**What is the "Provocative Questions" Project?**

The provocative questions project is intended to assemble a list of important but non-obvious questions that will stimulate the National Cancer Institute’s (NCI) research communities to use laboratory, clinical, and population sciences in especially effective and imaginative ways. The questions should not be simple restatements of long-term goals of the National Cancer Program, which are to improve the prevention, detection, diagnosis, and treatment of all forms of cancer. Instead they should:

* Build on specific advances in our understanding of cancer and cancer control;
* Address broad issues in the biology of cancer that have proven difficult to resolve;
* Take into consideration the likelihood of progress in the foreseeable future (e.g. 5 to 10 years); and
* Address ways to overcome obstacles to achieving long-term goals.

<http://provocativequestions.nci.nih.gov/>

**2011 RFA (Request for Applications) Provocative Questions (PQs)**

PQ - 1 How does obesity contribute to cancer risk?

PQ - 2 What environmental factors change the risk of various cancers when people move from one geographic region to another?)

PQ - 3 Are there ways to objectively ascertain exposure to cancer risk using modern measurement technologies?

PQ - 4 Why don't more people alter behaviors known to increase the risk of cancers?

PQ - 5 Given the evidence that some drugs commonly and chronically used for other indications, such as an anti-inflammatory drug, can protect against cancer incidence and mortality, can we determine the mechanism by which any of these drugs work?

PQ - 6 What are the molecular and cellular mechanisms by which patients with certain chronic diseases have increased or decreased risks for developing cancer, and can these connections be exploited to develop novel preventive or therapeutic strategies?

PQ - 7 How does the lifespan of an organism affect the molecular mechanisms of cancer development, and can we use our deepening knowledge of aging to enhance prevention or treatment of cancer?

PQ - 8 Why do certain mutational events promote cancer phenotypes in some tissues and not in others?

PQ - 9 As genomic sequencing methods continue to identify large numbers of novel cancer mutations, how can we identify the mutations in a given tumor that are most critical to the maintenance of its oncogenic phenotype?

PQ - 10 As we improve methods to identify epigenetic changes that occur during tumor development, can we develop approaches to discriminate between "driver" and "passenger" epigenetic events?

PQ - 11 How do changes in RNA processing contribute to tumor development?

PQ - 12 Given the recent discovery of the link between a polyomavirus and Merkel cell cancer, what other cancers are caused by novel infectious agents and what are the mechanisms of tumor induction?

PQ - 13 Can tumors be detected when they are two to three orders of magnitude smaller than those currently detected with in vivo imaging modalities?

PQ - 14 Are there definable properties of a non-malignant lesion that predict the likelihood of progression to invasive or metastatic disease?

PQ - 15 Why do second, independent cancers occur at higher rates in patients who have survived a primary cancer than in a cancer-naïve population?

PQ - 16 How do we determine the clinical significance of finding cells from a primary tumor at another site?

PQ - 17 Since current methods to assess potential cancer treatments are cumbersome, expensive, and often inaccurate, can we develop other methods to rapidly test interventions for cancer treatment or prevention?

PQ - 18 Are there new technologies to inhibit traditionally "undruggable" target molecules, such as transcription factors, that are required for the oncogenic phenotype?

PQ - 19 Why are some disseminated cancers cured by chemotherapy alone?

PQ - 20 Given the recent successes in cancer immunotherapy, can biomarkers or signatures be identified that can serve as predictors or surrogates of therapeutic efficacy?

PQ - 21 Given the appearance of resistance in response to cell killing therapies, can we extend survival by using approaches that keep tumors static?

PQ - 22 Why do many cancer cells die when suddenly deprived of a protein encoded by an oncogene?

PQ - 23 Can we determine why some tumors evolve to aggressive malignancy after years of indolence?

PQ - 24 Given the difficulty of studying metastasis, can we develop new approaches, such as engineered tissue grafts, to investigate the biology of tumor spread?
**RFA Questions**

**PQ - 1**
**How does obesity contribute to cancer risk?**

**Background:** While many studies have documented an increased risk of cancer incidence and mortality in individuals who are obese, the mechanisms that underlie this risk remain poorly understood. What molecular changes induced by obesity actually promote cancer development? Can we describe these changes in ways that will allow a mechanistic link between risk and cancer cell biology? Are the risks reversible as some data suggest (R) and, if so, by what mechanism?

**Feasibility:** Recent studies of the endocrinology of eating disorders, the metabolic correlates of fat accumulation, the pathogenic consequences of obesity (such as diabetes mellitus), and the development of powerful molecular profiling methodologies have created opportunities for understanding the relationship of obesity to carcinogenesis at a mechanistic level. Relevant research could include molecular studies to identify metabolic and signaling pathways associated with obesity. Studies on the genetics of obesity may be helpful in identifying key regulatory pathways that may link to cancer development.

**Implications of success:** A deeper understanding of the mechanisms of the cancer risk posed by obesity could suggest new strategies for countering these risks. Understanding how obesity is mechanistically linked to cancer development would bridge epidemiologic identification of risk factors with the molecular biology of cancer development. This would be a remarkable confluence of two exceptionally important cancer research disciplines and would point the way to many more studies that could make obesity-related cancer pathogenesis much clearer.

([View Detail](http://provocativequestions.nci.nih.gov/rfa/how-does-obesity-contribute-to-cancer-risk/mainquestions_viewdetails))

**PQ - 2**
**What environmental factors change the risk of various cancers when people move from one geographic region to another?**

**Background:** Numerous studies have identified associations between the incidence of various cancers and local living conditions. There are many well-documented examples of cancer incidence changing as populations migrate from one site to another. These migrating populations will often adopt the cancer incidence profiles of their new host locale. In these instances, it is likely that environmental or cultural influences are contributing to the increased incidence of various cancers. Early studies identified this phenomenon and confirmed these relationships, but continued work on the identification of risk factors in migrating populations has languished in recent years. This question seeks to stimulate more sophisticated studies on epidemiological risk identified through studies of migration.

**Feasibility:** The methodologies for these studies are well established; however, with more complicated migration patterns seen in our model global economy, it may be necessary to consider more sophisticated metrics of population remodeling.

**Implications of success:** If new factors that contribute to changes in cancer incidence in migrating populations can be identified, our understanding of environmental carcinogenesis would be significantly enhanced. This information could have important implications for understanding cancer etiology, pathogenesis, and prevention.

([View Detail](http://provocativequestions.nci.nih.gov/rfa/what-environmental-factors-change-the-risk-of-various-cancers-when-people-move-from-one-geographic-region-to-another/mainquestions_viewdetails))

**PQ - 3**
**Are there ways to objectively ascertain exposure to cancer risk using modern measurement technologies?**

**Background:** Many methods that measure risk exposure rely on self-reporting or other survey approaches. Such surveys can be accurate in many cases, and they can be designed to increase their accuracy with good survey strategies. However, it would be valuable to develop more quantitative methods to record short-term or long-term exposures with quantitative readouts. With some methods, the techniques could measure biological readouts that might be directly linked to changes associated with cancer development.

**Feasibility:** This question calls for technological advances that can provide sensitive and accurate methods to measure exposure to agents thought to increase cancer risk. These methods might include devices to detect physical location, physical activity, exposure to carcinogenic agents, or changes in biological readouts that are altered in response to exposure. Detection of various small molecules by improving approaches in mass spectroscopy as well as various other "omic"-style methodologies may be useful in these approaches. New sensors that are tuned to known carcinogens could also be used. The range of measurement goals will include, but not be limited to, detecting exogenous molecules in biological samples, recording imbalances in endogenous metabolites, following changes in epigenetic patterns, or monitoring of time and location compared to potential physical carcinogenic sites through global positioning. In addition, monitors could be tuned to measure immediate short-term exposure or cumulative longer-term exposures.

**Implications of success:** Increasing the use of exposure measurements promises to give more accurate and quantitative values to factors that predict risk. If biological readouts are possible, the links to changes directly associated with cancer development may help speed the links between epidemiology and cancer biology.([View Detail](http://provocativequestions.nci.nih.gov/rfa/are-there-ways-to-objectively-ascertain-exposure-to-cancer-risk-using-modern-measurement-technologies/mainquestions_viewdetails))

**PQ - 4**
**Why don't more people alter behaviors known to increase the risk of cancers?**

**Background:** A wealth of epidemiological research shows that certain modifiable behaviors are linked to increased cancer risk. These include tobacco use, UV exposure, sexual behaviors, obesity, and lack of cancer screening. However, despite this knowledge, many people struggle with, or are unable to modify, these behaviors. By understanding basic mechanisms of executive control, emotion, and motivation, we might be better able to understand why people fail to alter behavioral patterns, and reduce this resistance to change.

**Feasibility:** Studies suggest that the message of behavior risk may not be conveyed by basic communication approaches. The substance of the message may not be understood or the mode of delivery may be ineffective. Further, even with an effective message and mode of delivery, individuals may be unable to act on the message to alter and maintain their behaviors. Recent advances in behavioral and neurological studies can help to understand where in the delivery of the message and in the efforts to change behavior, an individual loses the ability to avoid risky behavior.

**Implications of success:** Reductions in behavior that increase risk would have an enormous impact in the incidence of cancer.

([View Detail](http://provocativequestions.nci.nih.gov/rfa/why-dont-more-people-alter-behaviors-known-to-increase-the-risk-of-cancers-1/mainquestions_viewdetails))

**PQ - 5**
**Given the evidence that some drugs commonly and chronically used for other indications, such as an anti-inflammatory drug, can protect against cancer incidence and mortality, can we determine the mechanism by which any of these drugs work?**

**Background:** Given the evidence that some drugs commonly and chronically used for other indications, such as an anti-inflammatory drug, can protect against cancer incidence and mortality, can we determine the mechanism by which any of these drugs work?

**Feasibility:** Clinical data sets describing the consequences of long-term use of FDA-approved drugs could be mined for the association of drugs with incidence of various cancer types, while ruling out the possibility of a confounding interaction with the disease being treated. For those drugs already identified as being associated with a reduced risk of cancer, the mechanism(s) by which they reduce this risk remain be identified. In the case of aspirin, for example, most speculation on the mechanism of action has centered on changes in its anti-inflammatory activity. Since inflammation associated with cancer development is well studied, it may be possible to establish a causal link to changes in inflammation. Researchers should seek to move beyond correlative studies and establish careful mechanistic studies that link drug action to changes that alter cancer incidence.

**Implications of success:** Elucidating the mechanisms by which these agents work would be a major breakthrough in cancer prevention. This work could also provide molecular pathways that harbor other targets for prevention and encourage the development of second generation drugs that might diminish toxicities associated with current agents while maintaining efficacy. Success in these studies would provide models for the types of responses that mark good chemoprevention trials.

([View Detail](http://provocativequestions.nci.nih.gov/rfa/given-the-evidence-that-some-drugs-commonly-and-chronically-used-for-other-indications-such-as-an-anti-inflammatory-drug-can-protect-against-cancer-incidence-and-mortality-can-we-determine-the-mechanism-by-which-any-of-these-drugs-work/mainquestions_viewdetails))

**PQ - 6**
**What are the molecular and cellular mechanisms by which patients with certain chronic diseases have increased or decreased risks for developing cancer, and can these connections be exploited to develop novel preventive or therapeutic strategies?**

**Background:** People with Alzheimer’s, Parkinson’s and Huntington’s diseases, as well as Fragile X Syndrome patients, have a significantly lower risk of most cancers. An exception is melanoma, for which there is an increased risk for Parkinson’s patients. The reverse correlations also hold true. Cancer survivors have a significantly lower risk of developing many of these neurological diseases. It seems likely that if we understood in molecular terms why patients with these diseases or other chronic diseases have altered risk for cancer development, we might find leads for cancer prevention or treatment.

**Feasibility:** Exploiting this dichotomy may be difficult. Comprehensive databases needed to identify clinical correlations between chronic disease and cancer risk are not commonly annotated for these anti-correlations. However, the technology exists to find these disease/risk relationships. The molecular causes of these diseases or understanding the mechanisms of action for common therapies might be useful places to search for plausible links to cancer development. In some cases, there may be candidate genes or pathways for study. For example, some evidence suggests that suspected anti-cancer targets such as Pin1 are essential for the development of Alzheimer’s disease. Overall, finding the molecular linkage to explain these correlations would be a powerful base for future work.

**Implications of success:** Understanding the biochemical and genetic bases for these striking disease correlations may reveal novel insights into the mechanisms of cancer development as well as insights into the corresponding diseases. These molecular mechanisms would potentially provide new targets for therapies or prevention.

([View Detail](http://provocativequestions.nci.nih.gov/rfa/what-are-the-molecular-and-cellular-mechanisms-by-which-patients-with-certain-chronic-diseases-have-increased-or-decreased-risks-for-developing-cancer-and-can-these-connections-be-exploited-to-develop-novel-preventive-or-therapeutic-strategies/mainquestions_viewdetails))

**PQ - 7**
**How does the lifespan of an organism affect the molecular mechanisms of cancer development, and can we use our deepening knowledge of aging to enhance prevention or treatment of cancer?**

**Background:** The development of most common adult cancers is related to increasing life span and aging; however, the lifespan of animals that get cancer are remarkably different. Mice live only 2 years, dogs perhaps 20, and humans 80. Yet all three suffer cancers that appear to driven by similar mutations in evolutionarily related proteins. Conversely many long-lived animals, such as the sea turtle, appear to have very low rates of cancer incidence. How does the etiology of cancer drive tumor formation in one time frame in some animals and a different one in others? In addition, some types of tumors arise in particular ages. What predisposes some tumors to develop most commonly at these times? A better understanding of these relationships could reveal fundamental regulatory events that control cancer development and progression, offering new means of cancer prevention or early stage detection.

**Feasibility:** Some of the basic biological processes that control aging have been described, and our knowledge of the molecular drivers of aging continues to improve. For example, the clock gene, PER, is an oncogene is some cancers. As processes implicated in aging are studied in conjunction with animal tumor models, we will be able to understand how key characteristics of tumor development are modified. Similarly, the molecular profiles of related tumors that occur at characteristically different life stages may show distinct patterns that could point to some of the variables that control how tumor incidence can be linked to the properties of aging tissues.

**Implications of success:** Understanding which features of aging change the rate of tumor incidence promises to identify potential biological processes that could be targets for prevention and therapy. Deeper knowledge of the molecular links between aging and cancer incidence can also identify new markers for early diagnostic tests and risk assessment.

([View Detail](http://provocativequestions.nci.nih.gov/rfa/how-does-the-lifespan-of-an-organism-affect-the-molecular-mechanisms-of-cancer-development-and-can-we-use-our-deepening-knowledge-of-aging-to-enhance-prevention-or-treatment-of-cancer/mainquestions_viewdetails))

**PQ - 8**
**Why do certain mutational events promote cancer phenotypes in some tissues and not in others?**

**Background:** Cancer-causing mutations arise under different selection pressures during tumor development. It has been recognized for some time that the frequency or timing of various cancer mutations differs widely among tissues, but we have little mechanistic understanding about why this occurs. These observed variations presumably are imparted by such factors as different physiology of the cell of origin, different selective pressures generated from the surrounding microenvironment, or various changes established by earlier mutational events. This question seeks mechanistic explanations for these differences in selective pressures.

**Feasibility:** Modern molecular and cellular biological methods should allow many of these tissue-specific events to be identified and studied. Cell and tissue dependence on protein function is seen in many animal models of tumor development, and in many cases we understand the signaling pathways in sufficient detail to design experiments to tease out the key steps that allow for tissue specificity. Proscribed mutational order presumably is due to changes imposed by earlier events in tumor development. Direct measures within animal models and in human tumors should allow differences to be confirmed and evaluated.

**Implications of success:** Understanding why certain tissues rely so uniquely on one protein promises to help us understand the different roles of cancer mutations. How are these dependencies established? Why are these dependencies paramount in some tissues? Do these dependencies relate to oncogene addiction? Knowing how these dependencies develop also promises to allow us to lock-in these dependencies within tumors and strengthen therapeutic responses.

([View Detail](http://provocativequestions.nci.nih.gov/rfa/why-do-certain-mutational-events-promote-cancer-phenotypes-in-some-tissues-and-not-in-others/mainquestions_viewdetails))

**PQ - 9**
**As genomic sequencing methods continue to identify large numbers of novel cancer mutations, how can we identify the mutations in a given tumor that are most critical to the maintenance of its oncogenic phenotype?**

**Background:** DNA sequencing of cancer genomes has shown that individual tumors often contain many mutations that change protein coding regions, frequently as many as 30 to 150 changes in a single tumor. Many of the individually mutated genes are found in multiple tumors or are found in genes that have been implicated previously as cancer genes. These frequent mutations, often called “driver mutations”, are believed to be important for tumor development. However, sequencing studies have also detected many mutations that are found only rarely. It is not clear if or how these low frequency mutations might contribute to tumor development. This question asks how we can determine which mutations have key roles in tumor development?

**Feasibility:** The recent identification of mutations through genomic sequencing provides a gene list and mutations for study. The challenge of this Provocative Question is to establish methods that will determine which changes are important for tumor development and use these methods to study the roles of these mutations. The task is complicated because of the large number of mutations and because it is not clear when in tumor development the mutation appeared and consequently what selective pressure this mutation may have overcome.

**Implications of success:** Finding out which mutations are important for tumor development will provide an important set of proteins for drug discovery, shed light on the various selective pressures experienced in tumor development, and help us predict what mutations found in ongoing sequencing projects are likely to be important in tumorigenesis.

([View Detail](http://provocativequestions.nci.nih.gov/rfa/as-genomic-sequencing-methods-continue-to-identify-large-numbers-of-novel-cancer-mutations-how-can-we-identify-the-mutations-in-a-given-tumor-that-are-most-critical-to-the-maintenance-of-its-oncogenic-phenotype/mainquestions_viewdetails))

**PQ - 10**
**As we improve methods to identify epigenetic changes that occur during tumor development, can we develop approaches to discriminate between "driver" and "passenger" epigenetic events?**

**Background:** The continuing improvement in high-throughput analysis of epigenetic regulation is advancing our understanding of the complex nature of tumor development. Several observations argue that epigenetic regulation is key to many stages of tumor development. First, proteins that are important for epigenetic regulation are frequently mutated during tumor development, and these mutations are important for the cancer phenotype. These mutations include point mutations, translocation, amplifications, and loss of miRNA regulation. Second, some chemotherapeutic agents that target DNA methyltransferases or histone deacetylases have shown good efficacy in the clinic, suggesting the changes in these epigenetic regulatory events are key to maintaining the tumorigenetic phenotype. Third, the plasticity of tumor cells changing from one phenotypic state to another---for example during epithelial to mesenchymal transition (EMT) or following division of cancer stem or initiating cells---is under epigenetic regulation. Finally, there is growing evidence that at least some forms of drug resistance are due to changes regulated by the epigenetic state. As we are achieving higher resolution of epigenetic events, it will be increasingly important to learn which epigenetic changes are critical for tumor survival. This question sets the challenge to learn which epigenetic events are most important for tumor development and maintenance.

**Feasibility:** Modern molecular biological methods, including molecular profiling, high throughput ChIP analysis, and functional tests, will be needed to identify and study various epigenetic states. Computational methods to characterize various epigenetic regulatory states could be used to help define potentially important changes. Functional tests, including RNAi knockdown or overexpression of key proteins, may be helpful in changing chromatin structure and linking these changes to cancer phenotypes.

**Implications of success:** As a field, we anticipate that epigenetic regulation of chromatin states will play important roles in tumor development. These links seem most clear in cases in which mutations that directly alter the epigenetic state have been shown to be important for tumor development. However, many phenotypes of a cancer cell are certainly regulated by epigenetic changes not deregulated by mutation, and the demonstration of this link promises to open the way for the identification of new therapeutic or prevention targets. Similarly, advances in this area will likely provide important advances in the identification of new diagnostic markers.

([View Detail](http://provocativequestions.nci.nih.gov/rfa/as-we-improve-methods-to-identify-epigenetic-changes-that-occur-during-tumor-development-can-we-develop-approaches-to-discriminate-between-driver-and-passenger-epigenetic-events/mainquestions_viewdetails))

**PQ - 11**
**How do changes in RNA processing contribute to tumor development?**

**Background:** Recent exome and genome sequencing has described the appearance of a large number of unexpected tumor-specific alternative splicing and other changes in RNA processing events. Presumably some of the selected splicing events are beneficial for tumor development, but the functional significance of these events remains poorly understood. Other changes in RNA processing may alter protein levels or lead to changes in regulatory RNA molecules.

**Feasibility:** The discovery of these new alternative-splicing and other RNA processing events opens the way to study the roles of new protein products. These studies can proceed along standard lines of examination. Testing the function of these new protein products should be possible in standard cell and animal models. Other changes in RNA processing may lead to changes in levels of translation or regulation of RNA molecules.

**Implications of success:** True tumor-specific splicing events may provide new functional understanding of the drivers of tumor development. They may also provide novel cancer-specific markers of new proteins or protein domains for diagnostic and therapeutic target development.

([View Detail](http://provocativequestions.nci.nih.gov/rfa/how-do-changes-in-rna-processing-contribute-to-tumor-development/mainquestions_viewdetails))

**PQ - 12**
**Given the recent discovery of the link between a polyomavirus and Merkel cell cancer, what other cancers are caused by novel infectious agents and what are the mechanisms of tumor induction?**

**Background:** To date, a number of cancer-causing infectious agents have been identified, such as HPV as the causative agent of cervical cancer and H. pylori and its role in gastric cancer. It seems likely that there are other infectious agents not yet identified that influence cancer development. This question calls for the identification of other agents that may contribute to cancer development and for studies to understand the mechanisms of tumor induction.

**Feasibility:** Multiple approaches in various disciplines may be used to support studies for this question. Epidemiological studies may suggest an association of infection and increased risk. Global health studies may provide locales where more poorly studied cancers might show a causal link to infections. High-throughput sequencing and bioinformatics have made it possible to identify viral mRNA in tumor tissues, and similar strategies may prove useful here. Given the success of this research area in the past, it seems likely that many inventive and useful approaches will be available to successful applicants.

**Implications of success:** Identifying new infectious agents that cause cancer and understanding how they influence cancer development have been powerful avenues of research in the past. There is every reason to believe that continued discovery of new cancer-causing infectious agents will continue to result in similar rewards. If they cause a common cancer, developing successful strategies to modulate or prevent their cancer-causing effects can have a tremendous impact on cancer mortality.

([View Detail](http://provocativequestions.nci.nih.gov/rfa/given-the-recent-discovery-of-the-link-between-a-polyomavirus-and-merkel-cell-cancer-what-other-cancers-are-caused-by-novel-infectious-agents-and-what-are-the-mechanisms-of-tumor-induction/mainquestions_viewdetails))

**PQ - 13**
**Can tumors be detected when they are two to three orders of magnitude smaller than those currently detected with in vivo imaging modalities?**

Background: Current imaging modalities allow detection of tumors composed of approximately 107 cells or in the range of 1 cubic millimeter. Any increase in imaging sensitivity provides valuable advances in tumor detection; however, a major increase in detection sensitivity would provide a radical change in how we might employ imagining in clinical practice. While new advances are continually being reported and are currently the goal of NCI’s imaging grant portfolio, here we call for methods that might radically change the sensitivity of these imaging methods.

Feasibility: This question calls for a huge jump in imaging sensitivity. How this increase might be achieved is left to the imagination of the community. However, one can recognize that strategies to increase sensitivity might include such approaches as matching imaging probes with biologic targets that provide some enzymatic amplification, developing much more sensitive imaging probes, or greatly improved camera sensitivity.

Implications of success: The ability to detect very small clusters of cells in patients and in experimental cancer models is important from both detection and therapeutic perspectives—to find cancer at its earliest stages, to understand how and when tumors spread, to study how dissemination correlates with malignant progression, to improve strategies for treatment with precisely targeted radiation or drugs, and to monitor therapeutic responses.

([View Detail](http://provocativequestions.nci.nih.gov/rfa/can-tumors-be-detected-when-they-are-two-to-three-orders-of-magnitude-smaller-than-those-currently-detected-with-in-vivo-imaging-modalities/mainquestions_viewdetails))

**PQ - 14**
**Are there definable properties of a non-malignant lesion that predict the likelihood of progression to invasive or metastatic disease?**

Background: Not all cancers detected early are worth treating. However, uncertainties about the clinical behavior of a non-malignant lesion often leads to more aggressive treatment than may be warranted, which can result in net harm to the patient. Currently, the detection of non-malignant (presumptive pre-malignant) lesions, such as so-called “in situ carcinomas” of the prostate gland or breast, are often treated vigorously because of the possibility that they are likely to adopt aggressive behaviors with time. In addition, the inherent uncertainty in predicting the outcome of a given cancer can result in poor communication of the actual risk to the patient, promoting decisions that may not be appropriate for the given benefit/risk profile.

Feasibility: Major advances in genomic and proteomic technologies that can genotype and phenotype very small collections of cells, together with a greater awareness of the tumor microenvironment, are resulting in a better understanding of how molecular profiles relate to phenotype. New knowledge will help determine whether malignant properties are conferred stochastically, or whether early lesions differ in their likelihood of malignant progression in definable and reproducible ways, thus allowing for more accurate prognostic determinants. Prospective studies could lead to substantial improvements in the accuracy with which the clinical behavior of a given lesion can be predicted.

Implications of success: Improved prediction of clinical risk could help clinicians in communicating risk/benefit profiles for treatment options. Patients could make better informed decisions, thus matching the diagnosis with the most appropriate treatment. These developments could also identify where therapeutic advances are most needed. Insight into the biological basis for this stratification would be an important advance, with likely relevance to analogous lesions of several tissues. These changes could improve the overall benefit of early detection by reducing the risk of harm from overtreatment.

([View Detail](http://provocativequestions.nci.nih.gov/rfa/are-there-definable-properties-of-a-non-malignant-lesion-that-predict-the-likelihood-of-progression-to-invasive-or-metastatic-disease/mainquestions_viewdetails))

**PQ - 15**
**Why do second, independent cancers occur at higher rates in patients who have survived a primary cancer than in a cancer-naïve population?**

Background: Second cancers are a major problem for cancer survivors. Grouped as a single outcome in the Surveillance Epidemiology and End Results (SEER) database, second cancers rank fourth in overall cancer incidence and are often associated with poor outcomes. However, researchers have not taken full advantage of this population to study risk factors and mechanisms. The influence of prior therapeutic interventions (including chemo- and radio-therapies) and somatic mutations in this population has been studied to some degree. However, the extent to which underlying genetic predispositions, environmental factors, and life-style behaviors influence risk remain relatively underexplored. It is likely that at least some of the identified risk factors and mechanisms would also be relevant to people who have not had a first cancer.

Feasibility: Given the high risk of these of these patients and their involvement with medical oncology personnel, it should be substantially easier to monitor cancer survivors for the development of a second cancer than to observe healthy individuals for the development of a first cancer. Cancer survivors are often followed prospectively for treatment response and complications, as well as disease progression. Technologies that identify somatic alterations can be integrated with genome-wide annotation of germ-line DNA to investigate the relationship between genetic susceptibility in high-risk individuals and second cancers. With the advent of new, more efficient technologies, it is feasible to broaden these efforts to large-scale clinical trial studies. Efforts to capture clinical, epidemiological, and therapeutic data could also be centered on the development of large-scale cohorts of cancer survivors at risk for second cancers. Because of their heightened risk of cancer, this population of patients may be more motivated, and therefore well suited, for prospective prevention studies, such as chemoprevention or behavioral modifications. Increasing use of electronic medical records could facilitate such studies, including the identification of appropriate patients for particular studies.

Implications of success: Studying patients who have had primary cancers for the development of second cancers could help uncover pathogenic mechanisms of both cancers, including shared etiologic pathways and therapy-related risks. These insights are likely to inform new strategies for preventive interventions.

([View Detail](http://provocativequestions.nci.nih.gov/rfa/why-do-second-independent-cancers-occur-at-higher-rates-in-patients-who-have-survived-a-primary-cancer-than-in-a-cancer-naive-population/mainquestions_viewdetails))

**PQ - 16**
**How do we determine the clinical significance of finding cells from a primary tumor at another site?**

Background: Metastatic disease is the major cause of death from cancer. However, just as not all primary cancers are prone to metastasize, not all tumor cells found at secondary sites are life-threatening. Dissemination from a primary tumor site can occur relatively early in tumor development, and cells at secondary sites may have properties that range from dormancy to aggressive malignancy. Furthermore, relatively quiescent tumor cells may require additional genetic and/or epigenetic alterations, perhaps in conjunction with non-cell autonomous alterations, to achieve a fully malignant phenotype at the secondary site. Yet, because the spread of tumor cells is usually viewed as an unfavorable prognostic indicator, detection of such cells commonly represents a rationale for more intensive therapy, which may or may not be warranted.

Feasibility: New experimental methods allow sensitive techniques for detecting and characterizing small numbers of tumor cells at secondary sites, and improved animal models of cancer have created opportunities for expanding our knowledge of disseminated cells and refining our lexicon for classifying them. For instance, recent advances in DNA sequencing enable the generation of phylogenetic trees of tumor cell populations to determine their clonal relationships and evolutionary distance from each other, and from portions of the primary tumor that are at different stages of progression. With these new tools, it may now be possible to define the malignant potential of disseminated cells.

Implications of success: Such analyses could enhance our understanding of the mechanisms that account for either a lack of oncogenicity or malignant behavior of tumor cells at a secondary site, as well as improve our ability to predict the biological behavior of tumor cells found at those sites. This information would give clinicians a clearer picture of when intervention is needed and when such tumor cells can be safely left alone or followed for potential later action.

([View Detail](http://provocativequestions.nci.nih.gov/rfa/how-do-we-determine-the-clinical-significance-of-finding-cells-from-a-primary-tumor-at-%20another-site/mainquestions_viewdetails))

**PQ - 17**
**Since current methods to assess potential cancer treatments are cumbersome, expensive, and often inaccurate, can we develop other methods to rapidly test interventions for cancer treatment or prevention?**

Background: There are no reliable models that predict drug response in human tumors. Tumor cells in culture are widely used to help identify and characterize potential drug targets, and they can serve as useful models to check initial drug penetration of cell membranes and target engagement. Mouse xenograft or genetically engineered mouse models often provide good settings to test drug pharmacodynamics, but seldom yield reliable measures of drug efficacy. Other animal models are used extensively for drug pharmacokinetic tests, but none of these models are useful mimics of drug activity in humans. This Provocative Question calls for the development and testing of new systems that accurately predict how drugs will act in humans.

Feasibility: Advances in 3-dimensional cell culture suggest that multiple cell types can be assembled in vitro and that engineered tissues often mimic many of the features of human organs. If systems can be developed that mimic the natural environment of tumors, perhaps these models will recapitulate drug action. It also seems possible that complex cell-free systems could be developed that would recapitulate at least some features of drug responses. Since it seems unlikely that any one new system will serve as an accurate model for all tumors, each may need to be tuned to the particular features of a particular tumor type or subtype.

Implications of success: If systems can be developed that accurately predict drug responses in human, advances in drug treatment or prevention would be dramatically streamlined, and the time frame for drug development shortened considerably. These new systems might also allow strategies for combination therapies to advance from empirical tests to approaches that are based on the biology of the tumor and its environment. The ultimate benefit for patients would be immense.

([View Detail](http://provocativequestions.nci.nih.gov/rfa/since-current-methods-to-assess-potential-cancer-treatments-are-cumbersome-expensive-and-often-inaccurate-can-we-develop-other-methods-to-rapidly-test-interventions-for-cancer-treatment-or-prevention/mainquestions_viewdetails))

**PQ - 18**
**Are there new technologies to inhibit traditionally "undruggable" target molecules, such as transcription factors, that are required for the oncogenic phenotype?**

Background: Many tumor cells are known to be dependent on the expression and function of transcription factors or other proteins that are not easily targeted by standard drug development strategies. Typically, these proteins do not have enzymatic activities that can be inhibited by small molecule organic drugs. Nevertheless, cancer cells are often fully dependent on the continued expression and biological activity of these proteins, as shown by RNAi experiments or other functional tests. Many groups have tried to identify small molecule inhibitors that would interfere with the function of these proteins by blocking their interaction with other essential proteins. However, except for rare cases, these approaches have not led to drug candidates for clinical trials. Still other groups have looked for allosteric inhibitors that might change protein function through binding to targeted proteins and altering an essential function. Here, also, little success has been reported. Currently NCI is funding a small number of investigators to look for inhibitors of protein/protein interaction using a series of approaches. Because solving this problem would have such a large impact in the development of new cancer therapies, this question is included to continue driving the field’s quest for new and unusually creative approaches to inhibit these traditionally “undruggable” targets.

Feasibility: This question seeks new ideas to develop approaches for drug development for protein/protein interactions or other non-enzymatic inhibition of oncoprotein function.

Implications of success: New classes of drugs designed to block the actions of these refractory targets would provide a wide range of opportunities for cancer treatment and prevention.

([View Detail](http://provocativequestions.nci.nih.gov/rfa/are-there-new-technologies-to-inhibit-traditionally-undruggable-target-molecules-such-as-transcription-factors-that-are-required-for-the-oncogenic-phenotype/mainquestions_viewdetails))

**PQ - 19**
**Why are some disseminated cancers cured by chemotherapy alone?**

Background: Although chemotherapy is often effective, it is only rarely curative. However, It is well established that certain disseminated cancers can be completely cured with chemotherapy, even with drugs that are often of much less value in other settings. The tumors that can be cured include solid tumors (testicular carcinoma, choriocarcinoma, and Wilms’ tumor) and hematological malignancies (ALL, Burkitt’s lymphoma, and some diffuse large B-cell lymphoma). However, there is little understanding of the underlying mechanisms that might explain why these cancers can be completely cured with chemotherapy.

Feasibility: This question has largely been ignored since it was recognized, often decades ago, that such tumors could be cured by standard chemotherapeutic strategies. New methods are available for studying the biology of these “curable” cancers and for exploring the mechanisms by which the effective drugs work.

Implications of success: If we could identify the properties of cancers that render them susceptible to eradication by chemotherapy, we might better understand how certain therapies work, contemplate converting relatively insensitive tumors to highly sensitive ones, or develop new approaches to the treatment of intransigent malignancies.

([View Detail](http://provocativequestions.nci.nih.gov/rfa/why-are-some-disseminated-cancers-cured-by-chemotherapy-alone/mainquestions_viewdetails))

**PQ - 20**
**Given the recent successes in cancer immunotherapy, can biomarkers or signatures be identified that can serve as predictors or surrogates of therapeutic efficacy?**

Background: There is increasing excitement about the use of immunotherapies in the treatment of cancer. While biomarkers that predict therapeutic efficacy or that can be used to measure the progress of treatment are still missing for many cancer treatments, with other treatments there are large-scale efforts in progress to identify these markers. Because of the relatively recent success in immunotherapies, there is a clear need to jumpstart the search for such biomarkers for these treatment modalities.

Feasibility: The sophistication of the immunology field may provide a particular advantage in the search for surrogates for therapeutic efficacy. The long and rich advances of this field have helped shape a deep appreciation of immune responses, and within this knowledge there may be clever approaches to identify useful markers. The search for predictors of therapeutic efficacy may also benefit from this information, but may also rely on advances in molecular profiling.

Implications of success: Biomarkers for predicting therapeutic responses or for following treatment success would greatly advance the immunotherapy field, and as we struggle to find such markers in all areas, any success will serve as a useful model for others.

([View Detail](http://provocativequestions.nci.nih.gov/rfa/given-the-recent-successes-in-cancer-immunotherapy-can-biomarkers-or-signatures-be-identified-that-can-serve-as-predictors-or-surrogates-of-therapeutic-efficacy/mainquestions_viewdetails))

**PQ - 21**
**Given the appearance of resistance in response to cell killing therapies, can we extend survival by using approaches that keep tumors static?**

**Background:** One of the most disappointing features of the development of new targeted therapeutics is how routinely drug resistance emerges. Evolutionary theory suggests that strong selection will always result in the emergence of resistant populations as long as some portion of the stressed population can adjust to the selective pressure. Similar theories also suggest that lessening the selective pressure to a level that seeks to hold the population in check may succeed at least for extended periods of time. Evolutionary fitness suggests that many mutations that arise after selection for cell killing are likely to be slightly deleterious in nature. While strong selection will easily let the mutated population emerge, if the selection is modest, the population may develop a new balance that reflects a combination of original tumor cells, dying tumor cells, and minor populations of the drug-resistant tumor cells whose fitness is impaired. Other types of selective pressures also may be valuable in these settings. For example, developing and using drugs that select for outcomes that are not solely inducers of cell killing may help establish a balance that would help create tumor stasis rather than strong selection for drug resistance. This Provocative Question suggests we should test the validity of these approaches as novel means to treat cancer. Ultimately, this may not produce a cure for a particular cancer but rather a method to treat cancer as a chronic disease.

**Feasibility:** Testing this theory is best done in animal models. Existing agents at low doses may provide good test cases; however, agents that induce other outcomes besides cell killing also should be considered, perhaps in combination.

**Implications of success:** These approaches present novel ideas for cancer therapy, but they highlight the importance of making sure we know what outcome for cancer patients is ultimately most useful. Living for some time with a debilitating tumor may be preferable to a rapid tumor regression with an almost certain drug resistant relapse.

([View Detail](http://provocativequestions.nci.nih.gov/rfa/given-the-appearance-of-resistance-in-response-to-cell-killing-therapies-can-we-extend-survival-by-using-approaches-that-keep-tumors-static/mainquestions_viewdetails))

**PQ - 22**
**Why do many cancer cells die when suddenly deprived of a protein encoded by an oncogene?**

**Background:** The viability of cancer cells is dependent on the continued production and activity of various pro-oncogenic proteins. In some cases, when therapies target these oncoproteins, individual tumor cells may die abruptly. This process is often called "oncogene addiction," and rapid regression of several tumor types with targeted therapies has been seen in patients. While this cell death is an encouraging outcome for therapeutic approaches, we have little knowledge of why these cells become so strongly dependent on the continued expression of an active mutated oncogene, particularly because the initiating cells often express the normal proto-oncoprotein. This Provocative Question asks why tumor cells die so rapidly when the addicting oncoprotein is depleted or its enzymatic activity blocked by a targeted therapy.

**Feasibility:** Many examples of oncogene-dependence, both in human cancers and mouse models of cancer, are now subjects of great interest, because the “addicting” oncogene products are promising targets for modern cancer therapy. The signaling networks in which they are active are also being studied to identify other therapeutic targets. Modern molecular biological methods focused on protein function should be useful in studying why cells become addicted to these oncoproteins and die so rapidly when they are lost.

**Implications of success:** Knowledge of how a cell develops vulnerability to the loss an oncogenic protein, and undergoes programmed cell death in consequence, would likely suggest additional novel targets for therapy. In addition, it might offer insight into the question of which tumors are most susceptible to targeted therapies and the problem of eliminating all cells in a tumor with such therapies.

([View Detail](http://provocativequestions.nci.nih.gov/rfa/why-do-many-cancer-cells-die-when-suddenly-deprived-of-a-protein-encoded-by-an-oncogene/mainquestions_viewdetails))

**PQ - 23**
**Can we determine why some tumors evolve to aggressive malignancy after years of indolence?**

**Background:** Indolent tumors have been detected in a wide range of tumor sites. Very little is known about why these tumors persist for extended periods of time and then evolve to malignancy. Some are recognized as indolent after treatment, while others appear as a stage of natural tumor development before treatment. Still others are seen only at autopsy. Research to characterize these various tumors could help to understand what controls this state. Is it a true proliferatively dormant state or an active state that just balances cell division and death? How is this state maintained? Do tumors of the same site undergo similar transitions as they move from dormancy to malignancy? Can we predict which tumors will remain dormant and which one will progress?

**Feasibility:** Many of the tools for tumor profiling will be useful to help characterize these tumors. Modern molecular and cellular techniques can be used to help understand which pathways are active and essential in indolent states.

**Implications of success:** Expanded insight into the mechanisms that control tumor development promises to enrich our understanding of the cancer process. Characterization of indolent tumors will help us understand the mechanisms that hold tumor progression in check. Indolent tumors seldom pose any inherent risk to patients, so approaches that would hold other tumors in this state or that would extend the time that indolence persists could provide important therapeutic benefits.

([View Detail](http://provocativequestions.nci.nih.gov/rfa/can-we-determine-why-some-tumors-evolve-to-aggressive-malignancy-after-years-of-indolence/mainquestions_viewdetails))

**PQ - 24**
**Given the difficulty of studying metastasis, can we develop new approaches, such as engineered tissue grafts, to investigate the biology of tumor spread?**

**Background:** Metastasis continues to be difficult to study. We have almost no reproducible systems to study this deadly process. Mouse tail vein injections of tumor cells often leads to tumor growth at various sites in a process that mimics metastasis to some degree. Some genetically engineered mouse models will metastasize, but the process is hard to stage or follow in any rigorous detail. This Provocative Question calls for the development of new approaches to study metastasis.

**Feasibility:** While the range of potential approaches to develop methods to study metastasis is left to the imagination and creativity of the community, one potential exciting approach is the construction of engineered tissue beds that could serve as sites for invasion of metastasizing tumor cells. Such sites could be modified to determine which physical or biological properties promote more successful invasive and subsequent tumor proliferation. Many parameters of metastasis could be measured if it were known when and where to follow this process, and such sites could allow more careful analysis of what events guide the development of metastasis. These types of suggestions also raise a large number of other potential approaches that might make the study of metastasis more controllable and thus more readily compared among tumor types and more readily modifiable.

**Implications of success:** In many ways, metastasis is the most important stage of tumor development. Developing new methods to allow its careful study would provide important new avenues to learning about this stage of tumor development.