

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.

Proofs-of-concept based on existing infrastructure

- 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-documented 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 opportunities 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 implementation 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 education 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

12 month deliverables

- 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 opportunities 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 identified 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 implementation 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