduce colorectal cancer incidence and associated mortality. Women with inherited breast cancer susceptibility gene mutations have a substantially higher breast and ovarian cancer risk than those without susceptibility mutations, with a cumulative risk of developing breast and ovarian cancer of up to 80% and 40%, respectively. Women with a personal or family cancer history indicative of a BRCA1/2 mutation may benefit from genetic counseling and testing. For those who test positive, currently available

interventions can decrease breast and ovarian cancer incidence by up to 95% and 90%, respectively, and reduce breast and ovarian cancer mortality as well.

Many of the individuals with these conditions are not aware that they are at increased risk for cancer, or that their cancer diagnosis is attributable to an underlying predisposition that is likely shared with family members. The application of established, preventive and early detection interventions in this population is clinically relevant, aligns with existing CDC priorities and best practices, and is likely to have a measurable impact on the cancer burden in the U.S. While using colorectal cancer screening to identify probands is an appropriate place to start, other identification approaches (e.g., testing for LS at the first colon cancer screening) should be considered for the future. Additional preventive strategies, such as the use of normal-dose aspirin in patients with LS, may provide a model for low-cost/high-benefit interventions; in this case, however, biomarkers are needed to identify people who should not take aspirin. More importantly, the approaches that will be developed by this initiative can be adapted to the detection, characterization, and prevention of common sporadic cancers, thus facilitating the realization of a national goal of cancer prevention in the general population.

Does it address an unmet need or important gap in knowledge or practice?

In addition to the unmet needs discussed in the "where are we now section?" above, there are several other important unmet needs, knowledge gaps, and practice gaps:

- We are not currently identifying all of the people who are living with inherited germline cancer risk; as such, we are failing to provide optimal guidance regarding cancer screening and prevention to those at highest risk, which represents a key unseen disparity that must be addressed. This disparity is magnified at the intersections of other disparities, such as race, socioeconomic status, health literacy, and access to care.
- Many of our current screening modalities are invasive, costly, and may lead to overtreatment. The development of more robust biomarkers for non-invasive detection of early lesions, and the acquisition of new knowledge to stratify those that are indolent from those that are likely to progress, will improve cancer outcomes.
- We do not understand why some people who are at the highest risk of cancer never develop it; understanding intrinsic protective factors (immune-based or other mechanisms) could be a key to innovative cancer prevention strategies.
- As tumor somatic genotyping becomes standard-of-care, it creates the potential to identify patients carrying germline mutations that pose hereditary cancer risk. However, to identify these patients and serve them, a new infrastructure must be created to deal with germline information created during the course of somatic molecular testing. We risk underserving the population with germline cancer risk mutations if we do not act on such knowledge. In addition, other actionable mutations may be found that may or may not be relevant to a cancer diagnosis, but may nevertheless have the potential to affect an individual's—and a family's—life. Research on the best way to handle these types of "incidental" findings is just beginning (overlap with Clinical Trials Working Group).

Strategy: What will it take to get there?

1. Case ascertainment – Improve and expand the identification of individuals at high risk due to germline mutations through
    a. A data-sharing initiative supported by state-of-the-art informatics infrastructure that would permit the voluntary deposition of germline and tumor data and encourage research participation by at-risk individuals. Uniform testing of all sporadic colorectal, endometrial, ovarian and breast cancer patients for mutations associated with genes implicated in LS or HBOC. Reporting of all findings to state cancer registries is recommended.
    b. Education of primary care providers to increase use of appropriate screening, counseling and evidence-based genetic tests; and
    c. Improvement in public understanding of genetics and associated testing, risk, counseling and preventive strategies as they relate to cancer.
2. Delivery of evidence-based services – Establish and expand state and national public health genomics programs consisting of
    a. Expanded access to genetic testing and counseling services; this effort will require increased numbers of genetic counselors and evaluation of alternative counseling models to increase access;
    b. Dissemination of current standards of care for individuals with germline risk to educate all health care professionals; and incorporation of criteria into electronic health records to promote compliance; and
    c. Monitoring of inherited cancer cases to see to what extent carriers were identified before diagnosis, and if so, had appropriate surveillance and care.
3. Pre-Cancer Genome Atlas (PCGA) Initiative in Germline Mutation Carriers – Comprehensively characterize the early stages of neoplastic development at a molecular level in germline mutation carriers using available "omic" technologies to elucidate mechanisms underlying indolence or progression of identified lesions. This includes continued development of a standardized genotyping–next-generation sequencing pipeline for analysis of both tumor and normal DNA.
4. Tools to promote data sharing – Develop informatics tools that will permit the creation of a national data-sharing initiative to aggregate and link clinical-grade cancer genomic data with clinical outcomes from tens of thousands of cancer patients that receive tumor genotyping and care at numerous academic and private oncology practices nationwide (synergy with Data Sharing Working Group). The development of the data-sharing platform(s) addresses an unmet need by providing the statistical power necessary to detect germline cases of common and rare cancers and uncertain variants in common cancers. As is the case for the data-sharing consortiums currently under development, the development of new data-sharing tools and platforms would provide new knowledge about aggregating, harmonizing, and sharing clinical-grade, next-generation sequencing data obtained during routine medical practice.
5. Functional analysis of "variants of uncertain significance" – To provide reliable guidance to individuals and families about their relative cancer risk, it will be critical to develop a database for collection and characterization of genetic variants in known cancer-causing genes; the purpose of this database will be to categorize each newly identified variant

according to pathogenicity. To achieve rapid characterization of the newly identified variants, it is imperative to support the development of sophisticated, quantitative, high-throughput functional assays. This research would provide information to guide variant interpretation and inform genetic counseling.

6. Translation of PCGA insights into novel biomarkers and improved risk modeling – Leverage biological insights from PCGA to inform development of clinical screening tools that will probe novel blood, tissue, and imaging biomarkers to improve risk modeling and assessment, and to be used as possible intermediate efficacy endpoints.
7. Smaller, faster interventional trials - Conduct several small biomarker-driven intervention trials of lifestyle interventions, targeted agents, immunopreventive agents, or agent combinations prioritized to advance health and reduce cancer risks of several at-risk tissues/organs in these high-risk individuals.
8. Extending success to somatic cancers in the general population - Collect and molecularly characterize sporadic pre-cancers and early cancers to identify subsets of the general population that, despite not having a germline mutation, nevertheless have pre-cancers or cancers that are mechanistically aligned with the molecular aberrations identified in the germline carriers. We expect these individuals to benefit from the findings in the high-risk individuals.
9. Best practices that ensure participation across populations – Throughout all phases of the initiative, prioritize diversity and inclusion in the recruitment and participation of individuals to expand the knowledge base of germline risk and enhance the ability to generalize findings across the full spectrum of the U.S. population. Also, it will be critical to ensure protection against genetic discrimination and to disseminate information to providers and individuals on the available protections.

The first demonstration project will focus on LS. An overview and detailed strategy for detection and ascertainment of individuals at risk for LS as well as a cost estimate are attached (Appendix). A similar pathway analysis-based strategy can be used for detection and ascertainment of individuals at risk for HBOC and has been drafted and attached (Appendix).

Barriers to progress

- At present, the majority of clinical tumor genotyping pipelines across the U.S. only analyze tumor DNA, only rarely is germline DNA systematically analyzed in parallel.
- The optimal time for screening for germline mutations is not known. Scientific models that examine DNA repair deficiencies and immune response over time would provide evidence-based data to inform screening.
- There are insufficient numbers of genetic counselors to meet the needs of germline mutation carriers and their families now; and the demand for this expert counsel would increase with the significant increase in number of individuals requiring genetic counseling. Challenges in interpretation of some genetic test results—particularly variants of uncertain significance—present particular barriers.

- Many individuals reside in remote settings with limited access to genetic counseling services, highlighting the need for expanded capacity for "telegenetics" or other novel approaches to communicate and educate about genetic risk.
- Perception of or misconceptions about genetic discrimination are prevalent in some populations.
- A lack of insurance, or underinsurance, among poor and minority groups, and state variability in Medicaid coverage pose significant challenges to accessing genetic testing and counseling and the downstream preventive services for those determined to be high-risk. Some private insurers fail to cover preventive services that are critical for realizing the full potential of genetic risk assessment in our nation's population. Individuals with low socioeconomic status are likely to have disproportionately limited access, a situation that will further exacerbate cancer health disparities if not addressed in a concerted and comprehensive fashion. Inadequate infrastructure to support and advise those with an inherited susceptibility could inadvertently result in health disparities.
- People who learn that they have Lynch syndrome do not always have colonoscopies.
- Current sociodemographic, socioeconomic, cultural and geographic barriers to evidence-based care will likely affect this demonstration project, especially in its goal of broad participation and thus the potential for benefit across the entire population.
- There are many well-document barriers to prevention strategies that are likely to be faced by this initiative and are as follows (summarized from PMID: 23821092):
  - the success of prevention is invisible
  - prevention requires persistent behavior change, and may be long delayed
  - statistical lives have little emotional effect
  - benefits often do not accrue to the payer
  - avoidable harm is accepted as normal, preventive advice may be inconsistent, and bias against errors of commission may deter action
  - prevention is expected to produce a net financial return, a mark not set for treatment strategies
  - commercial interests as well as personal, religious, or cultural beliefs may conflict with disease prevention
- Certain cancers will be more difficult to prevent: LS is easier to address because colon cancer can be prevented through the removal of pre-cancerous lesions whereas breast cancer cannot be as easily prevented by screening for BRCA 1/2.
- Both cost and precise linkages between screening and mutation may discourage universal screening of a specific population for a specific mutation (e.g., screening all women for BRCA). Those identified as having a germline mutation may experience psychosocial distress, for which adequate support should be available before identification.

What does success look like?

Effective strategies that are ready for implementation will identify those at highest cancer risk due to germline mutations and will facilitate a decrease in cancer incidence and death in this population:

- An expanded knowledge landscape of germline risk and an ability to translate new discoveries about risk reduction across the full spectrum of the U.S. population.
- The availability of germline risk cohorts for voluntary participation in an array of intensive, prevention interventional trials. Cohorts with cancer family history do tend to be more willing to enroll in related research.
- Enhanced scientific understanding of cancer initiation and identification of new targets for the treatment of pre-malignancies, including tumor–host interactions, with development of innovative hypotheses for how to detect and prevent tumor development.
- Availability of an annotated catalogue of genomic variants in cancer associated genes, with associated functional annotation for assessment of pathogenicity.
- Completion of target-driven interventional trials for those at highest cancer risk.
- Availability of improved risk-prediction models and biomarkers and better *in vivo* models of prevention.
- Completion of in-depth biochemical and molecular analyses of variants of uncertain significance to determine disease relevance and translation to clinical utility for tumor genotyping.
- The availability of compelling data supporting the necessary policy changes and/or creation and implementation of new policies to ensure universal coverage of genetic testing/counseling and standard of care preventive services for all individuals, either those determined to be at high risk due to germline mutations or those who are first- and second-degree relatives of carriers, regardless of insurance status.

The proposed Precision Prevention and Early Detection Moonshot Demonstration Project builds on our expanding genetic understanding of the causes of cancer. This risk stratification approach will allow the systematic identification and notification of individuals and families with cancer-predisposing germline mutations. In these high-risk individuals, the recommended demonstration project will enable the deployment of early detection approaches, with the goals of discovering biomarkers for the development of pre-cancerous lesions or tumors, new mechanisms by which cancer develops, and optimal interventions. The Precision Prevention and Early Detection Working Group's recommendation was designed to build on existing cancer research infrastructure and capitalize on the rapid timeline that a high-risk cohort will enable. Knowledge gained could be applied to common non-hereditary cancers in the broader population.

Appendix:
Lynch Syndrome Demonstration Project

Saving Lives through Precision Prevention and Early Detection of Cancer

Context

- More than half of all cancers could be prevented
- Early detection of cancer dramatically improves outcomes, both in terms of survival and survivorship
- We know that some cancers run in families: the predisposition to cancer is inherited
- We now have the opportunity to identify these families and the affected individuals with the goal of reducing or eliminating their risk of developing a lethal cancer. This opportunity is due to the widespread availability of genetic testing and screening programs
- With appropriate attention to implementation, identification of at-risk individuals may empower individuals to make and act upon informed, cancer-preventing health decisions

New science has created exceptional opportunity

- Cancer is known to be a genetic disease (http://www.cancer.gov)
- Genetic changes that increase cancer risk can be inherited and affect predisposition to develop the disease
- Mutations in cancer-associated genes are linked to more than 50 hereditary cancer syndromes (http://www.cancer.gov)
- Each hereditary cancer syndrome is characterized by its own array of genes, in which heritable mutations can confer increased cancer risk
- Determining which genes are altered in a particular tumor helps doctors tailor treatments to individual patients with cancers for which targeted therapies have been developed
- Technological advances in genome science now enable rapid identification of individuals who harbor an inherited risk of cancer by direct DNA sequencing
- The cost of sequencing a full human genome has decreased from $100M in 2001 to a few thousand dollars in 2016 (National Human Genome Research Institute). Now DNA sequencing and related strategies are routinely used in the clinical setting
- Application of behavioral theories and methods of cancer risk perception, cancer communication, and health decision-making are needed to ensure that this Lynch Syndrome Demonstration Project achieves the desired life-saving outcomes

A major unmet medical need: Lives are being lost unnecessarily

- Lynch syndrome (LS) is the most common inherited colorectal and endometrial cancer syndrome (PMCID: PMC3076593)
- LS not only results in early onset and high rates of multiple cancer types, primarily colorectal and endometrial (uterine) cancers, but it also increases predisposition to stomach, ovarian, urinary tract, pancreas, brain, skin, and other malignancies. Women with LS have almost the same risk of endometrial cancer as colon cancer, and the tumors are generally the more aggressive subtypes (PMCID: PMC2815724)
- Up to about 1 million people are estimated to live with Lynch syndrome in the U.S. (PMCID: PMC3076593); the prevalence is even higher in other countries (PMID: 10829038)
- Individuals with LS have a 12–80% lifetime risk of developing colorectal cancer compared to 4.5% in the general population (PMCID: PMC2767441; PMID 21642682)
- It is known that a high proportion of LS carriers (more than 500,000 individuals in the U.S. today) have no knowledge of their high cancer risk and are not receiving appropriate screening and surveillance to maximize chances of early detection and reduction of risk from suffering from and dying of cancer (http://www.egappreviews.org/recommendations/index.htm), the American College of Gastroenterology, and the American Medical Association)
- LS accounts for 10%–15% of all colorectal cancers diagnosed before age 50; and 3–5% of all colorectal cancer cases and 2–3% of all endometrial cancers overall (PMID: 26970132)
- Median age of colon cancer diagnosis in setting of LS is 45 years old—younger than the average age of colon cancer diagnosis in the general population *and* before the age at which colorectal cancer screening is recommended for the general population (PMCID: MC2767441)
- Progression from benign adenoma to malignant carcinoma is estimated to be at least four times faster for patients with LS compared to sporadic cancer patients; occurring in 2–3 years for patients with LS (PMCID: PMC307367)
- The average age of diagnosis of endometrial cancer in LS is in the early 40s, compared to the early 60s for the general population. Management of endometrial cancer risk in individuals with LS would provide opportunities for research into early detection, addressing an important women's health issue
- Emerging data indicate that patients with LS may uniquely benefit from clinically available immunotherapy approaches (i.e., PD-1/PD-L1 directed therapies). Thus, identification of LS among newly diagnosed patients offers a real opportunity to improve treatment outcomes (PMCID: PMC4481136)

The Blue Ribbon Panel's proposal to address this grand challenge

- Initiate screening of ALL new colorectal and endometrial cancers for LS according to American College of Gastroenterology and American Medical Association guidelines (PMCID: PMC2767441; PMCID: PMC3820559; PMCID: PMC4123330). In general, the strategy involves an initial screen for mismatch repair deficiency by

immunohistochemistry for the DNA mismatch repair proteins and MLH1 promoter methylation status or, when indicated, followed by assessment of somatic *BRAF* mutation status in colorectal cancer to distinguish patients with possible LS from those with sporadic forms of mismatch repair–deficient colorectal cancer (PMCID: PMC3793257). Bioinformatics analyses can be leveraged to avoid unnecessary germline screening and limit costs (PMCID: PMC4559104)

- Include all patients, regardless of gender, socio-economic status, and race. LS has similar incidence in both genders and all races (PMCID: PMC4648287)
- Conduct targeted sequencing of genomic DNA for those identified as potential LS carriers to validate the presence of a LS mutation
- Once LS carriers are identified, inform these individuals of opportunitities for testing close blood relatives, and affected relatives will be invited to participate. As part of the engagement of these individuals, educational brochures—guided by best practices in health communication and message-framing science and including benefits of early diagnosis and prevention strategies—will be provided
- Individuals related to known LS mutation carriers will be evaluated for the presence or absence of predisposing mutations. The test will not be a comprehensive whole genome analysis; rather, it will be comprised of a next-generation sequencing custom panel of genes commonly observed to be altered in LS. Use of a next-generation sequencing custom panel approach has the advantage of providing definitive information at a minimal cost. A family history assessment will be included to help relatives establish whether they might benefit from more comprehensive cancer risk assessment
- Enable rapid national deployment by using the nation's established network of NCI-Designated Cancer Centers and NCI-Community Oncology Research Program sites. The National Clinical Trials Network is another potential resource to identify and engage individuals with LS. The implementaiton of this strategy will result in a new national network of individuals and families with LS that will facilitate voluntary enrollment into existing and new interventional trials
- Expand national genetic counseling capabilities and access to genetic counseling services to address geographic and educaton barriers

Immediate benefit for people in the U.S.

- This Demonstration Project is focused on a group of individuals at highest risk for cancer due to LS. Building upon prior experience with *BRCA1 and BRCA2* mutations, it will also provide an implementation model with potential utility for many other at-risk cancer patient populations
- Colorectal cancer is diagnosed in approximately 140,000 men and women, and endometrial cancer in approximately 55,000 women in the U.S. each year (American Cancer Society)
- Approximately 3–5% of individuals diagnosed with colon and 2% of those with endometrial cancers have Lynch syndrome. Thus between 5,300 and 8,100 individuals total will be identified with the disorder and will serve as the index family members for constructing family trees

- From each index family member, an average of three first-degree relatives will be found to be carriers of a predisposing mutation and therefore have LS, expanding the known population at risk to up to 24,000 Americans in year one alone
- Those individuals identified as LS carriers will receive information about appropriate screening guidelines to prevent disease or detect it early
- In previous pilot studies, interventional screening for LS resulted in a 62% reduction in colorectal cancer, more favorable tumor stage at diagnosis, and a 72% reduction in the number of deaths (PMID: 12473880)

Opportunities for new knowledge to IMPROVE prevention and treatment: Fueling future discoveries

- Study of high-risk families provides an opportunity to identify early markers of disease that might be detected in blood, saliva, or urine. The goal would be to develop new ways to detect cancer early through less costly and less invasive approaches
- Some individuals with LS do not develop cancer. Why not? Researchers can use a variety of approaches to define intrinsic protective factors from these individuals. Optimally, this knowledge will be used to develop an intervention useful for the broader population
- In suspected LS subjects, extended gene panel testing has identified high-penetrance mutations in other cancer predisposition genes, many of which were unexpected based on patients' histories (PMCID: PMC4550537). Detailed genomic analyses on these patients will provide a comprehensive understanding of the diversity of genes driving CRC risk and progression
- A large network of LS families could be invited to participate in research studies to define the best implementation and engagement strategies for disease prevention, including lifestyle interventions or chemoprevention
- Individuals with LS who took daily aspirin for at least 2 years had 63% fewer colon cancers than those taking placebo (PMCID: PMC3243929), but taking aspirin can cause serious side effects in some individuals. The use of normal-dose aspirin in patients with LS, may provide a model for low-cost/high-benefit interventions, but biomarkers are needed to identify people who should not take aspirin. The network of individuals with LS would enable rapid clinical investigation of non-surgical chemopreventive strategies for risk reduction.
- There is opportunity to develop new treatments for LS-related tumors and vaccine approaches for prevention of LS-based cancers. Given the DNA mismatch repair deficiencies associated with LS, the tumors may display neo-antigens, and thus may be particularly amenable to immunomodulatory interventions in both the prevention and treatment settings
- Innovative LS therapies may also be relevant to the treatment of sporadic cancers that share similar genetic profiles
- Study of innovative implementation strategies to improve access to, engagement in, and quality of genetic counseling, early detection, screening and follow-up will improve health outcomes for families with LS

- Study of strategies to implement evidence-based screening and lifestyle interventions can improve the degree to which optimal healthcare becomes standard care for families with LS
- The findings will advance basic behavioral science knowledge and understanding of theories and methods of cancer risk perception, cancer communication and health decision-making

This Demonstration Project is uniquely possible in the setting of families with LS

- Colorectal cancer due to LS is diagnosed 24–25 years earlier compared to the general population. Cancer development can occur before 30 years of age. The average age of diagnosis of endometrial cancer in LS is in the early 40s, compared to the early 60s for the general population (PMCID: PMC2767441)
- LS patients have more colonoscopies and hysterectomies, providing opportunities for biospecimen collection from consenting individuals to facilitate molecular evaluation of pre-malignant specimens and to study the pathway of cancer initiation and progression at the molecular level over a shorter timeframe. Strategies should be developed to encourage people who learn that they have LS to have a colonoscopy as not everyone goes through with the screening.
- Partnering with families with a history of LS will allow for faster and more economical clinical testing of new prevention strategies, the efficacy of which can be assessed faster than in the general population
- While using colorectal cancer screening to identify probands is an appropriate place to start, other identification approaches (e.g., testing for LS at the first colon cancer screening) should be considered for the future.

Estimated timeline for measurable impact

<u>12 month deliverables</u>

- Identification of 5,000–8,000 new colorectal and endometrial cancer patients with LS from among all patients with those diagnoses
- Identification of up to an additional 24,000 total new LS carrier individuals who could benefit from existing early detection and risk-reduction strategies and who may consider participating in research
- Banking of blood and germline DNA samples, as well as fixed and fresh-frozen tissue when feasible, for individuals with LS
- Banking of readily available body fluids and premalignant lesions for detailed studies designed to develop new biomarkers for early disease detection
- Assessment and development of a national strategy to expand the workforce required to provide genetic counseling
- Development of strategies to implement and scale-up early detection, screening and lifestyle interventions to reach thousands of families with LS

5 year deliverables

- The creation of a network linking these LS carriers to existing research opportunities through synergy with Data-Sharing and Clinical Trials Working Groups
- Mechanistic discoveries to provide new understanding of LS cancer initiation and progression
- Development of new information on biomarkers of early LS tumors to facilitate non-invasive screening that can be broadly deployed
- Testing of novel prevention strategies in the context of all the newly identified high-risk individuals, and recruitment of previously identified LS carriers to studies investigating screening approaches, cancer progression, biomarkers, and cancer preventative strategies, among others
- Development of novel chemoprevention approaches
- Early detection of germline risk and cancer will improve outcomes in terms of survivorship
- Effective strategies to scale up LS screening and deliver evidence-based care

Concluding Points

- This demonstration project will eventually save thousands of lives each year by appropriate colorectal cancer screening of individuals with LS. Screening has previously been shown to reduce colorectal cancer by 62% and deaths by 72% (PMID: 12473880; PMCID: PMC1283179; PMID: 10784581), and reducing endometrial cancer incidence by 90–100% (PMID: 16421367)
- The identification and functional characterization of genetic variants of uncertain significance coupled to advances in genetic risk education and communication will provide a model for how to best address genetic variants of uncertain significance in other conditions, both in terms of acquisition of new knowledge and also the delivery of genetic findings to patients
- The same genes involved in inherited cancer syndromes are often altered in sporadic cancers; thus discoveries within this LS Demonstration Project that yield deeper mechanistic understanding of tumor initiation and progression, identification and characterization of novel biomarkers for detection of pre-malignant lesions, and development of novel prevention strategies may be applicable to classes of sporadic cancers that share molecular and genetic features with LS
- In addition to providing immediate high impact for patients and their families, the demonstration project develops a network of individuals and families with LS to engage in a myriad of ongoing studies designed to advance prevention and early detection of LS-derived cancers
- This demonstration project is complementary to the 1-million person cohort study that is part of the U.S. Precision Medicine Initiative. From this population-based study an additional 5,300-8,100 individuals with LS could be identified and serve as nuclei to build out family trees and identify additional affected persons

Appendix:
Hereditary Breast/Ovarian Cancer Syndrome Demonstration Project

Strategy for Saving Lives through Precision Prevention and Early Detection of Cancer

Context

- More than half of all cancers could be prevented
- Early detection of cancer dramatically improves outcomes, both in terms of survival and survivorship
- We know that some cancers run in families: the predisposition to cancer is inherited
- We now have the opportunity to identify these families and the affected individuals with the goal of reducing or eliminating their risk of developing a lethal cancer. This opportunity is due to the widespread availability of genetic testing and screening programs
- With appropriate attention to implementation, identification of at-risk individuals may empower individuals to make and act upon informed, cancer-preventing health decisions

New science has created exceptional opportunity

- Cancer is known to be a genetic disease (1).
- Genetic changes that increase cancer risk can be inherited from our parents and affect our predisposition to develop the disease.
- Mutations in cancer-associated genes are linked to more than 50 hereditary cancer syndromes (1).
- Each hereditary cancer syndrome is characterized by its own array of genes, in which heritable mutations can confer increased cancer risk.
- Determining which genes are altered in a particular tumor can help doctors tailor treatments to individual patients with cancers for which targeted therapies have been developed.
- Technological advances in genome science now enable rapid identification of individuals who harbor an inherited risk of cancer by direct DNA sequencing.
- The cost of sequencing a full human genome has decreased from $100M in 2001 to a few thousand dollars in 2016 (2). Now DNA sequencing and related strategies are routinely used in the clinical setting.

A major unmet medical need: Lives are being lost unnecessarily

- Hereditary Breast/Ovarian Cancer syndrome (HBOC) is among the most common inherited cancer syndromes (3). In this document, HBOC includes hereditary predisposition to breast and ovarian cancers beyond the *BRCA1* and *BRCA2* genes.

- HBOC results in early onset and high rates of multiple cancer types, primarily breast and ovarian cancers, but also increases predisposition to pancreatic cancer, an aggressive form of prostate cancer, melanoma, and other malignancies (4).
- Approximately 250,000–450,000 women are estimated to live with HBOC syndrome in the U.S.(5); the prevalence is even higher in other countries (5).
- Individuals with HBOC have a 25–80% (average 52%) lifetime risk of developing breast cancer, and a 40–60% (*BRCA1*) or 15–20% (*BRCA2*) lifetime risk of ovarian cancer (6) compared to 12% and 1.4%, respectively, in the general population.
- It is known that a high proportion of HBOC carriers have no knowledge of their high cancer risk and are not receiving appropriate surveillance and risk reduction to maximize chances of early detection and reduction of risk from suffering and dying of cancer. This includes cancer survivors.
- HBOC accounts for about 5–10% of all breast cancers diagnosed before age 50 (7) and more than 15% of all ovarian cancer cases (8).
- Median age of breast cancer diagnosis in setting of HBOC is about 45 years (6)—younger than the average age at which breast cancer occurs in the general population and before the age at which mammography screening is recommended for the general population. There is no effective screening for ovarian cancer, which can occur in HBOC across the age spectrum after age 30.
- Progression from benign to malignant disease has been shown to be accelerated at least in *BRCA1*-associated breast cancers leading to an increased rate of interval cancers (between breast imaging tests); *BRCA2*-associated cancers are frequently detected by mammogram plus breast MRI (9,10).
- Ovarian cancer remains a particularly challenging cancer that is nearly completely preventable by surgery but cannot yet be detected through surveillance measures. Premenopausal surgical removal of ovaries and fallopian tubes is important to reduce not only the risk of and mortality from ovarian cancer, but also the risk of and mortality from breast cancer in mutation carriers (11). This is the most compelling reason for a program in HBOC, since otherwise women who do not recognize their HBOC risk are dying unnecessarily from these cancers.
- The state of the art currently is that genetic testing has expanded to characterize genetic breast and ovarian risk beyond *BRCA1* and *BRCA2*. In order to make this Demonstration Project similar to the Lynch Syndrome Demonstration Project and to use currently available clinical testing, we will use the term HBOC to encompass a variety of hereditary syndromes that result in inherited predisposition to breast and/or ovarian cancers with moderate to high penetrance; the precise risks of some of these syndromes are still in the process of being defined.

The Blue Ribbon Panel's proposal to address this grand challenge

- Offer men with breast cancer, women with breast cancer diagnosed age <50, and women with ovarian cancer genetic testing to make this proposal parallel to the Lynch Syndrome Demonstration Project. This strategy will perform multigene panel next-generation

sequencing of genomic DNA for those identified as potential HBOC carriers to assess for germline mutations. This strategy will create a justifiable and parallel cohort to complement the Lynch Syndrome Demonstration Project.

- Include all patients, regardless of gender, socio-economic status, and race. HBOC occurs similarly in both genders and all races (12). However, males are less likely to agree to participate in a program for HBOC so the assembled cohort will likely ultimately be comprised of a predominance of women. Men have generally been shown to be less aware of benefit to themselves and motivated to undergo HBOC testing primarily to benefit female relatives (13). Recent data on the risk of more aggressive prostate cancer in male *BRCA2* mutation carriers may increase interest in HBOC testing for men (14)
- Inform identified HBOC carriers of opportunitities available for testing family members, and invite close relatives to participate. As part of the engagement of these individuals, provide educational brochures focused on HBOC, including benefits of early diagnosis and prevention strategies.
- Offer genetic counseling and testing for the presence or absence of predisposing mutations to idenfitied HBOC carrier family members. The test will not be a comprehensive whole genome analysis; rather, it will be comprised of a next-generation sequencing custom panel of genes altered in HBOC. Use of a next-generation panel approach has the advantage of providing definitive information at a minimal cost. A family history assessment will be included to help relatives establish whether they might benefit from more comprehensive cancer risk assessment.
- Enable rapid national deployment by using the nation's established network of NCI-Designated Cancer Centers and NCI-Community Oncology Research Program sites. The National Clinical Trials Network is another potential resource to identify and engage individuals with HBOC. The implementaiton of this strategy will result in a new national network of individuals and families with HBOC that will facilitate voluntary enrollment into existing and new interventional trials
- Expand national genetic counseling capabilities and access to genetic counseling and management of increased cancer risks associated with carrying a cancer-predisposing mutation to address both geographic and payment barriers. There are complexities of communication of risk assessment, risk communication, and management options, particularly since not all genes conferring breast and ovarian cancers are known, and the risks associated with some genes are not yet completely characterized. These complexities can be challenging, and it will be critical to conduct this program with cultural sensitivity to ensure equal access to care.

Immediate benefit for people in the U.S.

- This Demonstration Project is focused on a group of individuals at highest risk for cancer due to HBOC. It also provides an implementation model with potential utility for many other cancer patient populations.

- Invasive breast cancer is diagnosed in approximately 230,000 women (46,000 women under age 50), 2,000 men in the US each year (American Cancer Society), and ovarian cancer is diagnosed in approximately 23,000 women (14,15).
- Approximately 5–10% of female breast cancer patients are diagnosed age <50, and 15% of male breast cancer patients and 17% of ovarian cancer patients have HBOC syndrome underlying their diagnoses (16,17). Thus we predict that about 7,000 individuals will be initially identified with HBOC and will serve as the index family members for constructing family trees.
- From each index family member, on average 3–4 first-degree relatives will also be carriers of the predisposing mutation, and therefore have HBOC, expanding the known population at risk to up to 28,000 Americans in year one alone.
- Those individuals identified as HBOC carriers will receive information about appropriate screening guidelines, appropriate risk reducing behaviors, and active interventions to prevent disease or detect it early.
- In previous analyses, risk-reducing surgeries for HBOC resulted in a 50% reduction in breast cancer mortality and an 80% reduction in ovarian cancer deaths (18).

Opportunities for new knowledge to IMPROVE prevention and treatment: Fueling future discoveries

- Study of high-risk families provides an opportunity to identify early markers of disease that might be detected in blood, saliva, or urine. The goal would be to develop new ways to detect cancer early through less costly and less invasive approaches.
- Some individuals with HBOC do not develop cancer. Why not? Researchers can use a variety of approaches to define intrinsic protective factors from these individuals. Optimally, this knowledge will be used to develop an intervention useful for the broader population.
- A large network of HBOC families could be invited to participate in research studies to define the best strategies for disease prevention, including lifestyle interventions or chemoprevention.
- There is great interest in identifying effective early detection strategies for ovarian cancers in Individuals with HBOC. The network of individuals with HBOC would also enable rapid clinical investigation of non-surgical (chemoprevention) strategies for breast and ovarian cancer risk reduction.
- Immune strategies and other agents targeting the DNA-repair deficiencies that characterize *BRCA*-associated cancers are in development for treatment of HBOC-related cancers. There is also opportunity to extend these new treatments and vaccine approaches for cancer prevention in HBOC carriers, as well as to develop scientific models to examine DNA repair deficiencies and immune response over time to help identify the optimal time for screening for germline mutations.
- Innovative HBOC therapies are also being shown to be relevant to the treatment of some sporadic cancers that share similar genetic profiles.

- Study of innovative implementation strategies to improve access to, engagement in, and quality of genetic counseling, early detection, screening and follow-up will improve health outcomes for families with HBOC.
- Study of strategies to implement evidence-based screening and lifestyle interventions can improve the degree to which optimal healthcare becomes standard care for families with HBOC.
- The findings will advance basic behavioral science knowledge and understanding of theories and methods of cancer risk perception, cancer communication and health decision-making.
- Project design should consider results from relevant work supported by other organizations, such as the Cancer Global Alliance's *BRCA* challenge includes germline variant alleles for breast cancer.

This Demonstration Project is uniquely possible in the setting of high-risk families with HBOC

- Cancer due to HBOC is diagnosed 24–25 years earlier compared to the general population (6). Cancer development can occur before 30 years of age.
- Tumors in individuals with HBOC develop much more quickly compared to the general population, thus providing a unique opportunity to study the full pathway of cancer initiation and progression at the molecular level at a much reduced timeframe.
- Partnering with families with a history of HBOC will allow for faster and more economical clinical testing of new prevention strategies whose efficacy can be assessed faster than in the general population.

Estimated Timeline for Measurable Impact

12 month deliverables

- Identification of 7,000 new breast and ovarian cancer patients with HBOC.
- Identification of up to an additional 28,000 total new HBOC carrier individuals, who could benefit from existing early detection and risk-reduction strategies, and who may consider participating in research.
- Banking of biological samples for individuals with HBOC.
- Assessment and development of a national strategy to expand the workforce required to provide genetic counseling.

5 year deliverables

- The creation of a network linking these HBOC carriers to existing research opportunities through synergy with Data Sharing and Clinical Trials Working Groups.
- Mechanistic discoveries to provide new understanding of HBOC cancer initiation and progression.
- Development of new information on biomarkers of early HBOC tumors to facilitate non-invasive screening that can be broadly deployed.

- Testing of novel prevention strategies in the context of all the newly identified high-risk individuals, and recruitment of previously-identified HBOC carriers to studies regarding screening, cancer progression, biomarkers, and cancer preventative studies, among others.
- Advance development of novel chemoprevention approaches.
- Improved survivorship of patients with HBOC.
- Effective strategies to scale up HBOC screening and deliver evidence-based care.

Concluding Points

- This Demonstration Project will save thousands of lives each year by appropriate cancer screening of individuals with HBOC. Screening has been shown to reduce HBOC (PMID:12586815).
- The same genes involved in inherited cancer syndromes are often altered in sporadic cancers; thus our discoveries with the HBOC Demonstration Project are expected to have broad applicability.
- In addition to providing immediate high impact for patients and their families, the Demonstration Project develops a network of individuals and families with HBOC to engage in myriad ongoing studies designed to advance prevention and early detection of HBOC-associated cancers.
- This Demonstration Project is complementary to the 1 M person cohort study that is part of our nation's Precision Medicine Initiative. From this population-based study we would expect to find an additional 2,500–5,000 individuals with HBOC that could also serve as nuclei to construct family trees and identify additional at-risk individuals

Fusion Oncoproteins in Childhood Cancers
Recommendation of the Blue Ribbon Panel Pediatric Working Group

Recurrent translocations are a hallmark of childhood cancer and are often pathognomonic of specific cancer types (e.g., EWS-FLI1 in Ewing Sarcoma or PAX-FOXO in alveolar rhabdomyosarcoma). These translocations generate fusion oncoproteins that target 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. The goals of this proposal are to enhance our understanding of the molecular and biochemical mechanisms of transformation driven by fusion oncoproteins, to develop faithful models of these pediatric cancers, to identify their key dependencies, and to use this information to develop novel therapeutic approaches that target these mechanisms.

Recommendation:

1) Develop model systems of each cancer to be studied. This should include mouse models (patient-derived xenograft (PDX) and genetically engineered mouse models (GEM), cell line models, and potentially iPS models of each cancer subtype for mechanistic interrogation of fusion protein biology. Fusions proteins to be interrogated include EWS-FLI1, EWS-ERG, PAX-FOXO, SS18-SSX, MLL-fusions, NUP98-NSD1, ETV6-RUNX1, E2A-PBX, FUS-ERG, and others as defined by working groups. Because many fusion oncoproteins have a distinct biology, collaborative efforts should start with a studies of 10 to 15 oncoproteins. Brain tumors (astrocytomas, medulloblastomas) are cancers of particular interest as several fusion oncoproteins are missing. Newly developed models will provide preclinical models for the assessment of candidate therapeutics

2) Perform detailed cell biological, gene expression and chromatin based/epigenomic studies of these models to define how each fusion protein influences gene expression to perturb normal cellular programs to block lineage differentiation and development. Regulation, particularly epigenomic regulation, likely will take a more predominant role in childhood cancer studies over time.

3) Perform detailed proteomic analyses to identify protein complexes bound to fusion oncoproteins. Perform structural studies to define the three dimensional structure of the domains within the fusion proteins and associated protein complex members; a structural understanding will elucidate the low mutational burden seen in pediatric cancers. Leverage this structural data to nominate domains that are potentially targetable by small molecules that either directly interfere with protein function or that can be designed to induce targeted degradation of the fusion oncoprotein.

4) Complement the proteomic studies with high resolution CRISPR “domain scanning” of fusion oncogenes and associated complex members in cell lines/samples that harbor

pediatric cancer translocations (EWS-FLI1, EWS-ERG, PAX-FOXO, SS18-SSX, MLL-fusions, NUP98-NSD1, ETV6-RUNX1, E2A-PBX, FUS-ERG, others) to identify the key functional domains for targeting.

5) Determine the **dependencies** of specific translocation associated tumors through functional genomic screening (CRISPR and shRNA) of cell lines derived from these cancers. This 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.

6) Develop **therapeutic approaches** that target fusion protein stability, function and/or interaction with critical protein complex members. Focus on small molecule approaches to target enzymes identified in fusion protein complexes, to disrupt critical complex interactions or to promote degradation of fusion proteins or associated complex members. Determine if competitive inhibitors, irreversible inhibitors or degradation is the best approach to inhibit fusion protein function. Novel synthetic lethal dependencies identified in functional genomic screens should also identify other novel therapeutic targets that could potentially be targeted either through drug repurposing or de novo small-molecule screens for new inhibitory drugs.

Where are we now?

- Current state
    - Recent studies suggest that most fusion proteins work via deregulation of protein complexes that control gene expression or chromatin state, which provides a path toward mechanistic understanding. However our mechanistic understanding of the protein complexes required to drive cancer associated gene expression remains rudimentary.
    - It is generally recognized that fusion oncoproteins represent critical drivers of many childhood cancers and that they transform developmentally restricted cells of origin. To date, however, there has been no systematic attempt to determine the dependencies generated by these unique oncogene/cell of origin combinations. Recent developments in CRISPR-Cas9 associated screening will allow detailed assessment of genes required for specific fusion oncoprotein-associated tumors and to also define specific functional domains within each protein that are of critical importance.
    - Recent drug development efforts suggest 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 specifically focused 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.

- The recent development of small molecules approaches that can induce targeted degradation of oncoproteins suggests that more detailed understanding of the domain structure of fusion oncoproteins may open novel avenues for therapeutic development.

- Barriers
  - The number of models of fusion oncoprotein-driven pediatric cancers is limited. For some diseases there is a marked paucity of models for studying the basic molecular mechanisms of the disease as well as therapeutic approaches.
  - There is a lack of systematic characterization of genomic and epigenomic characteristics of fusion-driven pediatric cancer models. Co-localization of this data within a single database would be highly valuable but has not been attempted.
  - While CRISPR/Cas9 screening is widely used, 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.
  - 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 expertise. Such groups with overlapping/complimentary interests specific pediatric cancers are rarely found within one lab/institution. Collaboration is critical. Collaboration would be spurred by targeted efforts to develop therapies for specific childhood cancers.

Where do we need to be in 1-5 years?

- Key priorities
  1) Develop a comprehensive collection of genomically characterized cell line, mouse, and iPSC models of fusion-driven pediatric cancers.

  2) Advance our understanding of the mechanisms of action of each of the common fusion oncoproteins in childhood cancers.

  3) 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 CRISPR/Cas9 and shRNA screening.

4) Determine the key protein members of each fusion oncoprotein protein complex and their key functional domains.

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

6) Develop a network of collaborating investigators with expertise in proteomics/structural biology, genomics/epigenomics, chemistry, experimental therapeutics, and disease-specific biology.

- Rationale for investing
    - Despite significant progress made in the treatment of children with cancer, in the U.S. cancer remains the leading cause of death from disease in children, with significant short and long term toxicity of treatment continuing to impact the majority of children with cancer.

    - Fusion oncoproteins are well-defined cancer drivers that are found in *de novo* and relapsed refractory childhood cancers. They are often found in cancers that are otherwise genetically "silent". Therefore they represent highly credentialed targets for potential therapeutic development.

    - Understanding in these pediatric cancers will also inform adult cancers with similar fusion oncoproteins (e.g., TMPRSS2-ERG in prostate cancer)

    - Development of systematic approaches to target these oncoproteins will serve as a paradigm for targeting diseases driven by other "undruggable" proteins.

What will it take to get there?

1) Establish collaborative groups of scientists focused on development of model systems, cell biological studies and epigenomic studies to define mechanisms of action of each of the fusion oncoproteins. The groups could coalesce around specific fusion oncoproteins and/or specific technologies (i.e. epigenomics), starting with 10 to 15 oncoproteins.
2) Establish collaborative efforts, such as centers, for proteomic and biochemical studies. Establish a limited number of centers with expertise in the most sophisticated proteomic approaches to identify protein complexes associated with each fusion oncoproteins, and forge collaboration with groups focused on cell biology/epigenomic studies.

3) Develop collaborative efforts, such as centers of expertise, for structural biological studies to be performed on functional domains in fusion oncoproteins and critical protein complex subunits.

4) Identify groups expert in chemistry and chemical biological approaches to perform small molecule screens, initiate structure-guided small molecule development, and medicinal chemistry to design/refine small molecule probes that can be used for target validation and ultimately initial in vivo pre-clinical studies.

5) Develop collaborative efforts, such as centers of expertise, for assessment of new small molecules *in vitro* and *in vivo* with an early focus on combination therapeutic approaches.

What would success look like?

This proposal would provide insight into childhood cancer development and potentially uncover new therapeutic opportunities. Fusion oncoproteins are well-defined pediatric cancer drivers where focused experimentation could rapidly drive the field forward. The work described here should 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 biological, epigenomic, proteomic and drug development spectrum should lead to the development of novel small molecule probe compounds and potentially drugs. This would galvanize continuing 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.

IMMUNOGENOMICS-IMMUNOTARGETS FOR CHILDHOOD CANCERS

RECOMMENDATION OF THE BLUE RIBBON PANEL PEDIATRIC WORKING GROUP

Recommendation

Define the cell surface landscape of high-risk pediatric cancers and how it differs from normal childhood tissues in order to develop highly specific immunotherapies. Central to the definition of "optimal immunotherapeutic target" is selective uniform expression on tumor cells and a requirement of the molecule for cellular viability. In parallel, enhance our understanding of the fundamental biology responsible for the immunosuppressive microenvironment that exists within pediatric solid tumors. Discovery of pediatric cancer immunotherapeutic targets combined with an improved understanding of the immunosuppressive tumor microenvironment will lead to new, more effective immune based therapeutic regimens for currently incurable pediatric cancers.

Where we are now?

We have witnessed an unparalleled period of discovery of pediatric cancer tumor cell intrinsic oncogenic drivers, with advanced sequencing technologies delivering robust information on pediatric cancer initiation and progression. In parallel, immunotherapeutic approaches to childhood cancer has been clearly credentialed, with sustained complete responses in children with refractory leukemia using an anti-CD19 chimeric antigen receptor engineered T cell approach, and with improvement in survival for children with high-risk neuroblastoma using an anti-GD2 chimeric monoclonal antibody strategy. However, for most patients with high-risk or refractory childhood cancers there is no effective immunotherapeutic option. This reflects both a lack of credentialed immunotherapy targets as well as a poor understanding of the immunosuppressive tumor microenvironment (TME), which contributes to the limited effectiveness of immunotherapies for childhood cancers.

There are several major barriers to fully realizing the potential of immunotherapeutic approaches to childhood cancers. First, childhood cancers typically have relatively low mutation burdens, and thus are much less likely to express neoantigens and/or be susceptible to immune checkpoint blockade therapies. This is also true of the majority of malignancies that afflict adolescents and young adults, 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 in regard to expression relative to normal

developing tissues in children from birth through adolescence. Third, while it is clear that suppressive effects mediated by the tumor microenvironment play a major role in immune evasion both in adult and pediatric cancers, essential core elements of the tumor microenvironment are not well understood, and the degree to which pediatric versus adult solid tumors are similar or distinct in this regard are not yet known.

We have a unique opportunity to identify optimal immunotherapeutic targets for childhood cancer, define the essential elements responsible for tumor cell intrinsic and extrinsic mechanisms of immune evasion, develop novel regimens (e.g., vaccines) to target both the tumor and the immunosuppressive microenvironment, and develop a new generation of basket-design clinical trials that define eligibility by the presence of the newly defined immunotherapeutic target biomarker.

Where do we need to be?

- While a tremendous amount of discovery-based genomic profiling work has been completed, we first need to integrate DNA and RNA sequencing approaches with cellular membrane proteomic profiling to define the proteins that are uniquely and abundantly expressed on pediatric cancers, and show little or no expression in normal childhood tissues. Recent examples in the identification of Var2, MCAM and GPC2 as novel pediatric cancer specific immunotherapeutic targets can serve as exemplars for future efforts.

- Next, there needs to be integrated public-private partnership to develop the right immunotherapeutic tools (drugs) to exploit these targets. Both protein-based (antibody; antibody drug conjugates) and cellular-based (engineered T or NK cells) therapies will be created. Embryonal antigens could serve as potential vaccine targets. A combination of epigenetic agents should be considered.

- Third, murine models that recapitulate the immunosuppressive tumor microenvironment characteristic of embryonal solid tumors need to be developed and we need to create a robust preclinical testing program that leverages immune competent models and the infrastructure to both test new strategies for anti-tumor efficacy, but also toxicity in the right systems.

What will it take to get there?

- Intensified discovery efforts to define the optimal immunotherapeutic targets in childhood cancers via cell surface proteomic profiling (transmembrane and MHC-restricted) of high-risk pediatric cancers, with an emphasis on samples with complete

DNA and RNA sequencing and diagnostic-relapse pairs and or primary-metastatic site pairs. A parallel profiling of normal tissues from birth through adolescence is required. CRISPR screens directed towards candidate immunotherapeutic targets would define cancer-specific vulnerabilities.

- Investment in yeast and phage display technologies to develop the highly specific scFv binders for novel pediatric cancer immunotherapy targets.

- Dedicated efforts to define the cancer cell intrinsic and extrinsic mechanisms of immune evasion during tumorigenesis and therapy.

- Investment in the development of immune competent pediatric cancer models, and a distributed mouse hospital dedicated to novel immunotherapy preclinical testing, including pharmacokinetics and toxicology in appropriate models. Key to this effort will be preclinical testing of combination approaches integrating immunotherapy into standard of care and/or small molecular therapeutic regimens.

- Investment in extant clinical trials networks to allow for rapid testing and dissemination of novel cell-based immunotherapies.

What does success look like?

Credentialing of new immunotherapeutic strategies focused on pediatric cancer specific targets that show broad activity across histotypes in a biomarker-restricted fashion. This would result in improved cure rates for multiple high-risk pediatric cancers where progress has been limited with dose intensive chemoradiotherapy.

New Therapeutic Targets to Overcome Cancer Drug Resistance
(Joint Recommendation from Pediatric Cancers and Tumor Evolution)

What is the recommendation (1-3 sentences)?

Launch multi-disciplinary studies to identify new drug targets elaborated by cancer drug resistant states. Such studies will include approaches to overcome drug resistance in exemplary pediatric and adult tumor types and therapeutic contexts.

Where are we are now (2-3 paragraphs)?

- Summary of the current state of the science/practice

  Most cancer patients die because their tumors exhibit intrinsic resistance or develop acquired resistance to available therapies. However, our knowledge of the spectrum and mechanistic underpinnings of drug-resistant cell states remains incomplete. It has become well-recognized that resistance can be highly multifactorial and heterogeneous, with multiple independent resistance mechanisms operant in the same patient, tumor focus, or even the same tumor cell. Furthermore, some drug resistance programs may be non-cell autonomous and may overlap significantly with programs that drive metastasis and overall tumor survival/maintenance.

- Identify barriers to progress and/or emerging opportunities

  Barriers to progress in understanding cancer cell resistance exist on genetic, molecular, cellular, and physiological levels. Understanding why, when, and how resistance develops is complicated by gaps in understanding regarding, but not limited to, tumor cellular heterogeneity; cell plasticity among potential cancer stem cell/tumor initiating cell populations; rewired and/or reprogrammed signaling pathways; compensatory signaling mechanisms; positive/negative signaling feedback loops; contributions of genetic polymorphisms (SNPs, CNVs); and the contribution of non-cancer cell components within the tumor microenvironment. Moreover, this multifactorial and heterogeneous nature of resistance means that multiple mechanisms can be operant in the same patient and even the same cell. That said, a growing body of evidence suggests that many individual resistance mechanisms may converge onto certain drug-resistant cell states, the understanding of which may provide new opportunities for combination therapies capable of circumventing this challenge.

Where do we need to be (in 1-5 years)?

4. Apply systematic experimental studies in appropriate model systems to define spectra of resistance mechanisms and dependencies linked to drug-resistant states.

New genome editing (e.g. CRISPR) and unbiased small molecule screening to systematically discover their vulnerabilities and make it possible to identify genes and pathways that are essential to tumor cells that harbor specific genetic or molecular alterations. Specifically, it is paramount that there is a focus on pediatric cancers with a low probability of cure (metastatic solid tumors, select CNS tumors, AML, certain high risk subsets of ALL, and all refractory and recurrent cancers). These approaches may be leveraged to discover individual resistance

mechanisms, common resistant cell states onto which they may converge, and genes/pathways that become essential after evolution to drug resistance. The interrogation of translocation-based tumors and identification of ways to expand the view of signal transduction pathways, particularly those involved in metastatic disease, is important. This effort should yield many new insights into tumor pathways and molecular contexts underpinning drug resistance that could be exploited using existing or future therapeutic regimens.

Priority should be given to efforts that approximate the clinical environment linked to drug resistance as closely as possible. Examples include diverse models (e.g., organoids, patient-derived xenografts, co-cultures in physiologic/"hypoxic" conditions, genetically engineered mouse (GEM) models, etc.), and assessment of drug-resistant states in addition to "steady-state" 2-D cell culture. Patient-derived models will be of particular interest but mouse models capable of interrogating aspects of tumor evolution as they relate to drug resistance are also important, particularly as they allow investigators to address these processes in the context of an intact immune system. New technologies that assess drug resistance mechanisms in primary tumor material directly will be a plus. In addition, model systems that assess non-cell autonomous effectors of cancer drug resistance (e.g., derived from the microenvironment or immune cells) would also be of interest.

5. Comprehensive characterization of drug-resistant clinical specimens, including 3-dimensional and 4-dimensional cancer cell atlases linked to drug-resistant states.

Emerging single-cell technologies are making it possible to produce high-resolution characterization of all major cell types (malignant, microenvironment, and immune) in tumor tissues. Both this recommendation and the accompanying recommendation on metastasis could include single-cell and/or multiplexed in situ cellular analysis of biopsies obtained from individual cancer patients throughout the course of disease and treatment, including the advent of drug resistance. Single-cell analysis will ideally be combined with new *in situ* technologies that read out cell/tissue topology to ascertain the cellular adjacencies that may influence particular functional states. Moreover, the atlases generated by this approach should be linked to model systems that allow experimental testing of the hypotheses generated. Such information could bring forth major new insights into tumor biology and heterogeneity, as well as cell states that identify new therapeutic targets and predict treatment response in metastasis and drug resistance.

6. Develop a collection of drug-resistant cancer models designed to fill key gaps and emphasize areas of unmet medical need.

For many cancer types, we still lack appropriate experimental model systems that would allow us to study the salient tumorigenic programs linked to drug resistance and to discover new therapeutic targets. Recent years have witnessed advances that could enable a dramatic expansion in various types of models, including cell culture systems (e.g., organoids and tissue slice cultures where cells are in their unperturbed environment), patient-derived xenografts, genetically engineered mouse models, and the possibility of generating tumor-bearing mice with "humanized" immune systems. Thus, the above recommendations may include new cancer model generation that is most representative of clinical areas of unmet medical need.

Rationale for investing (Why is this priority ripe for accelerating?)—see above
Opportunity brought about by recent development in science, technology, practice: The advent of new tools to perturb cancer cells (e.g., through systematic gain- and loss-of-function studies), to culture such cells ex vivo or in PDX settings, and to conduct serial sampling of tumor cells throughout the course of treatment offer unprecedented opportunities
Does it address an unmet need or important gap in knowledge or practice?
The development of drug resistance underlies cancer recurrence and accounts for significant cancer-associated mortality. Notably, despite significant progress made in the treatment of children with cancer, in the U.S. cancer remains the leading cause of death from disease in children, with intrinsic and acquired resistance being central to mortality. With no current means to predict who will develop resistance, or when resistance will arise, there is a substantive gap in knowledge and a clinically unmet need.
What would be needed for success? *For example*:

- New or expanded resources: support for serial collection of tumor tissue and blood during treatment and upon frank drug resistance; deployment of technologies and analytical capabilities for high-resolution characterization of these tumor cells prior to treatment, during treatment, and upon resistance; implementation of experimental approaches to perturb appropriate models ex vivo, in vitro, or in vivo;
- Barriers/roadblocks eliminated or reduced: support scaling of existing experimental efforts, augment existing infrastructures for biopsies and blood collection; support for data generation efforts; establishment of new computational teams focused on deconvolving the biology linked to resistance
- New or enhanced technologies: scalable functional studies (gain-of-function studies, loss of function studies, genome editing efforts); single-cell analysis, high-content tissue topographic analysis, etc.

Strategy: What will it take to get there?

- Concrete actions to take in the next 1-5 years
  We recommend that the cancer moonshot effort pursue a multi-disciplinary effort that consists of both systematic experimental studies and comprehensive characterization of clinical specimens obtained prior to treatment and upon relapse to exemplary cancer therapeutics in selected tumor contexts (targeted therapy, immunotherapy, and/or chemo-radiotherapy). Collaborative efforts dedicated to the study of childhood cancers, which could include establishment of centers of excellence, in addition to separate studies of adult cancers should include: 1) adult and pediatric dependency screening; 2) pediatric and adult cancer model generation; 3) preclinical therapeutic testing. In addition, there should be a dedicated effort to develop and test circulating free DNA (cfDNA) methods in pediatric and adult cancers. This effort will incorporate technologies such as single-cell sequencing as well as tissue-based characterization, which may allow specific investigations into the roles of microenvironmental cells and specific patterns of heterogeneity in the overall tumor drug-resistant state. In parallel, both systematic and in-depth functional studies of drug resistance will be conducted using appropriate tumor model systems so that correlative features

observed in clinical specimens could be characterized mechanistically (and conversely, resistance mechanisms identified in vitro could be queried using the clinical data).

Similar to the "Metastasis" recommendation, these priorities may also require:

1. Scalable research biopsy and data generation programs. These initiatives will require fresh and/or serial biopsies of metastatic and drug-resistant specimens for deep tumor/microenvironmental characterizations and generation of ex new vivo models. Thus, the cancer moonshot should support collaborative efforts, such as the establishment and maintenance of centers of excellence, to procure these biopsies at scale and link them to state-of-the-art technologies for data generation and analysis (below Liquid biopsy protocols should be paired with tissue biopsy efforts to provide complementary cancer-derived materials (circulating tumor cells/DNA, exosomes, etc.). Materials obtained from these research biopsies should be seamlessly integrated with workflows capable of generating a wide range of data types.

2. Computational analysis capabilities. A critical need exists to develop algorithms that integrate and extract therapeutic meaning from data generated from metastatic biopsies using the latest technologies. Thus, we envision the establishment of collaborative efforts whose mission to design and implement such tools.

3. *Ex vivo* cultivation, perturbation, or target validation activities. Expansion of cancer models in vitro and in vivo would be aided by increased capacity for handling, distributing, and propagating cancer cell line and patient-derived xenograft models. Focused efforts to optimize approaches for generating and maintaining these models, building robust collections, and perhaps hosting research on these models done by individual investigators or moonshot teams should be considered.

What does success look like?

A cancer drug resistance landscape project, applied to representative tumor and therapeutic contexts (e.g., specific targeted therapy, immunotherapy, and chemo-radiotherapy regimens) in adult and pediatric cancers, should produce new information about the biology of drug-resistant states that directly informs the development and clinical testing of novel therapeutic combinations. The initiatives should make it possible to non-invasively detect and molecularly characterize recurrences at the earliest possible time point so that salvage therapy can be initiated at a point of minimal tumor burden, with minimal molecular diversity. By the end of five years, several of these might emerge that could be administered up-front in cancer patients and circumvent prevalent drug-resistant states (or even "push" cells into drug-sensitive states).

Appendix:
Survivorship, Global Disparities, Advocacy

SURVIVORSHIP. Currently, eight of every ten children and adolescents who are diagnosed with cancer will survive ≥ 5 years beyond their diagnosis. Childhood cancer survivors carry a tremendous cumulative burden of long-term morbidity, largely attributable to the therapeutic exposures used to treat the primary cancer. It is currently estimated that by 35 years from initial diagnosis, on average, a survivor will experience an average of three serious/life-threatening conditions. However, the significant inter-individual variability in the personal risk of developing these adverse outcomes suggests the role for individual variation in response to therapeutic exposures.

NCI-, foundation-, and institutionally-funded initiatives continue to provide critical information regarding outcomes among pediatric/adolescent cancer survivors. The Childhood Cancer Survivor Study (CCSS) represents a significant contributor to our understanding of the incidence and risk factors for adverse late-effects of the therapy. However, CCSS is limited by reliance upon self-report for the majority of outcomes and a biorepository that is not comprehensive relative to all members of the cohort or the type/quantity of material collected. The St. Jude Lifetime Cohort (SJLIFE) represents a population characterized by prospective comprehensive clinical assessment and collection of germline samples. However, SJLIFE is a single institution study of a more moderate sample size. The Children's Oncology Group has had a longstanding case-control study (COG-ALTE03N1) that represents a multi-institutional initiative (>100 institutions) with clinically-validated outcomes and biological specimens from childhood cancer survivors with adverse outcomes (cases) and without (controls). Funded by the NCI and foundation grants, the goal of this study is to understand the molecular pathogenesis of treatment-related adverse outcomes. However, The COG study is a prevalent case-control study with the attendant risk of potential survival bias. Intact, all 3 initiatives (CCSS, STLIFE, COG-ALTE03N1) are subject to survival bias – because of enrollment of patients several years after completion of treatment.

1. Enhance and expand efforts to undertake a comprehensive assessment of the pathogenesis of exposure-specific long-term morbidity.
2. Aggressively pursue development, testing, and dissemination of clinically relevant risk prediction models that identify patients at highest risk of treatment-related complications (risk prediction models based on demographic, clinical and molecular predictors of adverse outcomes) and use these risk prediction models to facilitate personalized treatment, and post-treatment screening for early detection, and targeted interventions.
3. Establish centers of excellence for these initiatives.
4. The recommendations for research would be exposure-specific and thus would result in support of research that directly influences long-term cancer morbidity and premature mortality across all cancer diagnoses.

GLOBAL DISPARITIES IN CHILDHOOD CANCER CARE AND CONTROL. Advances in the treatment of childhood cancers have resulted in part from the development of national and international collaborative initiatives that have defined biological determinants and generated risk-adapted therapies that maximize cure while minimizing acute and long-term effects. Currently, greater than 80% of children with cancer treated with modern multidisciplinary treatments in developed countries survive ≥ 5 years; however, of the approximately 160,000 children and adolescents who are diagnosed with cancer every year worldwide, 80% live in low and middle-income countries (LMIC), where access to quality care is limited and chances of cure are low. The disease burden is not fully known due to the lack of population-based cancer registries in low-resource countries; regional and ethnic variations in the incidence of the different childhood cancers suggest unique interactions between genetic and environmental factors that could provide opportunities for etiological research. In sum, childhood cancer burden is shifted towards LMIC; global initiatives directed at pediatric cancer care and control are needed.

1. Develop a comprehensive assessment of the global childhood cancer burden that integrates epidemiology, health-services, and outcomes research. Through this initiative, an estimation of incidence and prevalence of childhood cancer, and a reliable evaluation of outcomes and barriers to access to care will be performed. Proper integration of epidemiological initiatives will also provide relevant cues to etiological research and facilitate collaborative research opportunities.
2. Develop a scaled approach to access to childhood cancer care and control worldwide, and a costing evaluation that includes cost effective analyses as well as modeling and simulation methods. Through this initiative, a detailed tiered system approach that integrates different dimensions in health systems and health services, and patient and family centered quality interventions, will provide innovative cost-effective models to enhance access to care.
3. Develop and support research and educational national regional networks to facilitate the implementation of the recommendations 1 and 2 and the development of capacity-building and research initiatives designed to address the local and regional disease burden worldwide. Through this initiative, sustainable national and regional models that aim to build capacity, facilitate access to care, and enhance quality will be developed. The integration of the research method and the development of solid research infrastructures will further the reach of this initiative and establish links for collaborative research with North American cancer centers.

CHILDHOOD CANCER RESEARCH ADVOCACY The childhood cancer patient advocate community is passionate and their missions range from funding research to providing support for patients and families. Opportunities exist to enhance, improve, and accelerate research initiatives for those willing to tap into that passion and energy and find productive ways to engage with them. A key goal is to leverage the power of the childhood cancer patient advocacy community to enhance childhood cancer research.

The DIPG community provides one vivid example of how effective parent communication has led to research success. Those in the DIPG patient community heard repeatedly that relapse tissue is critical to advancement of research, so they spearheaded an initiative to improve tissue acquisition. Such efforts have a higher likelihood of success when patient advocate groups are part of the research process from the beginning of a project. Genomic-based research provides another fertile opportunity for advocacy organizations to partner. A two-way flow of information will help educate patient and families about the opportunities to participate in studies as well as limitations of this type of research.

Bringing the voice of the patient and families to the table is vital for researchers and for the childhood cancer community. Given the large funding role of childhood cancer groups, strengthening communication channels will yield more transparent conversation about common goals and challenges. Allowing this conversation to happen on a broader in-depth scale may also lead to smarter funding decisions and increased efficiency and effectiveness. Creating collaborative opportunities to enhance research advocates knowledge and understanding of the landscape of childhood cancer research will ensure the patient voice exists in the research process.

1. Train Research Advocates from the patient advocacy community about the clinical research process and build their scientific knowledge of childhood cancer.
2. Incorporate trained patient Research Advocates in the peer review and scientific process when possible
3. Enhance coordination amongst childhood cancer groups with research community to ensure productive funding opportunities

Enhanced Data Sharing Working Group Recommendation: The Cancer Data Ecosystem

What is the recommendation (1-3 sentences)?

Our ability to accelerate progress towards improving cancer outcomes demands that researchers, clinicians, and patients across the country collaborate in sharing their collective data and knowledge about the disease. The Vice President's National Cancer Moonshot Initiative provides an unprecedented opportunity to create a national infrastructure for sharing cancer data. This infrastructure will support the development of a Cancer Data Ecosystem that will enable all participants across the cancer research and care continuum to contribute, access, combine and analyze diverse data that will enable new discoveries and lead to lowering the burden of cancer in our country.

Where are we are now (2-3 paragraphs)?

- **Summary of the current state of the science/practice**

The current dramatic and important revolution in biomedical research, influencing our understanding of cancer and how to treat it, are fueled by large data sets and complex analyses. Under the current cancer research and care paradigm, many powerful sources of data and potential insight are generated but are not being fully leveraged. These data are critical for identifying and utilizing associations between molecular data (e.g., from patient samples or model systems), other patient data, treatment, and response; however there are technical and logistical challenges for researchers to locate, integrate, and translate these stores of data from existing resources and repositories.

Recognizing the need for large datasets, several alliances and collaborative efforts have been initiated by different stakeholders to create an environment for sharing and collaboration such as Platform for Engaging Everyone Responsibly (PEER), Oncology Research Information Exchange Network (ORIEN), Project Genomic Evidence Neoplasia Information Exchange (GENIE), and Learning Intelligence Network for Quality (CancerLinQ). These individual efforts differ in many ways regarding design, construction and access to data; these differences challenge our ability to integrate these data and make these initiatives interoperable and synergistic. Given the diversity of goals of numerous stakeholders who are creating and using large data sets, and in the spirit of the precision medicine maxim that "one size does not fit all," accommodating and building upon the many cancer programs and dataset collaboratives already in place is a crucial goal of the proposed Cancer Data Ecosystem.

In addition, these efforts differ in their data governance approach, with some using an "opt-in" approach and requiring patient consent with patients donating their clinical data, tissue and molecular data (e.g., ORIEN, Project GENIE), The Cancer Genome Atlas [TCGA]); while others use an "opt-out" approach and use de-identified data from patient records (e.g., CancerLinQ). Still others, like Surveillance, Epidemiology, and End Results Program (SEER) and the CDC National Program of Cancer Registries (NPCR), include all cancer patients in a given catchment area. This

highlights the need for a clear data governance and management model to address data quality and access, as addressed in the *policy recommendations* companion document.

- **Identify barriers to progress and/or emerging opportunities**

The establishment of the Cancer Data Ecosystem is an emerging opportunity that would support research across the spectrum from basic research, through patient engagement, to care delivery. The proposed Cancer Data Ecosystem will allow both public and private information resources to be readily discovered and connected through the use of a common information architecture. This need is evident in several of the recommendations from all the other Blue Ribbon Panel (BRP) working groups that require large scale data collection and integration across many sources. These include a variety of projects and repositories, such as national clinical trials, patient registries, a Pre-cancer Genome Atlas, a repository of pediatric-cancer-related data from model organism systems, and a Cancer Immunity Atlas. Without an infrastructure for sharing and integrating these new data, we risk building more data silos and missing important opportunities for new insights that would be available if these data were "born interoperable". Implementing and unifying these new repositories through the underlying data science infrastructure of the Cancer Data Ecosystem will ensure they can be linked with one another and with future information resources that adopt this common platform. By building the proposed technical capabilities and making appropriate changes to key policies and governance models, long-standing challenges such as those listed below are now addressable.

Lack of searchable and interconnected data repositories with associated tools and services The many existing repositories of data are not always easy to find and are typically inconsistent with each other (e.g., use different nomenclatures, coding, data models, and definitions), making it difficult to integrate and analyze multiple datasets. In addition, they are generally not easily accessible via application program interfaces (APIs) and often reside within institutional boundaries. This creates a barrier for new discoveries by preventing integrative analysis of large amounts of data, which often requires co-localization of data and compute. While important advances have been made with regard to computing infrastructure for cancer genomics (e.g., Genomic Data Commons [GDC], NCI Cloud Pilots, Global Alliance for Genomics and Health [GA4GH] APIs etc), on the whole, this has not yet occurred for many important cancer data sources and data types.

Barriers preventing patients and researchers from contributing their data. A variety of sociological, technical, and policy issues make data sharing difficult for both researchers and patients. Most cancer researchers deposit their data in shared repositories when a study has been completed, rather than working in a data sharing environment while the research is ongoing. As a result, when researchers attempt to share data they are faced with multiple databases and multiple formats; often, they do not have the expertise or support structure needed to make their data sharable by ensuring it conforms to specific standards and formats. Data should be born digital and interoperable. Researchers also face conflicting incentives for meaningfully sharing data such as intellectual property/licensing, promotion and tenure incentives. Likewise, patients who want to share their medical records are faced with the

challenge of accessing these records, multiple sources of records, and the lack of appropriate user interfaces or repositories for securely managing and sharing their data. In addition, patients may have concerns related to privacy, potential downstream consequences of sharing their data, and lack of control over how their data is used. In many cases, participants may also feel disconnected from the research process as they do not always receive information in return for sharing data. Initiatives such as PCORNet (the National Patient-Centered Clinical Research Network), FDA's Sentinel Initiative, and Sync for Science have made great strides in accelerating patient-centered research and these efforts should be leveraged and expanded through this BRP recommendation. Policy related issues are discussed in detail in the companion policy document.

Standards and Interoperability: In addition to facilitating the sharing and ease of use of multiple existing data resources, a primary goal for the Cancer Data Ecosystem is to host contributions from different sources across the translational spectrum and provide a common data dictionary and tooling that promotes interoperability. The current lack of agreed upon ontologies, vocabularies, and data models severely impacts interoperability, integration, and analysis across multiple datasets, projects, and repositories. Agreed upon standards representing phenotypic data are particularly lacking. Evidence and provenance of the data must also be systematically recorded for algorithmic use and quality assurance. The ability to index and normalize definitions of data elements from all contributing sources will promote an "awareness of the possible" and encourage collaboration. Finally, there is a lack of tools to facilitate ease of use of adopting existing standards for researchers at the time of data generation as well as incentives for the use of such tools.

Consent and data-use agreements: The models for involving patients in research have not kept pace with the growth in the generation of biomedical data or with the growing desire to be directly involved and contribute to scientific knowledge. Uniform processes to increase and assess participant informed-ness at moment of enrollment are needed, as well as the ability for participants to manage their own data preferences in an ongoing and interactive way. In addition, there must be rules for handling participant data including ability to return data to the participant, as well as more streamlined ways of moving data out to researchers. Electronic, trackable, and machine-readable consents and terms-of-use agreements for data and other services would enable monitoring, computationally enforcing, and updating these agreements - tasks that are currently difficult. Ongoing efforts in these areas, such as those from Sage Bionetworks and Genetic Alliance, should be leveraged and built upon.

Recommendations for incentivizing the adoption of common data schemas and electronic consent are further detailed in the companion policy document.

Where do we need to be (in 1-5 years)?

The goal of this recommendation is to create a scalable and sustainable translational Cancer Data Ecosystem which will enable basic science researchers, clinicians, and patients to contribute, share, combine, and analyze cancer relevant data, in order to accelerate the pace of

discovery and lead to better patient outcomes and understanding of the underlying mechanisms of cancer. The Cancer Data Ecosystem will provide the data science infrastructure - including APIs, data schemas, consent templates, and service registration - necessary to connect repositories, analytical tools, and knowledge bases. Ultimately, knowledge held in the Cancer Data Ecosystem will enable the creation and evolution of new cancer treatment models, help initiate new clinical trials, and improve the overall quality of care for cancer patients.

In addition to technical capacity building, developing this Cancer Data Ecosystem will require changes in policies that currently inhibit data sharing; these policy changes are detailed in the accompanying *policy recommendations* document.

A central tenet of the Cancer Data Ecosystem is to enable patients and healthy individuals to directly contribute their data, or request an institution to do so on their behalf, for scientific research. The public will directly participate and derive immediate value from their interactions and contributions. It will provide patients with useful knowledge, community, and options as they move through their cancer journey, such as understanding the prevalence of their disease and clinical presentation, their anticipated standard of care, and the availability of nearby clinical trials. Ultimately, it is envisioned that the Cancer Data Ecosystem will support the ability of patients and their caregivers to participate in personalized healthcare decisions made jointly with their oncologists.

The Cancer Data Ecosystem will provide the appropriate level 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 cancer survivors.

Cancer Data Ecosystem Infrastructure: The fundamental infrastructure connecting the components of the Cancer Data Ecosystem are a centralized API, data schema, and a common data dictionary necessary for interoperability of the federated repositories, analytical services, and portals of the Ecosystem. The infrastructure will also provide a set of machine-readable consent and terms-of-use templates that will allow participants to quickly and easily understand access requirements and act on recommendations and findings tailored to them. All of the participating services (repositories, analytical services, and portals) of the Cancer Data Ecosystem will be registered in a central index to provide a "Yellow Pages" where participants will be able to find services of interest including machine-readable information about the inputs, outputs, terms-of-use, and credentials required by a service.

Cancer Data Ecosystem Components: The Cancer Data Ecosystem will be comprised of a dynamic collection of interoperable repositories, analytical services, and interactive portals that will allow data to be queried, aggregated, analyzed, and visualized in unique and powerful ways by researchers, patients, and clinicians. The flagship service of the Cancer Data Ecosystem will be a public-facing portal that will enable patients and healthy individuals to contribute their data (clinical, genetic, imaging, etc.) for scientific research. This portal will provide methods to collect and integrate individual-level patient data from their entire life experience, cancer journey, and all interactions with the healthcare system and provide the results of research performed with their data back to them in understandable terms.

In addition to data contributed by patients, the Cancer Data Ecosystem will support data repositories, curated knowledge bases, standard nomenclatures and ontologies, tools and services from diverse research programs and care systems. Participation in the Cancer Data Ecosystem will allow these resources to be integrated with a broader collection of data and tools, maximizing their potential value to cancer treatment and discovery. Newly-developed information resources, including those proposed through the domain-specific BRP working groups, will provide the initial focus for the Cancer Data Ecosystem. Looking forward, the breadth of the Cancer Data Ecosystem is envisioned to include the following categories of existing and future components (see figure below):

Software Tools

- Research Tools and Services: Clinical research tools leveraging the data repositories and knowledge bases will identify outcomes to inform activities such as the design of future prospective trials, clinical trial recruitment feasibility analysis, or provide a retrospective cohort as a comparator arm. Basic research tools will support new discoveries into cancer biology as well as translational research such as the discovery of new drug-biomarker interactions that lead to further preclinical and clinical studies.

- Patient-centered Tools and Services: Patient-centered tools including dynamic consent, access to current information about specific conditions, clinical trials, research opportunities, and integration with the many cancer advocacy and disease-focused communities.

- Clinical Decision Support Tools and Services: Point of care tools leveraging the knowledge base and data repositories will be integrated into clinical workflows and clinical information systems, enabling healthcare providers and patients to engage in shared decision making for treatment prioritization for individual patients. The subsequent treatment decisions will inform the further refinement of the knowledge base and treatment prioritization algorithms, and the patient specific treatment outcomes will be incorporated into the patient-centric data repository.

Curated knowledge Bases and Data Repositories

The above components would serve to connect, extract data from, and enable analysis of the following two components, which consist both of currently existing efforts as well as future efforts:

- Multimodal Patient Data Repositories: These data repositories consist of multi-modal data derived from patient-centric or pre-clinical sources and include data donated by patients, healthcare systems, laboratories, payors, registrars, researchers, and data collaboratives. Patient-centric data sources include linked data generated as part of patient care, patient experiences, or clinical research. Examples of existing data

repositories include the Genomic Data Commons (GDC), the Cancer Imaging Archive (TCIA), SEER, datasets from the Multiple Myeloma Research Foundation (MMFR), and the Million Veterans Program.

- Curated Knowledge Bases: Curated knowledge bases consist of computable assertions regarding the clinical utility of germline, somatic, epigenetic and imaging (including pathology and radiology images) biomarker alterations across the cancer care continuum. They include information derived from the biomedical literature, clinical practice guidelines, and open or completed clinical trials, as well as aggregated assertions from the patient-centric databases. Examples of existing knowledge bases include the Pharmacogenomics Knowledgebase (PharmGKB), Reactome, the Monarch Initiative, and My Cancer Genome.

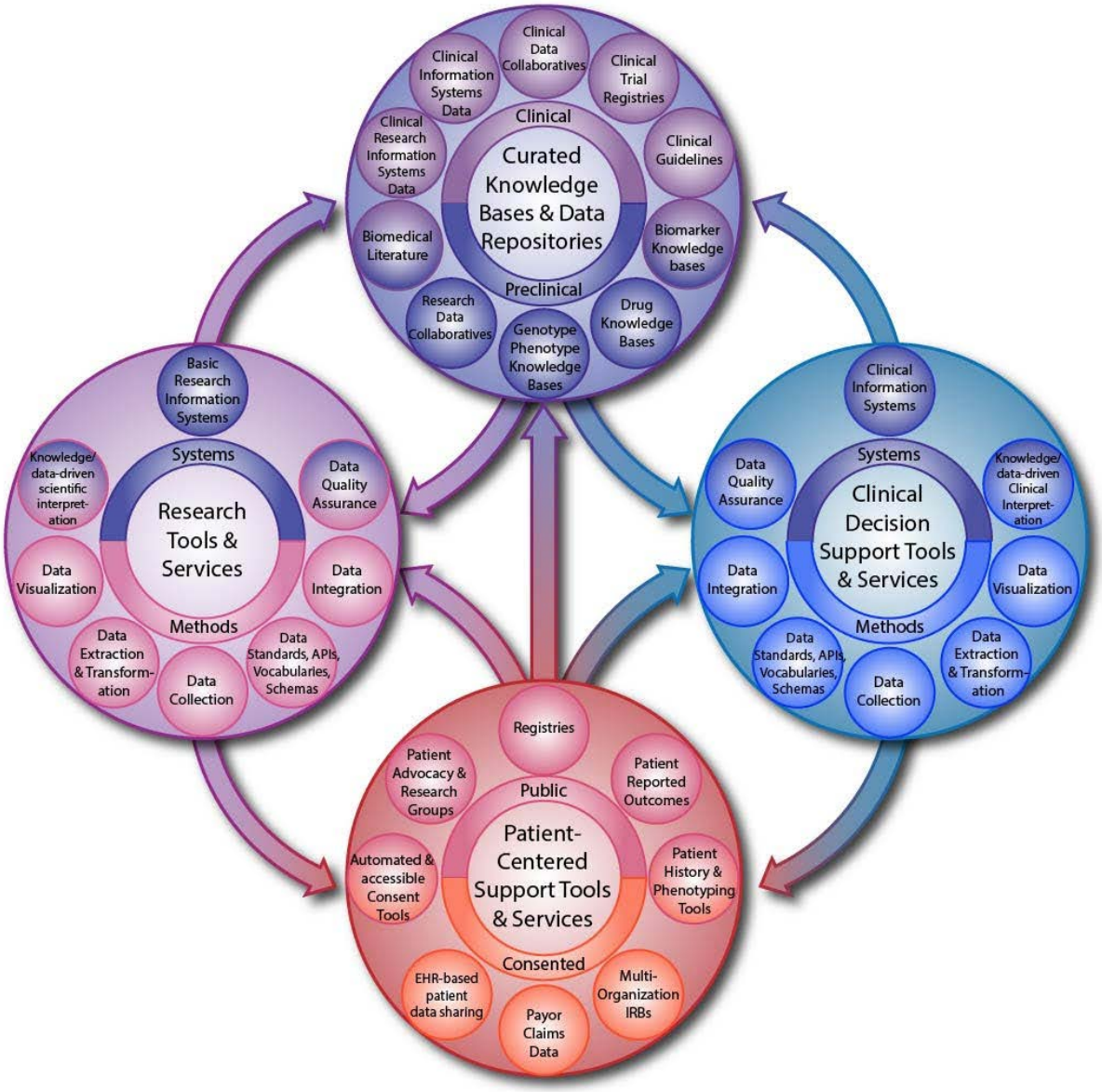

Figure 1: Components of the proposed Cancer Data Ecosystem. Circles represent different types of services in the Cancer Data Ecosystem, including data services, tools and portals. Arrows represent exchange of data, models and analysis results. The provenance, evidence, as well as quality metrics of each of the data elements will be recorded. A centralized registry of all services (ie. "Yellow Pages") will enable discovery of services as well as their inputs, outputs and terms-of-use in a machine-readable form.

- **Rationale for investing (Why is this priority ripe for accelerating?)**

An ecosystem approach is essential to ensuring interoperability, access to, and analysis of information resources that will be launched as part of the larger National Cancer Moonshot Initiative as well as future resources implemented through this platform. Developing the fundamental and enabling data science infrastructure necessary to connect these many resources and to make them findable and accessible will facilitate knowledge management and discovery.

Several BRP working groups have identified the need for new data, new analysis methods, and methods to access and integrate these new data with existing data. Defining and building the essential underlying data science infrastructure, standards, methods, and portals for the Cancer Data Ecosystem will serve as a central unifying structure for these new data and projects, providing tools to enable access, analysis, and interoperability across multiple data types and sources.

- **What would be needed for success?**

Critical to the success of the Cancer Data Ecosystem are changes to governance and policies that impede data sharing and data contributions from the public, research, and clinical care communities. The specific recommendations to address these barriers are outlined in the companion *policy recommendations* document. The technical recommendations are closely intertwined with the policy and governance recommendations and technical progress cannot be accomplished without accompanying changes to policy. In summary, the recommendations detailed in the policy document are to:

- Build easy ways for patients to contribute their data, whether directly or through a third party. This requires the elimination of policy barriers and addition of motivations to share data and consent for the use of the data for research purposes.
- Establish sustainable data governance to ensure long-term health of the ecosystem
- Develop standard electronic, trackable consent frameworks
- Develop standard data access frameworks for researchers and other stakeholders
- Develop standards and tools such that data is born interoperable.

Strategy: What will it take to get there?

The Cancer Data Ecosystem will necessarily develop through a phased approach, starting with core components of the infrastructure, the patient portal, and pilots to test different models for seeding the interconnected components. These projects will establish the foundation necessary for data, services, and definitions to flow through the Cancer Data Ecosystem and enable immediate engagement by the community.

Patient Portal: The flagship service of the Cancer Data Ecosystem will be a public-facing portal that enables patients and healthy individuals to contribute their data (clinical, genetic, imaging, etc.) for scientific research. This portal will provide methods and tools to collect and integrate individual-level patient data from their medical records, personal health data, and patient insights into disease progression, and provide the results of research performed with their data back to them in understandable terms. Network for direction patient engagment, described earlier in this report, envisions patients and providers directly sharing cancer outcome information and would serve as one of the initial pilots of this flagship service alongside other initiatives - such as PEER, Sync for Science and the Medicare Blue Button Initiative - that enable patient-directed contribution of data.

Infrastructure of the Cancer Data Ecosystem: The infrastructure that will allow data to be exchanged among participating services includes:

- The API, data schemas, and a common data dictionary for initial components of the Cancer Data Ecosystem. The API will be developed in collaboration with existing efforts such as GA4GH (for genomic data) and the newly developed NCI API for cancer clinical trials data (https://clinicaltrialsapi.cancer.gov).
- A registry of components that will state in a machine-readable format for each service its inputs, outputs, terms-of-use and credentials.
- A collection of data services that will link disparate information across samples, including clinical data, image data, and molecular data. Whenever possible, the Cancer Data Ecosystem will contain links to biospecimen repositories, patient-contributed samples, and model organisms that can be further analyzed to generate additional data.
- Enhanced cloud-computing platforms to enable tool developers to easily host their tools and provide them as a service in the Cancer Data Ecosystem. In the short term, the components and data should be redundantly hosted in different clouds. In the long term, as data grows, it will be more efficient to to store data on dedicated systems and to use smart caching of key data assets across clouds to allow for robust computational resources and choice in the marketplace.
- (Long term) Benchmarking tools and crediting mechanisms to evaluate the quality of the services, such as the DREAM Challenges.. This should be done jointly with efforts from the National Institute of Standards and Technology (NIST) and the US Food and Drug Administration (FDA).

Components of the Cancer Data Ecosystem: Priorities for the initial components of the Cancer Data Ecosystem will be driven by the needs identified by the BRP domain working groups. In addition, major ongoing efforts (of NCI and others) may also seed the Ecosystem. These ongoing efforts will need to be mapped to common vocabularies and data schema in order to interoperate in the Cancer Data Ecosystem. It is anticipated that the GDC will be a key initial component of the Cancer Data Ecosystem and will serve as the primary repository for genomic datasets.

- Tools for managing patient consents and handling the consenting process: To facilitate institutions' ability to share data in both the research and care settings, a small number of machine-readable, harmonized consent and access templates will be developed to be used by the data repositories. In the long term, the Cancer Data Ecosystem will include tools for managing patient consents and handling the consenting process. The Sage Bionetworks Participant Centered Consent Toolkit is a system in use today that is a model for such a service. The end result would drive towards sharing of outcomes and increasing the quality of care across healthcare providers.
- Center of Excellence for Cancer Data Harmonization: The Center of Excellence for Data Harmonization will have a mandate to provide tools, guidance, and training for harmonization for use of multi-modal research and clinical data. The Center of Excellence will support data curators and data shepherds to help upload and transform the data to common vocabularies and data schema. It will also provide similar utilities, guidance and training for tool developers to ensure that their tools adhere to the standards.

What does success look like?

Building upon the convergence of high throughput technologies, cloud computing and big data analytics, a focused national investment to develop a Cancer Data Ecosystem to dramatically accelerate discovery that will ultimately affect patient care. The creation of the basic infrastructure, the patient portal, and key initial services of the Cancer Data Ecosystem, will enable researchers to create new knowledge by accumulating and integrating much larger and diverse datasets. The patient portal will immediately affect the public and fundamentally change the interaction and engagement of patients and researchers. We anticipate that these initial components will be available and fully functioning within two years of initiating this program. The patient portal will allow all cancer patients to contribute their data to this widely accessible system and by Year 2, thousands of patients will have done so, providing access to dozens of researchers. By providing researchers, both basic and clinical, with the capability of exploring, analyzing and visualizing data across different tumor types and different populations, the cancer data ecosystem will grow, adapt, and evolve, attracting new data sets and new analytical methodologies.

As the participation in the Cancer Data Ecosystem grows, the goal is that by Year 5 the infrastructure and tools needed to integrate and analyze the data representing more than 1,000,000 patients will be supported by the Cancer Data Ecosystem. Utilizing the tools and services made available by the infrastructure of the Cancer Data Ecosystems to integrate and analyze a variety of data types and sources, researchers will be developing new treatments, screening and intervention strategies, decision support tools, and initiating more effective clinical trials.

Overall, an investment in this data science infrastructure will provide a sustainable Ecosystem to meet the growing demand of patients, clinicians and researchers for data access, data integration and analytical tools such as those articulated by the other working groups.

Immunotherapy and Prevention

Mission:

Create and implement a national strategy to discover and evaluate novel immunotherapies that, in the short term, increase the cure rate in cancer patients and eventually provide the opportunity to develop immune-based approaches that prevent cancers of all types. A subset of immune-responsive cancers, such as lung 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. Some of these cancers are high-risk because of genetic susceptibility (e.g., ovarian) and provide synergistic opportunities (e.g., develop biomarkers) with other recommendations of the Blue Ribbon Panel. In addition, a specific focus on a subset of pediatric tumors will be included since pediatric tumors are unique in their origins and biology.

To accelerate advances in immunotherapy for cancer treatment and prevention, we propose to develop a comprehensive program that would include constructing an immune atlas similar to The Cancer Genome Altas (TCGA), cataloging the genetic, epigenetic, and inflammatory pathways for each of several tumor types and their precursor lesions, together with a translational program that provides rigorous testing of novel immunotherapies that overcome fundamental obstacles to successful treatment. Critical to this program is the revealing of antigens that can be recognized by the immune system and the development of vaccines or engineered immune cells to target these antigens. The overriding goals are:

- To activate and redirect our own immune systems to attack and kill all cancers.

- To develop anti-cancer vaccines as potent as current polio, diphtheria, and rubella vaccines that will protect future generations from developing cancer.

Key Concepts:

1. Our immune system has the intrinsic potential to recognize cancer cells as “foreign” and kill them.
2. The key cell that mediates immune surveillance against cancer is called a T lymphocyte or “effector T cell”, which becomes activated to kill the cancer cell by recognizing those components in tumor cells that distinguish them from their normal counterparts. T cells can be stimulated or engineered to recognize unique molecular features of tumor cells.
3. Orchestrating the destruction of cancers that escape normal immune surveillance relies both on the ability to direct T cells to recognize the tumor as foreign and to overcome a disabling, immunosuppressive tumor microenvironment. The extended application of immunotherapy to treat a broad range of cancers will require the identification of novel tumor antigens, the ability to target T cells to recognize these antigens, and strategies to disrupt the immunosuppressive properties in the tumor microenvironment.
4. The interaction between the immune system and cancer reflects a fundamental principle that is applicable to all or nearly all tumor types.

5. The elimination of cancers "before" they develop and become malignant is an aspirational goal. As in cervical cancer, where vaccination against human papilloma virus has virtually eliminated the disease, the development of cancer vaccines to stimulate the T cell to recognize that cancer cells are foreign will **prevent** cancer.

Where we are now (successes and challenges of immunotherapy)?

We know what is possible! I 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. For many such patients, these life-saving drugs were their last hope years ago, and we are delighted to hear them and their families tell their stories today. However, the numbers of patients who benefit from these drugs are too few. Indeed, only 10-20% of these patients respond long-term to current immunotherapies. Furthermore, patients with many other types of cancer, such as ovarian, breast, pancreatic, brain, and prostate cancer in adults, as well as most pediatric cancers, have a brief or non-existent response to currently available immunotherapies. The challenge therefore is to increase efficacy, both in terms of the percentages of patients and the types of cancer that derive a benefit from immunotherapy.

Cancer prognosis is correlated with the presence of effector T cells in tumor sites. Hence, the ultimate goal for all approaches to treating cancer is getting activated effector T cells into the tumor to maximize anti-cancer T cell activity and improve prognosis. Although less data are available, T cells are likely the main effector cells in preventing all forms of cancer, including those that arise from viral infection and those that are due to genetic changes in normal tissue.

The immune system can be educated to prevent cancer. A few vaccines are approved for preventing virally-induced cancers (cervical and liver cancers). A long term goal of this initiative is to develop vaccine approaches that can prevent most forms of cancer that are not caused by viruses. To achieve this goal, we will also need to identify antigens that arise from the earliest genetic changes that initiate cancers, develop novel vaccine approaches that can produce T cells that recognize these antigens, and identify early signals within developing tumors that are barriers to T cell function at precancer sites.

In addition, cells of the immune system, particularly T cells, can be redirected to recognize and kill cancer cells by genetically engineering them to express receptor molecules that sense tumor antigens. These engineered T cells, when transferred back to patients, have been highly successful in treating certain blood cancers. Nonetheless, for most cancers, we know little about what antigens can be safely and effectively targeted to discriminate between cancer and normal tissues. To improve engineered T cell therapies, we will need to identify antigens or antigen combinations that are unique to cancer, develop receptors and circuits that allow targeting of these antigens, and improve our ability to optimize the efficacy and safety of these cellular therapeutics.

Hence, this moonshot program is focused on two key actionable, patient-based strategies that must be rapidly advanced in order to ensure maximal progress against all cancers in all individuals. The first is development of robust cancer immunotherapies, especially vaccines and engineered T cells that target relevant antigens that distinguish cancers and their premalignancies. The second is development of approaches to overcome an obstructive, immune- suppressive tumor environment. In short, we must learn how to both strengthen T cell immunity - either through immunization or engineering -- and concurrently how to disrupt a hostile tumor microenvironment that prevents T cell activation and infiltration into premalignant or cancerous tissue.

Recommendation 1: Cancer Moonshot Clinical Trial Immunotherapy Network

We are in an extraordinary period of opportunity, with the advent of unique technologies, including imaging, genomics, proteomics and ability to manipulate and analyze large datasets that can change the way we conduct and evaluate clinical interventions. The therapeutic potential of the adaptive immune system has not been effectively exploited due to two major barriers, our failure to identify unique cancer cell antigens that can be targeted by T cells, and the presence of an underlying immune-suppressive environment that surrounds the tumor and begins forming as early as the first premalignant change – barriers that only recently have been appreciated as the first immunotherapies have entered the market.

There are two kinds of cancers - those that tend to be sensitive to activated T cells (e.g., melanoma, kidney, bladder, and lung) and those that resist being controlled by activated T cells (e.g., prostate, ovary, breast, pancreas, and brain cancers). We must find answers soon to the following 2 questions by studying patients with these cancers.

1) Why do a minority of patients who have melanoma (e.g., President Jimmy Carter) or lung cancer respond to therapeutics like checkpoint blockade?

2) Why do cancers like prostate, pancreas, and ovarian cancer rarely respond to T cell activation checkpoint blockade or other immunotherapies?

We believe that success will depend on understanding each tumor's unique microenvironment consisting of cancer proteins and immune-suppressive pathways, as well as efficient and effective translation of pre-clinical studies into patients. This will require a nationwide infrastructure to facilitate immunotherapy trials, which may include a limited number of patients, but should be conducted as part of a larger clinical database to allow pooling of data, comparative analyses, and rapid implementation of combination therapies across a whole spectrum of therapies (i.e. immunotherapies, cell-based therapies— as well as small molecules— and more conventional targeted cancer therapies such as oncogene inhibitors and radiation (e.g., impact of heat, cryo-electron microscopy, ultrasound) that may engage and activate immunity as a consequence of immunogenic cell destruction). This will require the assembly of a national database that includes these trial data, as well as details of cancer histology, tumor antigens, markers of immune suppression, patient demographics, and clinical outcomes (i.e. the immune atlas described below). This is best accomplished via a coordinated effort of clinicians and scientists with a keen appreciation of the importance of collaboration.

We propose to **create a robust national clinical trials network** to overcome the barriers to cancer elimination present in many tumors.

Approach:

Create and implement a national strategy to discover and evaluate novel immunotherapies to produce cures both in patients with cancers where immunotherapy has demonstrated success, such as in lung cancer, renal cell cancer, and melanoma patients, and in patients with advanced cancers for which immunotherapy has demonstrated little success thus far, such as prostate, ovarian, pancreatic and brain cancer patients who currently have little hope for long-term survival. To accelerate advances in immunotherapy, we propose the "Cancer Moonshot Clinical Trial Immunotherapy Network" to take advantage of a standardized baseline protocol (including drug treatments, tissue acquisition, and biomarker interrogation) embedded into the broader community (both academic and industry) to test novel immunotherapies efficiently and with a deep understanding of how pathways work and influence each other, as well as additional fundamental obstacles to success. Specific areas that are burgeoning or would benefit from a more concerted effort include senescent cells and molecular signaling methodology.

The Network will focus on:

1. Tumor and premalignant lesion target identification
2. Tumor and premalignant lesion microenvironment to identify immune- suppressive signals (and mechanisms of checkpoint signaling, such as T cell metabolism) that prevent T cell activation and entry into premalignant and malignant lesions
3. Testing of new combinations of checkpoint and immune enhancers informed by these biomarker studies. Developing animal models appropriate for these immune studies.
4. Developing and testing cancer vaccines informed by target identification
5. Developing and testing therapeutic T cells engineered to recognize identified disease target antigens and to overcome immunosuppression

Our central premise is that we have **uncovered only the tip of the iceberg** in immunotherapy treatments, and that human studies using newly developed interdisciplinary, cutting edge, technologies are key to further advancements. Success will be recognized by the development of new combination immunotherapy treatments that increase the success of current immunotherapies today in more patients with many different cancers and lead to vaccines and cell therapies that can be employed for treatment and prevention of cancer, and therapeutic cures.

Recommendation 2: The Cancer Immunity Atlas (TCIA)

Critical to achieving benefit from immunotherapy for all patients with cancer and to developing vaccine approaches that prevent cancer in future generations is the creation of a comprehensive, dynamic and easily searchable database that aggregates multiple datasets to describe the immunological profile of human cancer and its premalignant lesions as well as the genetic and environmental factors that can influence cancer immunity. TCIA data will provide insight into cells that affect immune response but the Atlas will not test hypotheses. These data

should be linked to patient demographics and outcomes. The resulting biology is expected to engage technology and pharmaceutical companies. The data should be gathered from the proposed Clinical Trial Immunotherapy activity as well as from the external cancer research community and freely accessible to all researchers and to the general public.

Scope: The long-term goal should be to include all human cancers and their premalignant lesions (solid, liquid), with a special focus on pediatric cancers, but the project should begin by concentrating on at least two major adult and 2 major pediatric cancers and their associated premalignancies. At least one adult cancer type should be a cancer where immunotherapy has proved efficacious: melanoma, NSCLC, bladder, breast cancer (TNBC), colorectal cancer (MSI^{hi}). At least one adult cancer should be a cancer where responses are poor (CRC- MSI^{lo}, prostate, pancreatic). Including cancer types that have responders to currently employed immunotherapies and cancers that have non-responders to these same immunotherapy drugs will provide many opportunities to compare the differences in tumor micro-environments across cancers of the same and different sites of origin and biology. A set of pediatric cancers should include a responder and non-responder to a therapy as recommended by the Pediatric Oncology Working Group.

- Initial workflow should include the complete annotation of 1000 tumors in each indication using archival specimens. These data will serve as a general resource and training set for subsequent efforts, similar to that of The Cancer Genome Atlas (TCGA). Use of archival samples will accelerate population of the TCIA database.
- The highest priority and greatest value dataset, however, will be to collect and annotate biomarker data using paired samples from patients prior to and following treatment with approved immunotherapies (currently, anti-PD-L1/PD-1; anti-CTLA4 agents).
- Actual choice of indication(s) for the initial training set will be influenced by the availability of sample collections that will permit the planned analyses (see below). This decision can be made after consideration by the steering committee and its advisors.
- A next step would be the analysis of the evolution of cancer from premalignant to metastatic disease focusing on the cancer cell-immune system interactions.
- Similar analyses could be performed using samples from patients prior to and after treatment with adoptively transferred T cell therapies (currently in clinical trials).

Content: Data for each tumor and patient should include all relevant information. The TCIA database should be constructed using an open source, flexible structure that will permit the entry and relational searching of all forms of data ranging from sequence to imaging information. Priority should be given to the following:

- Tumor RNAseq, from bulk tissue and single cell
- Patient exome sequence for SNP identification
- Mutant neo-epitope discovery (in coordination with the Antigen Discovery and Tumor Microenvironment program)
- Cancer-testis, differentiation antigen, overexpressed shared antigens, viral antigen discovery

- TCR usage
- Microbiota (gut, lung, skin)
- Multiplexed IHC/IF analysis of tumor sections
    - T cell infiltrates
    - Myeloid/monocytic cell infiltrates
    - Stromal architecture
    - metabolism
- Radiologic imaging
- Treatment and medical history
- Non-oncology pharmaceutic history
- Geographic residence
- Patient demographics, including age, gender and ethnicity
- Mutational status for common cancer susceptibility genes (e.g. deleterious mutations in BRCA, p53, PALB2, mismatch repair genes, and others)

Technology development: TCIA should promote the development of new technologies and computational methods to support its mission and that would contribute to the emerging database. These can include:

- Radiologic imaging methods
- Nuclear medicine imaging methods: new metabolic probes, immunoPET
- Quantitative imaging of cell distribution and function in biopsy samples
- Cross-referencing to TCGA datasets
- Facile approaches to T cell epitope identification and TCR diversity
- Single cell transcriptome analyses in unprocessed tissue
- Multiplexed in situ hybridization transcriptome analyses
- Multiplexed morphological-immunohistochemical-molecular analyses in fixed tissue

ACCELERATING IMPLEMENTATION OF EVIDENCE-BASED CANCER PREVENTION AND SCREENING STRATEGIES

What is the recommendation?

Conduct implementation research to accelerate the adoption and deployment of sustainable, evidence-based cancer prevention and screening interventions at multiple levels and in different clinical and community settings. Advances in implementation science directed at the full integration of current evidence-based cancer prevention and screening interventions in 3 specific target areas across the country would dramatically accelerate progress in diminishing the cancer burden in the United States by averting an estimated 389,900 new cancer cases and 318,500 cancer deaths annually. Three high priority, high impact areas through which we can build the science of implementation are: HPV vaccination, colorectal cancer (CRC) screening, and tobacco control. This recommendation would significantly impact cancer outcomes in the general population as well as among populations that experience persistent cancer disparities (e.g. low income, minority, rural, and other underserved populations).

This recommendation will serve as a robust platform for accelerating the implementation of additional forthcoming population-level, cancer prevention and control recommendations resulting from other Cancer Moonshot initiatives, which could avert additional cases of cancer and deaths.

Where are we now?

In the US, we do not routinely implement proven cancer prevention and screening interventions on a large scale. Instead, we allow millions of people to develop and die from highly preventable forms of cancer. Furthermore, by not implementing these interventions in ways that reach populations with greatest need, we permit disparities to persist.

Summary of the current state of the science/practice

There now are proven cancer prevention strategies that, if widely used, would reduce cervical cancer mortality by 90%, CRC cancer mortality by 33-70%, and lung cancer by 60-95%, with relatively rapid returns. Yet, these strategies are not scaled sufficiently, leaving millions of Americans at high risk for preventable disease and death. If we can succeed in identifying effective implementation strategies for the three exemplar areas, we can not only make tremendous strides in improving health in these specific areas, but can also apply this knowledge toward implementing the full complement of evidence-based cancer interventions. Below is a current state of the science for each of the three exemplar areas:

- Persistent infection with oncogenic HPV types has a causal role in nearly all cervical cancers and in many vulvar, vaginal, penile, anal, and oropharyngeal cancers, with HPV 16 and 18 contributing the majority of these cancers [1,2]. Over 30,000 HPV-related cancers are diagnosed each year [3] in the US with great costs not only for treating these cancers but for treating pre-invasive disease, genital warts, and other conditions caused by HPV infection [4]. HPV vaccines (2-valent, 4-valent, and now 9-valent) are efficacious in reducing infection with

cancer-causing strains of HPV and reducing pre-invasive cervical lesions [5-8]. Unlike countries with national vaccination programs that report vaccination rates as high as 95% (e.g., Australia, Rwanda, UK), rates of the vaccine series completion are woefully low in the US – 40% among girls and 22% among boys (age 13-17, 2014).

- About 1 in 3 adults between 50 and 75 years old – about 23 million people -- are not up-to-date for CRC screening [9]. Populations with documented low screening rates include Hispanics, American Indians/Alaska Natives, Asians, rural populations, foreign-born, and those with lower education and income [10]. Equally important is the timely follow up for abnormal screening tests, which is lower in safety-net systems serving low-income and under-insured patients than in other settings [11].
    - 40 million US adults currently smoke [12]. Between 50-65% of all smokers will die from a tobacco-related disease, on average 14 years younger than non-smokers [13-14]. Lung cancer is the leading cancer killer in both men and women in the US; in 2015, about 30% of all cancer deaths were from lung cancer—a largely preventable disease [15]. There is very strong evidence on the benefits of comprehensive tobacco control (e.g. the effectiveness of clinical interventions for cessation [16], the impact of coverage for cessation medications on their uptake [17], taxes and public policies limiting tobacco use). Yet, this evidence has not been implemented consistently or adequately across the US. Among cancer patients/survivors, persistent tobacco use is estimated as at least 10% and causes adverse clinical outcomes resulting in a compelling need to improve implementation of evidence-based treatment of tobacco dependence in cancer care settings (US Department of Health and Human Services, 2014).

Barriers to progress and/or emerging opportunities

The major barrier relates to the lack of empirical support for large-scale implementation strategies to optimize use of proven cancer prevention and screening interventions. We selected HPV vaccination, CRC screening, and tobacco control, because these are examples where substantial progress has been made in identifying interventions that work, providing remarkable opportunity for acceleration of the uptake of these modalities in the population. Below are barriers specific to each area. Please note that in some of these, there are barriers related to regulatory and policy issues, which have been listed in a different document.

- Major reasons for low HPV vaccination rates include failure of physicians to recommend the vaccine during routine well-child visits, parental fears about the vaccine and possible side effects, lack of knowledge about the vaccine and its cancer prevention efficacy, cultural and spiritual practices in some populations, and mis-information about the relationship of the vaccine to sexual promiscuity [18,19]. The HPV vaccine should be regarded as cancer prevention – to avoid mis-association with sexual promiscuity. New HEDIS (2017) [19] and current Affordable Care Act provisions would support this strategy.
- Barriers for CRC screening include failure of physicians to recommend it to patients, lack of identification of those needing screening by electronic health records (EHR), and the belief that colonoscopy is the only screening tool. Moreover, discussion about the test itself and the function of the colon reduce discussion of the test by people who need it.

- Using the evidence available right now, there are extraordinary opportunities to dramatically reduce tobacco-related cancer morbidity and mortality. However, a major barrier relates to our limited knowledge about how to best implement and sustain comprehensive tobacco control in a range of situations, including where there is limited state-level policy support, through existing health-related infrastructure (e.g. cancer centers, health insurance products), and where tobacco-related disparities are high.

Key research priorities

Over the next 5 years, we encourage research that advances implementation science to develop and test effective, scalable multi-level (e.g. individual, family/caregiver, provider, system, community) and sustainable interventions in community settings to: 1) increase HPV vaccination initiation and completion rates; 2) increase CRC screening and follow-up of abnormal findings; and 3) reduce tobacco use. This research would directly impact cancer outcomes in the population and among populations that experience persistent cancer disparities (e.g. low income, minority, rural, and other underserved populations), as well as provide an evidence base to apply to the implementation of other cancer interventions. Below are specific research recommendations for each area; each should especially focus on safety-net settings such as health department clinics and federally qualified health centers (FQHCs).

To increase HPV vaccination rates in girls and boys, develop research to: 1) identify, understand, and develop strategies for bundling the recommendation for HPV vaccine with the Tdap and MCV4 vaccines at well-child visits at age 11-12; and 2) test multi-level implementation science approaches to improving rates of catch-up vaccination among girls age 13-26 and boys age 13-21 in all health care and other appropriate venues.

To increase CRC screening and follow-up rates, develop research to: 1) identify, understand, and develop multi-level strategies for increasing CRC screening and follow up of positive test results; and, 2) disseminate effective multilevel interventions in primary care settings.

For tobacco control research, develop a program of research to determine: 1) what factors lead to successful implementation of evidence-based comprehensive tobacco control strategies (CTCS) at the state level and through other systems (e.g. cancer centers), and to reduce the variability in implementation across states; and, 2) what factors can be modified to increase the percentage of low income and other under-served smokers that have access to and use CTCS.

Rationale for investing

Advances in implementation science are needed to accelerate the development and testing of effective, scalable strategies to optimize reach and overcome multi-level/multi-focal barriers to the adoption, implementation and sustainability of evidence-based prevention and screening interventions. The three exemplar areas were specifically selected because they are ripe for acceleration using implementation science, and at the same time can have a profound impact on cancer mortality. Together, they have the potential to save upwards of 318,000 lives annually and to prevent cancer in 389,900 people. Specific justifications for each area are:

- New 9-valent HPV vaccine will cover over 90% of cancer-causing HPV infections. In addition if 2 doses of the vaccine are approved in the US, opportunities to provide full coverage for many children will increase.
- We have CRC screening modalities that work, the capacity to implement these, and effective models for implementation. We also have evidence-based recommendations for follow-up of abnormal CRC screening tests.
- We have tobacco control strategies that work and effective models for implementation.

New or expanded research resources

- Develop new resources (registries, standardized outcomes tools), improve current resources and leverage existing NIH-funded network infrastructures (e.g., Cancer Centers, NCORP, CTSA) to rapidly develop and test implementation strategies for evidence-based interventions and evaluate and improve measures for implementation research and practice.
- Designated resources for development and maintenance of EHR capacity for implementation of evidence-based cancer prevention strategies in health care delivery settings.
- Examine current repositories of evidence-based practices and implementation strategies; and strengthen their potential usability for dissemination and efficient implementation of evidence-based interventions.
- Develop common measurement tools and centralized data capture platforms for key implementation constructs.
- Electronic technologies to establish: 1) state vaccine registries with reporting and surveillance capabilities; and 2) local and national reporting of CRC screening surveillance (as opposed to relying on self-reported data such as BRFSS).
- Training programs for clinicians and scientists in effective implementation research methods, especially those working in underserved communities.

New scientific approaches

- Implementation research should be conducted on how to tailor and deploy evidence-based interventions at multiple levels (e.g. individuals, providers, systems, communities) and in different clinical and community settings.
- Empirical research to understand how to increase: 1) acceptance of the HPV vaccine as a cancer prevention strategy; 2) acceptance of CRC screening modalities (i.e., stool tests, endoscopy) in the public, especially among underserved communities and moving away from primarily or solely marketing colonoscopy for screening; and 3) acceptance of tobacco as the primary preventable cause of cancer that can be overcome through comprehensive efforts across multiple settings, including health care systems, cancer care delivery, schools, workplaces, communities, and in public policies.

Concrete actions to take in the next 1-5 years

We believe that developing a research resource that includes evidence-based implementation strategies and a repository of implementation data focused on implementation in the three focal areas as well as others would be transformative through the accumulation of evidence-based strategies under a single entity. This would also provide a setting for archiving what strategies do not work and/or need to be de-implemented.

We also believe that development of a cohort of rapid implementation studies would significantly accelerate the field. Specific research within this group of studies could be conducted on scale-up, spread, combination of practices, and the context in which key prevention and treatment strategies become widely adopted, or not.

What does success look like?

Success would result in greatly reduced incidence of and mortality from preventable cancers, within 5-10 years. Success would also include research to identify effective implementation strategies that can be used across a wide range of cancer targets and discoveries. Specific metrics of success for each of the three exemplars include:

For HPV vaccination:

- Vaccination rates for girls and boys aged 13 of 80% for 3 shots (or 2 shots if US moves to that schedule). Based on Australia's experience, reduction in high grade cervical lesions will be seen within 5 years [20].
- Reduction of vaccine-type HPV prevalence in girls and boys by 50% within 5 years (from 11%-5%) [21].
- Reduction in 6 types of HPV-related cancers (cervical, vulvar, vaginal, penile, anal, oropharyngeal) until the majority are eliminated. Currently, 6 cancers are known to be caused by HPV – approximately 26,900 annually. It is estimated that with high levels (>80%) of HPV vaccine coverage in girls and boys, up to 26,900 of these cancers could be prevented annually as well as up to 6,100 deaths [22].

For CRC screening:

- Increasing CRC screening rates to 80% by 2018 would prevent an estimated 43,000 new cases and 21,000 deaths annually [23], and eliminating disparities in screening, and stage of disease in 5 years and incidence and mortality by 10 years.

For tobacco control:

- Increased percentage of smokers, and particularly low income smokers and other under-served smokers, with *access* to CTCS; 90% of state Medicaid programs and 90% of health insurers offering access to medications and counseling on all insurance products.
- Increased *use* of CTCS by low income and other under-served smokers; at least 50% of these smokers accessing CTCS annually.
- These recommendations would avert up to 320,000 new cancer cases and 291,400 cancer deaths. The overall impact for all-cause morbidity and mortality would be significantly greater [24].

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Implementation of Integrated and Evidenced-based Symptom Management Throughout the Cancer Trajectory

What is the Recommendation?

Poorly controlled symptoms cause unacceptable suffering for cancer patients and cancer survivors. This promotes the discontinuation of effective treatments and decreases survival. Poorly controlled symptoms also add to health care costs and are the most common reason for cancer patients' use of emergency departments and unplanned hospitalizations. Symptoms profoundly impact the quality of life of patients, survivors and their families and disrupt important societal and family roles. We are at a tipping point, that with new investment and a clear charge, symptoms can be dramatically reduced through the testing and implementation of technology-assisted comprehensive models of supportive care. Improved symptom care would significantly contribute to the efficacy of new and existing treatments by increasing patients' adherence and persistence with treatment through the completion of therapy. The Moonshot Initiative provides the opportunity to boldly address this issue.

Therefore, we recommend a strategic investment through implementation science approaches to accelerate the clinical adoption of technology-aided comprehensive and integrated systems that systematically-gather and monitor patient-reported symptom outcome data (PRO) and provide actionable decision support approaches utilizing evidence-based cancer symptom management guidelines to treat symptoms as they emerge throughout the cancer continuum.

Cancer treatments have successfully extended the survival and even cured an increasing number of people. Currently 5 percent of the population in the United States (approximately 15.5 million people) are cancer survivors, a figure that is anticipated to increase to 20.5 million by January 2024 (*American Cancer Society. Cancer Facts & Figures 2016. Atlanta: American Cancer Society; 2016)*. Annually 650,000 cancer patients are treated with chemotherapy and 470,000 receive radiation alone or in combination with chemotherapy (www.cdc.gov/cancer/providers.htm) (1). However both disease and treatment cause deleterious symptoms and side effects which occur during the course of treatment or can continue or appear long after treatment is completed (2). All patients experience unpleasant side effects, but nearly a third of those receiving chemotherapy or radiation therapy, (> 350,000 patients annually) report three or more co-occurring moderate to severe symptoms during treatment (3), which contributes to lower functional status and quality of life (4), leads to multiple costly visits to the emergency departments (with over half resulting in hospitalization) (5, 6), and can cause treatment delays and discontinuation of therapy (7-10). Treatment delays and lack of persistence with treatment due to symptoms are particularly concerning because they decrease treatment effectiveness and increase the risk for recurrence and death. Even after an initial successful treatment, patients requiring maintenance therapy (hormonal therapy or chemotherapy) experience unpleasant symptoms and often decide to stop taking the medication. Adherence and persistence with treatment is particularly important given the growing number of oral therapies both for initial treatment and maintenance therapy (11-13). Studies show, for example that up to 50% of breast cancer patients receiving hormonal therapy discontinue it before completing the recommended

5-year treatment, even though it is proven to significantly prolong disease free survival. The most common reason given for discontinuance is poorly controlled symptoms related to the treatment (14, 15). When symptoms are poorly controlled, cancer treatment adherence is particularly challenging for the medically underserved and those with low health literacy (16). Poorly controlled symptoms have also been shown to increase the likelihood of patients leaving the workforce and not returning to work, even those who were disease free (17-19). Given all of the evidence of the harmful effects of poorly controlled symptoms, there is a compelling need to improve symptom care so that patients and survivors have optimal quality of life, ensure their adherence to treatment, and improve the therapeutic response and extend survivals possible with current and emerging cancer treatments.

Barriers to Progress:

Lack of a systematic and effective way of ***assessing and addressing*** *disease and treatment related symptoms.* Symptoms and many side-effects are patient-reported experiences that present in varying patterns and intensities mostly when patients are at home after receiving treatment and during the survivorship period. This presents both assessment and management barriers for the cancer care team to remotely monitor symptoms and implement appropriate care. Patients and their family caregivers also find it difficult to know when and how to effectively communicate concerns. There is increasing recognition of the essential need for the implementation of tools to remotely collect patient-reported symptom data, bring poorly controlled symptoms to the attention of the cancer care team, and use the patient-reported outcome (PRO) data to guide symptom control efforts (20). PRO data has yet to be automatically integrated within the electronic health record or included in big data resources thus limiting our ability to utilize patient symptom reports to directly improve patient care or to track and benchmark symptom outcomes (21). We are now at a critical juncture to exploit these advances to reduce symptom burden through the convergence of electronic health records with systems that can collect PRO data electronically.

Poor implementation of evidence-based guidelines for symptom management: National evidence-based guidelines for symptom management and supportive care throughout the care trajectory (from diagnosis throughout cancer survivorship/end-of-life) are widely available and promulgated by a number of cancer organizations including the National Comprehensive Cancer Network (NCCN), the Oncology Nursing Society (ONS), Multinational Association of Supportive Care in Cancer (MASCC) and the American Society of Clinical Oncology (ASCO). Despite the availability of these systematic assessment tools and evidence-based supportive care guidelines, they are not systematically used in practice nor are they provided to clinicians in a readily actionable format and, as a result, cancer patients and survivors do not benefit from evidence-based approaches to reduce their symptom burden. Thus, utilizing what is already known and implementation science approaches, there is an immediate and enormous opportunity, if adequately resourced, to dramatically decrease the burden of poorly controlled symptoms and, as a result, reduce suffering, improve the quality of life of cancer survivors, increase treatment adherence, improve the willingness of patients to participate and persist with clinical trials, and decrease symptom-related avoidable emergency department and unplanned hospitalizations and their associated costs.

Opportunity and Priorities for Accelerated Implementation:

The field of symptom management in cancer is at a tipping point where the gap between current and more effective supportive and palliative care provision could be rapidly closed if we capitalize on recent scientific advances including the valid measurement and reporting of patient-reported outcomes (PROs), current evidence-based symptom treatment guidelines, and the integration and clinical adoption of comprehensive supportive care delivery models that improve cancer symptom care and outcomes. Technology-aided solutions now allow the development of efficient, comprehensive systems to monitor patient-reported symptom experience, coupled with a systematic approach to guideline-based symptom care, provided when and where the patient needs it (22-25). Like precision medicine that treats the signature components of the individual tumor, precision care tailors symptom care to the individual patient's signature symptom pattern as it emerges over time. It also helps overcome current access barriers and patient factors that interfere with effective symptom care such as geographic distance of the patient's residence from the cancer treatment facility. Thus, we recommend that funding from the "Moonshot Initiative" be invested in accelerating the implementation of systematically gathered patient-reported outcomes (PRO) and the adoption of evidence-based cancer symptom management guidelines to decrease the deleterious effects of cancer and its treatment.

Systematic Implementation of Patient-Reported Outcomes: Systematic symptom assessment, not confined to clinic/office visits, is a key component of improving symptom care throughout the cancer trajectory. There are recent advances in the systematic collection of patient-reported symptoms and functional status data through validated patient-reported outcome (PRO) tools such as those available through the NIH-supported PROMIS and PRO-CTCAE initiatives. The accelerated funding of implementation science research on how to deploy these PRO measurement technologies, would rapidly remove the current communication barrier between cancer care providers and their patients/survivors and family caregivers, providing the mechanism to report poorly controlled symptoms whenever and wherever they are present. There is also a need for research on how to integrate these systems into care delivery (including the electronic health record), the most effective ways 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, how to optimize use in diverse patient populations, how to expand their use with patient self-management strategies and e-Health applications, and how to use these systems to effectively address supportive and palliative care access barriers including outreach to underserved, rural, and frontier communities.

Implementation of Symptom Management Guidelines: Despite the availability of assessment tools and national evidence-based supportive care treatment guidelines, they are not systematically used in practice and, in particular, there is often a failure to intensify symptom care when initial symptom treatment is unsuccessful. Thus, there is an immediate and enormous opportunity to dramatically improve the quality of life of cancer patients and survivors if the gap could be closed between what is currently known about assessment and treatment of symptoms and what is currently done in practice. There is a need to accelerate innovative approaches and

systems that make existing evidenced-based supportive and palliative care guidelines actionable. Approaches must be efficient, use technology and assist health care providers to rapidly evaluate symptom data and utilize decision support systems for evidence-based approaches to treat poorly controlled symptoms whenever and wherever patients and survivors need help. Implementation research in this area could provide evidence on ways to more rapidly disseminate care guidelines in general.

Implementing Patient Self-Care and Family Caregiver Support: Although symptom management requires assessment and care by the cancer team, patients and their family caregivers must be knowledgeable and adopt both cognitive and behavioral approaches for self-management. Since cancer treatment is almost exclusively given on an outpatient basis, patients and their caregivers are dealing with symptoms and toxicities at home, on their own. Further research is urgently needed to test innovative ways to remotely engage and support patients and families in self-management behaviors, integrate and test new technologies and develop strategies that engage and support self-management in underserved populations such as low health literacy, non-English speakers, racially and ethnically diverse populations and those living in remote rural and frontier communities.

Identifying optimal cancer care models. There is a need to test and disseminate optimum models for the delivery of coordinated symptom care throughout the cancer trajectory. These models include evolving approaches toward delivery of primary and specialized forms of supportive and palliative care. Effective models would promote the coordination of care within the cancer team and with others involved in the care of the survivor, particularly the primary care provider, leading to improved support for adherence with oral therapies, reinforcement of optimal self-management strategies and timely provision of intensified symptom care for poorly controlled symptoms including assistance for cancer family caregivers. Implementation science approaches are required to determine optimal care models that include technology and bridge gaps in communication, coordination and provision of care and self-management support for patients and their family caregivers. In addition, current reimbursement mechanisms also hamper adoption of innovative symptom care models and systems, particularly care delivery that extends to the home or involves support to family caregivers and updated health policy and value-based reimbursement remedies are needed to ensure widespread uptake.

Technology-aided solutions now allow the development of efficient, comprehensive systems to monitor patient-reported symptom experience, coupled with a systematic approach to guideline-based symptom care, provided when and where the patient needs it. Like precision medicine that treats the signature components of the individual tumor, precision care tailors symptom care to the individual patient's signature symptom pattern as it emerges over time. It also helps overcome current access barriers and patient factors that interfere with effective symptom care such as geographic distance of the patient's residence from the cancer treatment facility.

Strategy: We therefore propose the following key priorities for accelerating research that, with additional investment and strategic focus, would transform symptom care and improve cancer outcomes in a short period of time. These strategies focus on accelerating two concurrent

opportunities: 1) To improve the systematic collection, integration, monitoring and benchmarking of PRO data and 2) To develop and deploy into cancer care settings, technology-aided comprehensive, integrated symptom monitoring and management systems.

- Conduct research that identifies the best approaches by which patient-reported symptom (PRO) data can be systematically and rapidly collected and used to trigger a coordinated actionable response within the cancer care team (and with others involved in the care of the survivor), that results in effective symptom control, improved quality of life, persistence with therapeutic cancer treatments and reduction in avoidable health care utilization.

- Promote the automatic integration of PRO data into the Electronic Health Record (EHR) and into all large cancer-related databases so outcomes can be closely tracked and more comprehensively capture the entire cancer experience so that gaps that require further research can be easily identified and benchmarking can accelerate systematic improvements in symptom outcomes. This would include the development of compatible software to provide seamless transitions between stand-alone PRO data collection packages and dissemination within EHRs and migration into large data sets.

- Through implementation science research, determine the optimal mechanisms (effective and scalable in different cancer care models) and support systems to accelerate the adoption and use of evidence-based guidelines to prevent, control, and manage symptoms related to cancer and its treatment within the cancer team and with others involved in the care of the survivor and provided to the patient and/or family caregiver wherever they reside.

<u>What is needed to achieve this:</u> The first step is to conduct a demonstration project to show the capability of comprehensive prototype systems that combine the various elements of symptom monitoring using PRO data, automated self-management coaching, and guideline-based decision support, to reduce symptoms and alter providers' management strategies for poorly controlled symptoms. Various prototypes models are already under development including several that have been funded by NCI. Once these system capabilities and outcomes are demonstrated, then multilevel interventions will be needed to address the integration and clinical adoption of these systems. This will require a combination of implementation efforts, research, overcoming technical barriers, and policy changes, which will be best accomplished in collaborative efforts across a variety of agencies and organizations. The combination of providing the appropriate technology to practices plus an incentive through a mandate (e.g. Committee on Cancer - CoC) will help with the final level of implementation and dissemination.

Patient Reported Outcome Specific Needs:

- To overcome technical barriers there needs to be a seamless interface for telehealth (phone, web, and handheld or wearable devices) that allow the reporting of patient symptoms with the major EHR systems, with easy to utilize and tailored assessment tools that address the range of symptoms associated with the prescribed treatment and type

of cancer, and populate the EHR systems including providing visualization of data and symptom patterns and indicate meaningful symptom scores requiring clinical attention and measuring effectiveness of interventions, triggering further actionable responses if not achieved. This will require industry-academic partnerships to engage vendors like Epic and Cerner and others.

- Research is needed in how to best visualize PRO information so the cancer care team can make rapid recommendations and management decisions in conjunction with easy-to-use decision support aids that seamlessly display current evidence-based approaches to symptom care.
- For systematic tracking of patient-reported outcomes, a standard set of measures should be adopted so that outcomes can be compared, allowing identification of best practices and symptoms in need of further research. The Centers for Medicare and Medicaid Services, which are involved in an effort to collect PRO data from a large number of health facilities, have identified PRO data elements that are relevant to symptom management.
- Meaningful score thresholds need to be defined for alerts and clinical action. There should be PRO value metrics for oncology endorsed by the National Quality Forum (NQF) and efforts to promote best practices and systematic improvement in patient-reported outcomes as a standard of care in oncology.
- Feasibility studies across diseases and care settings should be established to find best ways to engage patients and clinicians to work PRO reporting and management systems into practice and workflow. This would require participation of community stakeholders to develop and test implementation models in practice. Capability to tailor to specific treatment or disease symptom patterns and differing patient populations such as low literacy, ethnic, cultural or geographic differences will increase meaningful assessment and patient and survivor engagement in their use.
- There should be demonstration projects with the FDA in the use of these data for drug assessment.
- Ultimately the reporting and rapid collection of PROs and use of PRO symptom data to promptly intensify symptom care would be a requirement/standard of care expectation of all major cancer professional, public and advocacy groups (e.g., by the CoC, ASCO QOPI, ONS, ONC, etc.) and would also be integrated into all large cancer databases including SEER. Clinical trials also could collect PRO data and use PRO data to track side effects and determine why certain patients experience toxicities whereas other patients do not.

Evidence-Based Symptom Guideline Specific Needs:

- Discrepancies in supportive care guidelines across groups that promulgate these guidelines should be identified and consensus developed for best practices and efficiencies in rapidly updating as new science is produced.
- A systematic process should be utilized to identify symptoms that currently require evidence-based guidelines development and enact an inter-professional process to rapidly develop new guidelines.
- Evaluation studies are needed that test symptom decision support systems that interface

with the EHR and PRO data and link appropriate guideline recommendations for poorly controlled symptoms so that clinicians can rapidly and efficiently provide further evidenced-based care.

- There is a need to test technology-aided tools and e-Health approaches that provide symptom self-management coaching for patients and family caregiving as symptoms emerge and that assist patients to maintain the highest level of physical functioning and emotional wellbeing throughout the continuum of cancer (22-25). These patient-facing tools should be integrated with the patient reported symptom assessment system and the clinician decision support system so there is a comprehensive and coordinated approach to symptom care.
- Studies are needed to tailor symptom coaching so it is acceptable and engages patients/survivors and family caregivers. This includes tailoring for underserved populations such as low health literacy, non-English speakers, racially and ethnically diverse populations and those living in rural and frontier communities.
- There is a need for research projects that evaluate these comprehensive symptom care systems and identify their impact on symptom burden, quality of life, adherence and persistence with treatment, ability to maintain family and societal roles,, earlier identification of adverse events and late effects and decrease avoidable health care utilization (emergency department and unplanned hospitalizations).
- Implementation science studies are required to find best practices to engage clinicians to adopt and integrate guideline-based decision support symptom management systems into practice and workflow.
- Mechanisms for reimbursement of remote symptom monitoring and symptom care are required and incentives for adoption and maintenance of technology-aided systems will be needed for widespread clinical adoption.

Demonstration Project: A demonstration project to test prototype comprehensive symptom monitoring and management systems is being proposed (see Appendix). The demonstration project is designed to test existing automated, telehealth or e-health systems that track PRO's and symptoms, coaches patients/family caregivers and alerts providers when symptoms are poorly controlled and through decision support, prompts clinicians in the use evidence-based guidelines to respond.

What does success look like?

1) Systems for the routine monitoring and management of patient-reported symptoms are the standard of care for cancer patients in all care settings throughout the cancer continuum (from diagnosis throughout survivorship and at end-of-life) and tailored to differing patient and survivor needs. These systems rapidly link the cancer patient/survivor/family caregiver with knowledgeable and prepared health care providers for poorly controlled symptoms and provide timely self-management resources that effectively and efficiently control adverse symptoms and enable optimal quality of life. These systems are tailored to the needs of diverse communities and populations including those that live at a distance from their cancer treatment facility. There is adequate reimbursement for the deployment and use of these systems.

2) Routinely collected self-reported symptom data is an integral element of all national cancer databases and is actively utilized to a) revise and update evidence-based guidelines, b) track patient-reported outcomes, c) make comparisons, share best practices and encourage the attainment of a high standard for symptom control and supportive care nationally, and d) are systematically mined to identify gaps and new scientific questions that should be addressed through symptom science to improve outcomes.
3) Patients no longer dread the deleterious symptoms of cancer and its treatment, they are able to persist with and benefit from recommended therapy and participate in clinical trials, they are able to maintain optimal well-being and stay engaged in meaningful family and societal roles and there is a marked decrease in cancer care costs related to emergency department visits, urgent care, and unplanned hospital admissions.
4) Symptom Prevention and Management Research will fuel future discoveries including
    a. Research that solves symptom monitoring and management implementation barriers and integration into the mainstream of cancer care including the electronic health records. Scalability and widespread adoption will require collaboration with the commercial sector.
    b. Testing of innovative ways to remotely engage and support patients and families in self-management behaviors that can be integrated within comprehensive symptom management systems.
    c. New science that discovers innovative and improved approaches to accelerate precision care and addresses unanswered symptom science questions including:
        i. Identifying effective approaches and interventions to <u>prevent</u> symptoms.
        ii. Understanding who is at highest risk for particular symptoms and adverse outcomes (i.e. genetic, genomic and biomarkers of symptoms), how to tailor symptom care for these high risk groups, and determine who benefits most/least from specific symptom treatments.
        iii. Understanding mechanisms of effective symptom interventions (genetics, genomics and pathways) and utilize this information to develop additional treatments.
        iv. Understanding how to a<u>ccelerate recovery</u> from symptoms, and determine how to <u>optimize health and maintain wellbeing</u> of patients/survivors and their family caregivers throughout the cancer continuum.
        v. Determine best practices to tailor symptom care for underserved populations such as those with low health literacy, non-English speakers, racially and ethnically diverse populations and those living in remote rural and frontier communities.

Appendix:
Symptom Management Demonstration Project Proposal

Improving Quality of Life through Precision Care to Monitor and Alleviate Symptoms

State of the Science: *A Major Unmet Medical Need and Societal Concern: Diminished quality of life due to poorly controlled symptoms*

- Poorly controlled symptoms cause unacceptable suffering for cancer patients, survivors and their families, lowers the quality of life, interferes with adherence and continuation of lifesaving or life-extending therapies and adds to avoidable health care costs.
- Deleterious symptoms and side effects caused by cancer and its treatments occur in most patients, with nearly a third of patients receiving chemotherapy and/or radiation therapy (> 350,000 new patients per year) reporting 3 or more co-occurring moderate to severe symptoms (2, 3). Many symptoms occur during the course of treatment and for many survivors, they continue or appear as late effects long after treatment is completed.
- Poorly controlled symptoms contribute to [4-19]
    - lower physical functioning, psychological distress and suffering, loss of employment or extended medical leaves, and lower quality of life
    - multiple costly emergency department visits with over half resulting in unplanned hospitalizations
    - treatment delays, lack of adherence and discontinuation of therapy which decreases treatment effectiveness and increases the risk of recurrence and can lead to decreased survival and death.
    - refusal to participate in clinical trials
    - caregiving burden and stress for family caregivers
- Adherence and persistence with treatment is particularly important given the growing number of oral therapies both for initial treatment and as maintenance therapy after successful initial treatment [11-13]. Poorly controlled symptoms are the primary reason for lack of adherence [14-15].
- Intensifying symptom care is particularly difficult because symptoms fluctuate and occur after patients are at home in between scheduled clinic visits or after treatment ends making it difficult to monitor and communicate concerns between the cancer care team and patient/family caregivers.
- There are inadequate reimbursement models for symptom monitoring and symptom management nor are there incentives to adopt technology-assisted symptom monitoring and management systems.
- There is a compelling need to improve symptom care so that patients and survivors have optimal quality of life, ensure their adherence and persistence with treatment, and improve the therapeutic response and extended survivals possible with current and emerging cancer treatments.

New Science Creating an Exceptional Opportunity to Accelerate Research

- Symptom burden could be swiftly and significantly reduced through implementation science approaches to the application of current, evidenced-based advances to monitor and treat symptoms.
- Technology-aided solutions now allow the development of efficient, comprehensive systems to monitor patient-reported symptom experience, coupled with a systematic approach to guideline-based symptom care, provided when and where the patient needs it. Like precision medicine that treats the signature components of the individual tumor, precision care tailors symptom care to the individual patient's signature symptom pattern as it emerges over time. It also helps overcome current access barriers and patient factors that interfere with effective symptom care such as geographic distance of the patient's residence from the cancer treatment facility.
- Recent advances in technology-aided measurement and reporting of patient-reported symptom outcomes (PROs), such as PRO-CTCAE (26), now permits the deployment of automated measurement technologies which would provide the mechanism for patients to report poorly controlled symptoms whenever and wherever they are present.
- National cancer symptom and palliative care evidenced-based guidelines are readily available and regularly updated by a number of professional organizations. However, these guidelines are underutilized and not provided in a decision-support format that can be easily utilized in clinical settings (27, 28). This gap in actionable guidelines that facilitate adoption of current best symptom care practices could be quickly closed and achieve immediate patient benefit by utilizing implementation science approaches to promote adoption and development of decision-support systems for symptom management.
- While symptom management requires assessment and care by the cancer team, patients and their family caregivers must be knowledgeable and adopt both cognitive and behavioral approaches to symptom self-management. There is now an opportunity to capitalize on technology and e-Health approaches and integrate innovative self-management coaching and support for patients and family caregivers into emerging integrated comprehensive symptom care systems.
- Thus, there is an immediate and enormous opportunity to dramatically improve the quality of life and decrease the suffering of cancer patients and survivors by the development and deployment of comprehensive integrated models of coordinated symptom care aided by technology.

Demonstration Project Proposal to Address this Grand Challenge to Eradicate Symptoms

- A demonstration project would test prototypes of automated telehealth or e-health comprehensive and integrated PRO symptom management systems (22-25) that implement remote PRO symptom monitoring, tracking all common and expected symptoms (both physical and psychosocial), coach patients/family caregivers on self-management and alert cancer care providers of poorly controlled symptoms. The cancer care providers would be prompted through decision support aids to use evidence-based

symptom and palliative care guidelines to promptly intensify symptom care and would monitor effectiveness of interventions and alert clinicians when inadequate.

- Implementation of the demonstration project could take a variety of forms.
    - It could be conducted between an NCI designated cancer center and a Minority Underserved NCORP which would allow testing of the system in two different care settings.
    - Systems could be tested broadly across cancers commonly found in community oncology practices or could be narrowed to specific cancers such as non-Hodgkin lymphoma, breast or colorectal cancer in cancer centers where disease-specific specialty care is provided.
    - Systems could be tested that match patient/survivor needs during each phase of the cancer continuum- from diagnosis and treatment, transitioning to post treatment, recurrence free survivorship as well as advanced stage cancer including palliative and hospice care.
    - It could demonstrate the ability to bridge inequities in care through tailored approaches that effectively address patient and family caregiver needs in rural and frontier communities, ethnic and racial minorities, non-English speakers, or those with low health literacy.
- To explore potential scale-up and implementation issues, process and outcomes variables should be collected. Process variables could include patient/survivor and clinician adherence, engagement and satisfaction with the system, workflow issues, variation in provider type and process for responding to symptom alerts, and system level implementation barriers. Outcomes should include symptom severity and symptom reduction overall and by individual symptoms, physical functioning, treatment adherence and persistence, work absenteeism and presentism and health care utilization (emergency department visits and unplanned hospitalizations).

<u>Fueling Future Discoveries:</u> *New Opportunities Stemming from the Knowledge to Achieve Effective Symptom Prevention and Treatment*

- In addition to this demonstration project of system prototypes, future research is needed to address implementation issues and best practices to continually update and integrate these systems into care delivery including the electronic health record and collaborations needed for integration and commercialization.
- Further research will be needed to test innovative, technology-aided ways to remotely engage and support patients and families in self-management behaviors and incorporate these approaches into comprehensive symptom management systems.
- New science that discovers innovative and improved approaches to accelerate precision care and addresses unanswered symptom science questions including:
    - Identifying effective approaches and interventions to <u>prevent</u> symptoms.
    - Understanding who is at highest risk for particular symptoms and adverse outcomes (i.e. genetic, genomic and biomarkers of symptoms), how to

tailor symptom care for these high risk groups, and determine who benefits most/least from specific symptom treatments.

- Understanding mechanisms of effective symptom interventions (genetics, genomics and pathways) and utilize this information to develop additional treatments.
- Understanding how to accelerate recovery from symptoms, and determine how to optimize health and maintain wellbeing of patients/survivors and their family caregivers throughout the cancer continuum.
- Determine best practices to tailor symptom care for underserved populations such as those with low health literacy, non-English speakers, racially and ethnically diverse populations and those living in remote rural and frontier communities.

Summary

For decades, cancer patients and survivors have suffered from poorly controlled symptoms that have lowered their quality of life, interfered with adherence and persistence with lifesaving or life-extending therapies and added to avoidable health care costs. These symptoms do not cease with the completion of treatment and profoundly affect day-to-day functioning and the quality of people's lives. While there has been progress in treating cancer with growing survival and cures, to date there has been limited research dollars and science focused on addressing symptom burden, thus symptom burden has not diminished proportionally with other progress in the field. With an accelerated investment and focus on advancing symptom science, significant and meaningful progress can now be achieved in eliminating symptom burden as an expected companion to cancer and its treatment. An initial demonstration of the capability of scalable comprehensive integrated systems that facilitate ongoing monitoring and management of symptoms and encourage patient engagement and self-management will propel the field rapidly forward and provide gains that will otherwise take decades to achieve given the current pace of research.

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