Report to National Cancer Advisory Board

NCAB Working Group on Biomedical Technology

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Overview Report to NCAB

Report of Working Group
on Biomedical Technology

February 2005

1. Introduction
The long-term goal of the National Cancer Institute (NCI) is to eliminate deaths and suffering due to cancer. There are ~1.4 million new cases of cancer each year and ~560,000 deaths in the United States alone.

Fulfilling this goal demands a deeper understanding of the basis of cancer through research, and the application of this knowledge to develop more effective methods of prevention, detection, and treatment. It has become clear that progress on both these fronts is crucially dependent on technology.

We stand at a moment of enormous opportunity. Biomedicine is in the midst of a technological revolution, driven by advances in genomics, cell biology, chemistry and computational science. Extraordinary tools have already become available for probing and modulating cells and tissues, and continued improvements are expected in the decade ahead. These tools hold enormous promise for propelling biomedical progress against cancer.

Against this background, the Director of the National Cancer Institute requested that the National Cancer Advisory Board (NCAB) advise NCI how best to harness the power of biomedical technology to drive cancer research.

In September 2003, NCAB constituted an Ad Hoc Subcommittee on Biomedical Technology, and this subcommittee created a Working Group on Biomedical Technology to address this important issue. The working group is chaired by Drs. Lee Hartwell and Eric Lander and includes 18 members with expertise in basic, clinical and commercial science. (A roster of the committee’s membership is attached.)

The working group addressed the following question: “What specific projects and initiatives could NCI undertake that would have a broadly transforming impact on the entire field of cancer research, with the goal of eliminating death and suffering due to cancer?”

Such a transforming impact will likely come from major scientific advances in such areas as: understanding of the molecular mechanisms of cancer; assessment of risk for cancer; detection of cancer at the earliest stages; classification of cancer types to aid in development of treatments; and monitoring of response to treatment.

This report describes the themes that emerged in the course of the discussions and distills them into a handful of key recommendations.

2. Ongoing Initiatives at NCI
The working group began with the recognition that there are many programs underway at NCI that relate to the application of biotechnologies to cancer. Before exploring potential new directions, the working group thus familiarized itself with these efforts. We briefly describe three important types of activities.
2.1 Technology-related programs. NCI currently has a broad portfolio of technology-related programs. A few examples will illustrate the range of efforts.

- **Cancer genome anatomy project (CGAP).** This project is complementary to the Human Genome Project. One component, for example, focuses on characterization of mRNAs and thereby helps define the catalog of all human genes.

- **Alliance for nanotechnology in cancer.** This alliance aims to integrate nanotechnology development into basic and applied cancer research to facilitate the rapid application of this science to the clinic. It will support the development of nanomaterials and nanoscale devices for molecular imaging and early detection, reporters of efficacy, and multifunctional therapeutics to combat the cancer processes.

- **Cancer biomedical informatics grid (caBIG).** This effort focuses on creating a core informatics infrastructure, including a unifying architecture to transparently connect to information and tools across research institutions, especially cancer centers.

- **Development of clinical imaging drugs and enhancers (DCIDE).** This program supports development of imaging enhancers such as contrast agents or molecular probes. It is designed particularly to facilitate their translation from laboratory synthesis to IND application.

- **Biospecimen resources.** NCI has begun a pilot project to standardize approaches for collecting, processing and archiving highly annotated biospecimens for cancer research. The NCI-led initiative will further establish a state-of-the-art information system link to exchange data across the research enterprise.

- **Early detection research network (EDRN).** The EDRN is a comprehensive effort to discover the molecular signature of cancer in order to develop highly sensitive, specific and clinically reliable detection tools. This approach to biomarker discovery and validation integrates institutions into a single scientific consortium to bridge the gap between laboratory advances and clinical utility of biomarkers for early cancer detection and risk assessment.

- **Mouse models for human cancer consortium (MMHCC).** NCI developed MMHCC to answer the need for well-designed, thoroughly characterized animal model systems to inform basic, clinical, epidemiological and translational cancer investigations. The program involves manipulation of the germline of laboratory mice, coupled with a store of data on genetic alterations in human cancer and rapid acquisition of human and mouse genomic sequences.

- **Cancer imaging program.** This program has spearheaded collaborations to develop standardized designs for clinical trials involving imaging-guided interventions.

- **RNAi libraries.** The Division of Cancer Biology has supported efforts to create publicly available libraries of inhibitory RNAs (RNAi) that are broadly useful for interfering with gene function.

2.2 Think tanks. The NCI Division of Cancer Biology has engaged the scientific community in a series of “think tanks” to assess the state of cancer biology research and to identify emerging research areas. The areas addressed by the think tanks include: 1) tumor immunology, 2) tumor microenvironment, 3) tumor stem cells, 4) cell decision in response to DNA damage, 5) cancer etiology, 6) epigenetic mechanisms in cancer, 7) inflammation and cancer, 8) cancer susceptibility and resistance, and 9) integrative cancer biology.
Each think tank identified questions and barriers unique to the field. At the same time, common themes emerged in nearly all of the discussions. The most prominent common themes were the need to:

- support the development of systems approaches to the entire spectrum of cancer biology;
- elucidate the composition and function of both the normal and the tumor microenvironment and its interaction with the tumor;
- establish new mechanisms for both large- and small-scale collaborative projects that could be built on the foundations of the investigator-initiated RO1 or PO1 mechanisms; and
- establish collaborative and interdisciplinary training programs, and drive the development of technology for cancer research.

The discussions have resulted in both long- and short-term NCI goals and have already resulted in specific programs.

Responding to the need to develop the field of systems biology, NCI launched the Integrative Cancer Biology Program that will fund nine research groups to work cooperatively to develop the field, generate predictive computational or mathematical models of cancer, establish and coordinate training and outreach programs, and articulate to the NCI opportunities and need for resources in integrative cancer biology. This initiative will rely heavily on the development of new technologies, such as nanotechnology.

Responding to the need for training and technology, a new tumor microenvironment program is starting in 2005 that will train up to 80 investigators in the technologies of organotypic cultures, 3D matrix reconstitution and imaging modalities. Among the long-term goals is the creation of an infrastructure that will provide resources — central repositories of cell lines, reagents, technologies and protocols — and facilitate interdisciplinary collaborations for studies of the tumor microenvironment. Consequently, NCI is currently planning a new initiative to establish a “microenvironment network”. This is envisioned as a loosely structured collection of funded investigators who will work with NCI to create the needed infrastructure of resources and serve as a focal point to bring together the community of researchers in collaborative and cooperative interactions to speed progress in this field.

Additional programs are currently being planned.

### 2.3 Clinical trials working group (CTWG)

NCAB established a working group to improve the cancer clinical trials system, both in the immediate and long-term future. The CTWG, with broad representation from the oncology community, is charged with advising NCAB on the development, conduct, infrastructure, support, and coordination of cancer clinical trials across the full spectrum of NCI-supported clinical trials venues. The CTWG has prioritized major issues that currently hamper the optimal conduct of clinical trials and has established subcommittees to address these topics, including:

- standardization of clinical trial procedures and infrastructure;
- coordination of clinical trials;
- enhanced interactions between the clinical research community, NCI, the pharmaceutical industry, FDA, regulatory agencies, and patient advocates;
- core facilities development to improve scientific support for trials;
- improved clinical trial accrual management; and
- protocol prioritization process.

The CTWG expect to provide regular reports to the NCAB and make recommendations by June 2005.
With this background, the working group turned to its specific charge.

3. Focus Groups

The Working Group on Biomedical Technology held two initial meetings to discuss overarching themes and opportunities. To seek broad input on diverse areas, the working group then established five focus groups: 1) characterization of cancer in the cell, 2) characterization of cancer in the organism, 3) public health, 4) cancer therapeutics and clinical trials, and 5) technology access, development, and dissemination. A dozen or more scientists were enlisted from the greater scientific community for each focus group and each group held a meeting and presented a report to the Biomedical Technology Working Group. In all, the process involved thoughtful input from more than 50 scientists. (Rosters of focus groups are attached.)

We briefly summarize the themes that emerged from each of the focus groups and then distill the common themes.

3.1 Characterization of cancer in the cell. This focus group identified several key directions in which systematic work would have a wide impact:

- **Genomic characterization of cancer**. Cancer is a genomic disease, whose initiation and progression is driven by an accumulation of genomic lesions that confer upon tumors both special abilities and special liabilities. It is becoming clear that understanding the genomic lesions associated with each cancer type is central to the diagnosis and treatment of cancer, with such knowledge increasingly leading to the development of new drugs with higher efficacy and decreased side effects. The focus group concluded that it is now feasible to undertake a systematic program to identify all of the genomic lesions associated with all major cancers and that such information would transform cancer research.

- **Functional characterization of cancer**. Powerful new technologies are also making it increasingly feasible to characterize cancers at a functional level by studying the responses of tumor cells to various types of perturbations. Systematic studies with inhibitory RNA (RNAi) can identify the set of genes that are uniquely essential to a tumor’s viability. Systematic studies with RNAi and chemicals (such as drugs) can also identify distinctive “cellular signatures” that can be used to recognize previously unknown connections among cancer types and potential therapies through comprehensive databases. Substantial projects will be needed to develop this important direction.

- **Improved animal and cellular models of cancer**. There was strong support for new cancer models, both in animals and in cell culture. The group was strongly supportive of existing efforts to develop animal models and urged their expansion. The group also maintains that attention should be focused on solving the problems in creating cancer cell lines from many types of cancer, so that researchers would have such lines available for a broad range of functional studies.

The focus group also noted the need for i) improved collections of well-annotated patient samples, and ii) mechanisms to support “team science”, which it saw as key to many technology-based projects.

3.2 Characterization of cancer in the organism. The focus group concluded that the key area that would transform research efforts in basic science, translational science and clinical application would be the development of much better tools for the detection of cancer. The group focused on two parts of this problem.
• **In vivo imaging in patients.** There has been a recent explosion in new, powerful imaging technologies, including positron emissions technology (PET), magnetic resonance imaging (MRI), single-photon emission computerized tomography (SPECT), barium x-ray contrast studies, and ultrasound imaging. What is critically needed now is to develop better ways to use these technologies to perform functional imaging — that is, to detect specific proteins, signaling pathways or metabolites that are associated with cancer cells and cancer response. We need to be able to directly monitor the action of drugs, including their distribution in the body and their efficacy at modulating their intended targets. Rather than wait months to learn the effect of a drug, we need ways to gain early information that could be used both to guide clinical development of drugs and guide treatment for individual patients. Achieving these goals will require major progress in the development of functional imaging agents. The focus group concluded that existing efforts in this area should be greatly expanded.

• **Detection in patient samples.** The ability to detect cancer biomarkers in readily accessible patient samples, such as serum, would have enormous utility: it would facilitate better methods for 1) determining cancer risk, 2) detecting and localizing cancer at its earliest stage, 3) profiling cancers for therapeutic decision making, and 4) monitoring response to therapy in real time. Recently, there have been tremendous advances in technologies for systematic detection of proteins – including extensive knowledge of the human proteome from the Human Genome Project and increasingly accurate and sensitive tools for detecting proteins by mass spectrometry. What is needed now is systematic application of these capabilities in focused efforts to discover biomarkers for specific human cancers. Although diverse efforts are already underway, the focus group concluded that more systematic coordination and expanded efforts are needed.

The focus group also believed that both of these areas of cancer detection would be greatly aided by systematic characterization of cancers at the genomic and functional level.

In addition, the group saw the need for i) improved collections of well-annotated patient samples to facilitate studies of epidemiological risk, and ii) support for “team science”, which the group saw as a key to many technology-based projects.

### 3.3 Public health

The main focus of this group was ensuring that technologies would be developed, disseminated, and widely adopted throughout the clinical community. Several important themes emerged, including the need for:

• **Systematic study of inherited susceptibility factors** predisposing to cancer, in order to be able to identify patients at high risk.

• **Improved high-throughput technologies for proteomics and metabolomics**, which would have an impact both on functional characterization of cancer and on cancer detection.

• **Adapting advanced technologies to the setting of small laboratories**, to ensure that techniques for DNA, RNA, protein, metabolite and epigenetic analyses are broadly available to researchers.

• **Adapting advanced technologies to the clinical setting**, to ensure that they are robust and easily used. This is key to translating research findings (for example, gene expression patterns predictive of drug response) to the bedside.

• **Development of improved systems for streamlined sample collection, data acquisition and data analysis.** The focus group identified the need for standardized methods for data collection, laboratory information management systems (LIMS, providing information systems for data acquisition) and analysis information management systems (AIMS, providing general computational environments that can readily incorporate new techniques within a common framework).
The focus group also noted the need for i) improved collections of well-annotated patient samples to facilitate studies of epidemiological risk, and ii) support for “team science”.

3.4 Cancer therapeutics and clinical trials. This focus group discussion paralleled the other discussions with respect to several topics, including i) improved access to standardized archived samples, ii) standardization of data collection for clinical trials, including response assessments and molecular profiling, iii) improved animal models for cancer therapeutics that include assessments of toxicity, metabolism, and target modulation, and that emphasize efficacy, particularly of combination therapy, and iv) improved support for team projects and improved funding for academic–industry partnerships.

The important themes specific to this focus group were:

- **Restructuring clinical trials.** We need to increase the focus on smaller and smarter clinical trials. As more agents with known mechanisms of action enter the clinic there are greater opportunities to learn how best to use these agents in Phase I and Phase II clinical trials. This could be accelerated through the establishment of a consortium of collaborative Phase I/II centers with unique areas of expertise. Such a consortium could include centers with expertise in imaging, marker validation, pharmacokinetics, molecular diagnostics, expression profiling, etc. The purpose would be to learn as much as possible from the fewest number of patients about new agents entering clinical trials. A consortium would allow much more focused expertise to be incorporated in early clinical trials and greatly improve the quality of the science associated with clinical studies. It would allow clinical trials to identify patients who are most likely to respond to new agents, thus maximizing the chances of success of new agents.

- **Identifying persons at risk for developing cancer.** There are already several known genes that predispose to cancer in specific populations, such as the BRCA1 and BRCA2, p16INK4, pRB, and APC genes. Although this represents only a fraction of all cancers, it is quite large in terms of absolute numbers. Moreover, the impact of these cancers is quite significant because they tend to occur at a relatively young age. The group recommended that more efforts be devoted to identifying persons at risk. This would include full genetic analysis of at-risk populations, along with an investment in improving technology so that better, faster, and cheaper methods of identifying persons at risk are developed. The importance of this investment would become greater as additional genetic risks are identified.

- **Elimination of barriers to cancer drug development.** One major barrier to cancer drug development has been the difficulty accessing industrial compounds in academic laboratories imposed by the lengthy negotiations on material transfer agreements. Similarly, industry has cited impediments to the testing of drugs in specific defined genetic backgrounds due to patent protection on genetic technologies (such as the OncoMouse). Such an encumbrance to the flow of reagents creates a barrier to drug development. A second major barrier arises from current HIPPA regulations, which can hamper sample collection and analysis. It was strongly recommended that regulations governing these issues be reviewed by an appropriate group in order to strike a better balance between advancing research and providing protections to intellectual property as well as patients.

3.5 Technology access, development, and dissemination. This focus group discussion addressed the changing role of technology within the biomedical research enterprise. Access to technology has become a critical competitive advantage, and, with the shortening of technology life cycles, technology has become both indispensable and ultimately disposable. The group focused on three issues:
• **Ongoing Access to Technology.** Technology and the underlying infrastructure to support it has become a competitive advantage. The rapid pace of change coupled with the scaling of capabilities has made technology both indispensable as well as ultimately disposable. Predictable and ongoing access to capital expenditures is necessary for the development, maintenance and building of the infrastructure required to accelerate the translation of basic science into health care.

• **Work force and teamwork.** Fundamental changes in technology are altering the nature of work and the work force. The accelerating pace of research, the increase in its complexity, the rising expectations and the sense of urgency together require a level of integrated capability and span of activity from bench to bedside to market that is beyond the capacity of any single individual or laboratory. The traditional academic system of training, employment and reward based on individual contribution and incremental publication must accommodate systems based on teamwork that brings together a diversity of skills and produces tangible outputs. The group discussed the importance of giving increased attention to systems to support team science.

• **Barriers to flow of technology.** The group also expressed concern about barriers to the flow of technology — including intellectual property fragmentation, excessive transfer pricing for technology, failure to develop systems to validate and qualify new technology, approaches to facilitate the drug approval process, and so on. The problems often lie at the interface between stakeholders (e.g., Offices of Technology Licensing, Patent and Trademark Office, Food and Drug Administration, Institutional Review Boards, etc.). Despite the revolutionary changes in our science and the scientific enterprise, there has been little systematic consideration of the issues. The group concluded that there is a need for i) systematic evaluation of best practices (and counterexamples), and ii) development of concrete models to streamline access to technology. Recognizing that this likely falls outside the specific charge to and expertise of the subcommittee, the group recommends that NCI and NIH pursue these issues through appropriate channels.

4. Cross-Cutting Themes

Two strong themes emerged from the focus groups:

4.1 **Technology-based cancer challenges.** There are enormous opportunities to propel progress in cancer research by harnessing the power of technology to address key cancer challenges. The four challenges that emerged most clearly are:

1. **Genomic basis of cancer.** Comprehensive identification of all genomic alterations significantly associated with all major cancers.
2. **Detection of cancer.** Powerful methods based on functional imaging in vivo and molecular biomarkers in patient samples.
3. **Functional characterization of cancer.** Systematic characterization of cellular signatures of cancers (at various levels, such as RNA, protein and function), both alone and in response to modulators (such as RNAi and small molecules).
4. **Models of cancer.** Improved animal models of cancer that exploit our increased knowledge of the molecular basis of cancer and provide powerful models for the evaluation of therapeutics.

Although NCI already supports important work directed toward each of these cancer challenges, there was a consensus that major NCI-led or NCI-partnered programs to exploit the full power of technology could have a huge impact on cancer research in thousands of laboratories. NCI should develop plans for focused and sustained programs around such cancer challenges.
The working group made specific recommendations concerning the first two challenges and also proposed a general mechanism for identifying such projects on an ongoing basis. These are discussed below.

4.2 Systemic needs. Exploiting the full power of technology will require addressing certain systemic needs that affect cancer research broadly. The most important themes include:

   1. **Clinical samples.** Improved systems to collect, maintain, and distribute patient samples as a standardized, broadly usable, and highly annotated data-rich resource.

   2. **Information technologies.** Improved information systems are needed for sample management, data collection and data analysis.

   3. **Team science.** Mechanisms to support multidisciplinary teams to take on sustained projects.

   4. **Redesign of clinical trials.** NCI clinical trials in cancer should be redesigned to be more efficient with respect to speed, number of patients and biological information gained, by taking maximal advantage of technology.

   5. **Dissemination of technology.** Ensuring the broad availability of technology platforms in flexible forms suitable for both small and large laboratories and in robust forms suitable for clinical application.

The working group recognizes that a number of efforts are underway at NCI that address some of these needs. Examples include the NCI Clinical Trials Working Group; the NCI caBIG Bioinformatics Initiative; the recent National Biospecimen Network Blueprint and associated pilot project through the Prostate Cancer Research Funders group; the Mouse Models for Human Cancer Consortium, and the Nanotechnology Standardization Laboratory in the Alliance. The working group strongly endorsed the importance of such specific efforts.

The working group made one specific recommendation concerning one of the systemic needs (redesign of clinical trials) and one general recommendation concerning a mechanism for ongoing assessment of systemic needs and an evaluation of the progress toward meeting them.

5. Recommendations

Based on input from the focus groups and its own discussions, the working group makes four recommendations.

1. **Cancer Technology Working Group.** The first recommendation concerns the creation of a standing mechanism to identify technology-based opportunities to address cancer challenges:

   **Recommendation**
   
   NCI should constitute a standing Cancer Technology Working Group (CTWG), consisting of appropriate experts and seeking appropriate community input, with an ongoing charge to:
   
   i. identify opportunities for technology-based programs to address key cancer challenges, with the potential for broad impact on propelling progress toward the understanding, prevention, diagnosis and treatment of cancer;

   ii. evaluate whether the opportunities are ripe for solution;

   iii. prioritize the opportunities based on importance and feasibility; and

   iv. develop concrete recommendations for appropriate projects and initiatives to meet the challenges.

   In addition, the CTWG should periodically evaluate the systemic needs related to cancer technology and identify potential solutions.
The working group sought to test this approach by performing such an analysis with respect to current opportunities. The group considered the specific technology-based opportunities that emerged from the focus groups and identified two areas as highest priority. The working group developed specific recommendations and reports related to these two areas. (The other opportunities discussed above, as well as additional opportunities, should be considered further by the CTWG.)

2. Human Cancer Genome Project. The working group recommends the initiation of a bold technology-based project.

**Recommendation**

A Human Cancer Genome Project should be initiated with the aim of obtaining a comprehensive understanding of the genomic alterations that underlie all major cancers. Such a project greatly accelerates the discovery, development and evaluation of cancer diagnostics and therapeutics.

This recommendation is described in an attached report.

3. Cancer Molecular Diagnostics Initiative. The working group also recommends an important NCI-wide initiative.

**Recommendation**

A Cancer Molecular Diagnostics Initiative should be initiated to coordinate and expand research on (i) functional imaging of cancer in vivo, and (ii) biomarker identification and detection in patient samples. Improvements in cancer molecular diagnostics would improve the ability to assess cancer risk, to detect cancers at earlier stages and to permit real-time monitoring of responses to therapeutic intervention.

This recommendation is described in an attached report.

4. Restructuring clinical trials. Finally, the working group recognizes that successful application of technology against cancer will require rethinking the nature and structure of clinical trials. Clinical trials must be redesigned to ensure that one can learn as much as possible from the fewest number of patients about new agents with known mechanisms of action, to accelerate the pace of drug development and to validate new diagnostic and imaging agents, techniques and markers.

**Recommendation**

The working group recommends that NCI establish a “Phase I/II Consortium” to accelerate the translation of technological advances and scientifically validated targets into clinical trials. Such a consortium would include centers with expertise in such areas as imaging, marker validation, pharmacokinetics, molecular diagnostics, and expression profiling.

The working group recognizes that this recommendation falls outside its specific mandate and expertise and thus has not developed this recommendation. Because the group believes that this is a pressing need, it urges the NCI to rapidly engage a panel with the required expertise to develop a plan for such a consortium.
6. Conclusion

We stand at a unique moment in the fight against cancer. Scientific progress over the past quarter century has revealed the basic outlines of the cellular mechanisms of cancer and laid the foundation for powerful new approaches to the understanding, prevention, diagnosis and treatment of cancer. There is still a tremendous amount to do in both basic and clinical research. Technology now has great potential to accelerate this work by creating broad application methods, tools and databases. NCI should respond vigorously by creating regular mechanisms to identify and seize those technology-based opportunities likely to have a wide-ranging impact on cancer.
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The Working Group on Biomedical Technology strongly recommends the creation of a Human Cancer Genome Project (HCGP). The project’s goal would be to obtain a comprehensive description of the genetic basis of human cancer. Specifically, the project would aim to identify and characterize all the sites of genomic alteration associated at significant frequency with all major types of cancers.

Comprehensive knowledge of the genetic basis of cancer would provide a permanent foundation for all future cancer research and have far-reaching implications for basic, clinical and commercial efforts to understand, prevent and treat cancer. It has the capacity to reveal the subtypes of cancers and would systematically identify the cellular pathways that are deranged in each subtype. This would increase the effectiveness of research to understand tumor initiation and progression, susceptibility to carcinogenesis, development of cancer therapeutics, approaches for early detection of tumors and the design of clinical trials.

In this report, we describe the scientific rationale and feasibility of a Human Cancer Genome Project and the key scientific considerations in the design of such a project. We then offer a preliminary outline for such a project, including estimates of timeline and cost. We note that the outline is intended as a starting point that will need to be refined in the course of launching a Human Cancer Genome Project.

1. Biomedical Rationale

1.1 Cancer is a heterogeneous collection of heterogeneous diseases. The successful treatment of medical illness largely depends on the elucidation of disease pathogenesis. Achieving a deep understanding of the pathogenesis of cancer has been exceedingly difficult as there are distinct cancers arising from unique tissues (e.g., cancers of the breast, prostate, colon, lung, bladder, pancreas, brain and others) and within each tissue type there are distinct subgroups of cancers that manifest radically different clinical behavior. For example, prostate cancer can be an indolent disease remaining dormant throughout life or an aggressive disease leading to death. However, we have no clear understanding of why such tumors differ. Similar issues arise with respect to the wide diversity of clinical behaviors observed in most cancer types.

Cancer heterogeneity poses many problems for the clinical study and treatment of cancer. Patients with inherently different tumors may be lumped together as having a single disease (e.g., prostate cancer), when they should ideally be treated quite differently. Clinical trials to assess the therapeutic efficacy of pharmacologic agents may fail to recognize efficacious drugs because the trial fails to distinguish among cancers with distinct molecular mechanisms. Drugs developed for one purpose (related or unrelated to cancer) may never be tested against specific cancer types because it is not recognized that the cellular
target of the drug is deranged in that cancer type. Patients may receive therapy that is ineffective against their tumor-type rather than a targeted therapy that would be more effective, resulting in unnecessary morbidity.

More generally, drug development is currently impeded because it is difficult to identify the full range of molecular targets for potential cancer treatment. Without the ability to select molecular targets and patient populations in a rational manner, the cancer community has witnessed little progress in the development of novel drug candidates.

In addition, the heterogeneity of cancer limits the power of current epidemiological studies that aim to associate population-based factors (environmental and genetic) with cancer risk. Such studies will be enhanced if patients are correctly classified into more homogeneous groups according to their clinical characteristics and underlying molecular pathophysiology.

Systematic understanding of the genetic basis of all cancers would have a transforming effect on the study and treatment of cancer. It would resolve cancer into sets of more homogeneous sub-classes and identify the full range of molecular targets for intervention within the cancer cell.

Achieving this ambitious goal is now within reach as a result of several important developments. First, the Human Genome Project (HGP) provided the basic foundation by providing a roadmap of the normal human genome. Second, various genome-scale technologies have been developed that allow analysis of cancer genomes at high-throughput and increasingly affordable cost. Third, various pilot projects have demonstrated the power of such information by unveiling specific genetic alterations that have led to immediate clinical application. These developments lead us to conclude that there is no fundamental conceptual barrier to achieving a comprehensive understanding of the genetic basis of cancer. There are, however, numerous practical issues to overcome, including the need for focused technology development and improvement, for organized sample collection, and for efficient sample characterization. With appropriate focus and a unified approach, the overall goal could be achieved within a decade.

1.2 Cancer is fundamentally a disease of genomic alteration. Cancer cells typically carry genomic alterations that confer on tumors their distinctive abilities (such as the capacity to proliferate and metastasize, ignoring the normal signals that block cellular growth and migration) and liabilities (such as unique dependence on certain cellular pathways, which potentially render them sensitive to certain treatments that spare normal cells).

By the 1960s, the genetic basis of cancer was clear from cytogenetic studies that showed consistent translocations associated with specific cancers (notably the so-called Philadelphia chromosome in chronic myelogenous leukemia). But, the ability to recognize specific cancer-causing mutations awaited the recombinant DNA revolution of the 1970s. Following the identification of the first vertebrate and human oncogenes and the first tumor suppressor genes, there has been increasing work leading to identification of a number of such genes selectively mutated in human cancers. These discoveries have elucidated the cellular pathways governing processes such as cell-cycle progression, cell-death control, signal transduction, cell migration, protein translation, protein degradation and transcription.

At the same time, the scientific progress has underscored that we still understand only a fraction of the genes that play a crucial role in causing cancer. Cancer is a multi-step disease process, with experimental and epidemiological data in humans and model systems suggesting that the development of a cancer involves perhaps a dozen critical steps. Some of the genetic alterations may be inherited, but the vast majority are somatically acquired during progression from a normal cell to a cancer cell. For no human cancer do we have a comprehensive understanding of the events required.
1.3 Understanding of the genetic basis of cancer has the capacity to transform clinical treatment. Although scientific progress has been rapid, translation into clinical benefit has not been immediate. It will take time to develop effective strategies to exploit knowledge of the cancer genome. After a slow start, there has been an explosion in sophisticated efforts to exploit genomic alterations in the understanding, accurate diagnosis and safe and effective treatment of cancer. We briefly review some notable recent successes in which genomic understanding has led to important progress in clinical treatment through the development of therapeutic interventions or the identification of high-risk patients to receive intensive screening.

**Chronic myelogenous leukemia (CML): The BCR-ABL translocation and imatinib (Gleevec™).** Molecular and biochemical studies elucidated the function of the fusion protein product BCR-ABL encoded by the Philadelphia chromosome. Specifically, these studies convincingly demonstrated that the transforming capacity of this unique oncogene was directly linked to its biochemical activity as a kinase and provided the rationale and impetus for the development of selective kinase inhibitors against this protein. The molecule imatinib (Gleevec™) is a selective inhibitor of Abl, PDGFR and Kit kinases and has proven remarkably efficacious in the treatment of chronic phase CML. More generally, these findings demonstrated that kinase inhibitors were well-tolerated, contrary to initial concerns that such drugs would have dire toxicities. It is worth noting that the efficacy of imatinib was already clear in Phase I trials and FDA approval came after Phase II trials that demonstrated overwhelming clinical benefit in this genetically homogenous disease.

**Gastrointestinal stromal tumors: c-Kit and PDGFR mutation and imatinib (Gleevec™).** Gastrointestinal stromal tumor is an uncommon sarcoma poorly defined by histopathology. Recently, such tumors have been found to have mutations leading to activation of c-Kit or PDGFR. These findings led to the discovery that this type of tumor, when defined based on genetic alterations, is more common than previously recognized. It also suggested that imatinib might be efficacious against gastrointestinal stromal tumors, a prediction that has been dramatically confirmed by clinical trials.

**Several other cancers also respond to imatinib (Gleevec™).** Three other cancer types have recently been shown to harbor genetic alterations leading to the constitutive activation of PDGFR signaling that is the target of imatinib. Hypereosinophilic syndrome and chronic eosinophilic leukemia are characterized by a FIP1L1-PDGFR-alpha translocation leading to constitutive kinase activation. Dermatofibrosarcoma protuberans is characterized by a translocation between the COL1A1 gene and the gene encoding the ligand PDFGB, leading to an autocrine activation of PDFGR. In addition, some acute lymphoblastic leukemias (ALL) harbor the BCR-ABL translocation. For each of these diseases, imatinib has shown clinical activity that is often dramatic. In each case, there is a strong correlation between the genetic lesion and the effective therapeutic.

**Breast cancer: Her2 amplification and trastuzumab (Herceptin™).** In 1987 it became clear that the ErbB2 oncogene is amplified in 25–30% of breast carcinomas and that such amplification correlates with a poorer outcome. This finding, coupled with the discovery that ErbB2 encodes a transmembrane receptor tyrosine kinase, gave rise to the development of therapeutic strategies based on neutralizing antibodies directed against the extra-cellular domain of the ErbB2. In patients whose tumors harbor amplification of the gene, these antibodies (trastuzumab) exert significant clinical activity. Notably, there is emerging data that the best predictor of therapeutic benefit is the presence of a genetic alterations of the gene rather than increased RNA or protein expression.

**Lung adenocarcinoma: EGFR mutation and gefitinib (Iressa™)/erlotinib (Tarceva™).** Systematic studies of tumors in lung cancer patients revealed that ~5–10% of lung adenocarcinomas from patients of European ancestry and 25–30% of lung cancers in Japanese patients harbor activating
mutations in the *EGFR* gene. Strikingly, patients whose tumors carry *EGFR* mutations tend to have dramatic response to the anti-cancer drug gefitinib (Iressa™), an *EGFR* inhibitor that was developed without knowledge of the presence of activating mutations in *EGFR* in lung cancer. By contrast, other patients show little or no response. Importantly, Iressa nearly failed to win FDA approval because randomized clinical trials in hundreds of unselected patients showed no statistically significant survival benefit. Recent clinical trials in unselected patients have shown similar results. It is now clear that these results reflect the drug’s high efficacy in 5–15% of patients being masked by its relative ineffectiveness in the remainder. If the Iressa clinical trials had targeted only patients with *EGFR* mutations, it would likely have been possible to demonstrate dramatic efficacy in small Phase II trials with perhaps 50 patients (much as occurred for imatinib with CML). Thus, genetic selection strategies provide a mechanism for greatly decreasing the cost and accelerating the speed of such trials.

**Genetic insights are driving additional clinical drug development.** Clinical trials are currently underway with many additional novel therapeutic agents directed against targets identified through their genomic lesions in cancer. Examples include inhibitors of the serine-threonine kinase encoded by the *B-RAF* gene, found to be mutated in 80% of melanomas; inhibitors of the receptor tyrosine kinase encoded by the *FLT3* gene, found to be mutated in 25% of patients with acute myelocytic leukemia; and inhibitors of downstream components suppressed by the product of the *VHL* gene, which was found to be mutated in renal cell carcinoma. The early results of these trials are encouraging. Additional efforts are at earlier stages. In addition, striking new discoveries of mutations in cancer suggest further opportunities for drug development, such as the recent finding of mutations or amplification of phosphatidyl-inosital kinases in many epithelial and glial tumors and frequent mutations in the *Notch* gene in acute T cell leukemia.

The examples above demonstrate the importance of understanding the genomic lesions underlying cancers. Specifically, these include:

- **Identification of the cellular pathways that underlie cancer:** From a fundamental standpoint, identification of genomic lesions underlying cancer has proven to be one of the most powerful ways to understand signaling and other pathways that are present in normal cells and that go awry in cancer. The understanding of these pathways has consistently proven essential for the development of strategies to treat cancer. The identification of genes mutated in cancer is thus important, even for genes that are not themselves good therapeutic targets.

- **Improved selection of therapeutic targets.** In an increasing number of cases, the identification of the genomic lesions in cancer has revealed cellular pathways on which a tumor has become critically dependent. Because these represent unique properties of cancer cells, they provide excellent potential targets for therapy. (It should be noted that some of the genes mutated in cancer may represent functions that were important to tumorigenesis but are not essential to continued tumor maintenance. Biological knowledge of pathways and functional studies with such tools as RNAi can help identify the best point of therapeutic intervention.)

- **Faster and more efficient clinical trials.** By selecting patients who are most likely to respond to a drug’s mechanism of action (based on the mutations in the tumor), it should be possible to obtain indications of efficacy with a smaller number of patients (potentially even in Phase II rather than Phase III trials). This is important because it would make best use of the precious resource of patients participating in clinical trials. In addition, it would decrease the costs of clinical trials and correspondingly increase the number of trials that can be undertaken with fixed financial resources. Once a drug has been approved, the ability to identify patients most likely to respond will clearly be of great benefit to patients, physicians and payors.
• **Improved applications of drugs.** Identification of the molecular mechanisms in specific cancers may allow the extension of existing therapies to additional cancers, the understanding of drug interactions, and the rational development of combination therapies.

• **Resolution of cancer into more homogeneous groups.** Based on knowledge of underlying molecular mechanisms, patients can be differentiated into more appropriate subgroups for study and treatment. This will aid in understanding epidemiological risk factors and treatment responses.

• **Identification of markers for early detection.** Knowledge of the somatic genetic alterations that are commonly found in cancers provides targets for early detection strategies, based on analysis of DNA and protein in serum, urine and fecal samples.

1.4 Understanding inherited genomic variation has led to identification of patients at high risk. In addition to propelling therapeutic development, knowledge of the genetic basis of cancer has affected clinical practice by identifying patients at high risk and directing them to more intensive screening programs or other interventions. Some examples include the following:

   **Breast and ovarian cancer:** *BRCA1* and *BRCA2*. At least 10% of breast cancer is thought to be familial and the analysis of large families with highly penetrant hereditary breast and ovarian cancers has led to the identification of two susceptibility genes: *BRCA1* and *BRCA2*. Carriers of germline mutations in these genes are at very high risk for early onset breast cancer. The discovery of these genes has allowed the reliable determination of carrier status, the implementation of aggressive screening strategies in affected pre-symptomatic individuals, and the clinical testing of prevention strategies based on anti-estrogen and other therapies.

   **Colorectal cancer:** *HNPCC* and *FAP*. Familial predisposition to colorectal cancer is either associated or unassociated with polyposis. Familial adenomatous polyposis is a disorder related to mutations in the *APC* gene, a critical regulator of β-catenin. Hereditary non-polyposis colon cancer arises as a result of mutations in the genes encoding mismatch repair proteins. Carriers of both disorders can now be detected early, offered aggressive screening, and, if needed, prophylactic colectomy (in the case of *APC*). In addition, considerable effort is now being made to identify dietary, life-style and environmental risks that predispose to cancer. For example, epidemiologic data strongly suggests that dietary or supplemental folate suppresses the risk of colon cancer in individuals with a family history of the disease. This example also highlights an example in which a lifestyle or dietary factor may influence a subset of cancers rather than cancers as a whole.

   **Genetic variants with lower penetrance.** Familial correlation in cancer is much higher than can be explained by known high-penetrance cancer syndromes. For example, there is evidence that most of the breast cancer risk is carried by only a subset of the population. Studies are underway to evaluate common genetic variants that modulate risk, such as those involved in hormone metabolism in breast, ovarian, endometrial and prostate cancer, folate synthesis and metabolism genes in colon cancer, and so on. Systematic knowledge of the somatic changes in tumors may reveal specific genes and general pathways that should be evaluated in subsequent studies of individual risk.

2. **Scientific Foundation for a Human Cancer Genome Project**

   Notwithstanding the encouraging progress described above, our knowledge of the genomic alterations underlying cancer remains only fragmentary. It has been the result of a largely piecemeal approach involving many individual studies, typically focused on individual genes or cancers.
Recently, pilot projects have begun to explore systematic approaches to discovering the genomic alterations underlying cancer. Such studies have only just become possible with the recent availability of an essentially complete sequence of the human genome (in rough draft form in mid-2000 and in “finished” form in mid-2003).

The results of these recent pilot projects on systematic analysis of cancer genomes make clear that there is still a great deal of important information that remains to be discovered.

- **Genomic loss and amplification.** High-resolution genome-wide studies of genomic loss and amplification have begun to be undertaken in the last 5 years using a variety of technologies. These studies show that specific cancer types typically show consistent association with genomic loss or amplification in many specific regions, indicating that these regions harbor key cancer-associated genes. **Importantly, the vast majority of cancer-associated genes underlying these consistent genomic losses and amplifications remain unknown.**

- **Gene resequencing.** Knowledge of the human genome has enabled resequencing of candidate genes through PCR-based approaches. Several groups have begun to systematically study specific gene classes (such as kinases and phosphatases) in particular cancer types. Already, these systematic efforts have led to discoveries with major clinical implications, including the presence of mutations in \textit{B-RAF} in melanoma, \textit{PI3K} in colorectal cancer, and \textit{EGFR} in lung adenocarcinoma. Although these efforts are still small compared with the magnitude of the need, they clearly indicate that it is likely that the \textit{vast majority of cancer-associated genes that are consistently mutated in specific cancer types remain unknown.}

- **Chromosome rearrangements.** Chromosome rearrangements frequently underlie crucial events in tumorigenesis, sometimes by activating kinase pathways through fusion proteins or inactivating differentiation programs through gene disruption. They have been extensively studied in hematological malignancies, where there can be a single stereotypical translocation in some diseases (such as CML) and as many as 20 important translocations in others (such as AML). Adult solid tumors have not been as well characterized, in part owing to technical hurdles. It is clear that many of the key chromosomal rearrangements have yet to be identified and most of those that have been identified have yet to be characterized at the molecular level.

- **Epigenetic changes.** It is becoming clear that loss of function of tumor suppressor genes can occur by epigenetic modification of the genome, such as DNA methylation and histone modification. Although the effect has been demonstrated in a number of cases, technology to monitor epigenetic changes is still quite new. **The range of important epigenetic changes in cancer thus remains largely unexplored.**

In summary, deep and broad discovery efforts are still needed to systematically identify the genomic lesions underlying cancer and thereby to dissect much of the heterogeneity of the disease.

It is now time to launch a systematic program to gain a comprehensive description of the genomic alterations underlying cancer. Such an effort would provide the most important and most general foundation for basic, clinical and commercial work in cancer in the future.

A Human Cancer Genome Project would be a natural successor to the Human Genome Project, which ran from 1990–2003. Indeed, one of the central reasons for sequencing the human genome was the goal of understanding cancer. In 1986, Renato Dulbecco published an influential article in \textit{Science} entitled “A Turning Point in Cancer Research: Sequencing the Human Genome”. Writing at a time when only a small proportion of all human genes were known, he stated: “We have two options: either try to discover the genes important in malignancy by a piecemeal approach, or to sequence the whole genome of selected
animal species [including the human]”. He strongly advocated the latter systematic approach. Based on this and other calls, the HGP was eventually formulated and launched.

The program described in Dulbecco’s article has now been completed in the sense that the sequencing of the human genome by the HGP has led to the discovery of essentially all human genes. It is no longer necessary for cancer researchers to devote huge amounts of time and effort to the discovery of human genes per se. This basic knowledge has greatly accelerated cancer research.

But, the program remains incomplete in the sense that we still do not know which genomic alterations play key roles in cancer. This will require studying the human genome in many tumor samples in order to identify those alterations that are significantly associated with each major type of cancer.

Dulbecco’s question remains pertinent: Should the biomedical community accomplish this program through a piecemeal approach or through a systematic approach? We believe that a systematic approach will dramatically accelerate cancer research and treatment.

A systematic approach is appropriate for two reasons:

- The problem is reasonably well defined. It is possible to define a concrete goal that would provide a powerful and permanent foundation for future cancer research.
- The problem involves scalable work. It would be accomplished more cost effectively and more rapidly by mounting an organized project than through piecemeal efforts.

In both respects, the problem shares some similarities with the HGP.

3. Goals of a Human Cancer Genome Project

The general goal for a Human Cancer Genome Project could be stated as follows:

**Identify all genomic alterations significantly associated with all major cancer types.**

Achieving this goal will require:

i) creating a large collection of appropriate, clinically annotated samples from all major types of cancer; and

ii) completely characterizing each sample in terms of:

- all regions of genomic loss or amplification,
- all mutations in the coding regions of all human genes,
- all chromosomal rearrangements,
- all regions of aberrant methylation, and
- complete gene expression profile, as well as other appropriate technologies.

Such knowledge will propel work by thousands of investigators in cancer biology, epidemiology, diagnostics and therapeutics.

Various issues need to be considered to convert this general goal into a feasible project. They include definition of the genomic alterations to be considered (e.g., somatic vs. inherited); specification of the threshold for significant association with cancer (e.g., occurring at a frequency of 5%); identification of the types of cancer to be studied; and assessment of currently available and expected technology. We consider such issues in the next section.

4. Scientific Issues in Designing a Human Cancer Genome Project

The Working Group on Biomedical Technology explored the scientific issues in designing a Human Cancer Genome Project. The analysis drew upon input from a focus group on “Characterization of Cancer in the Cell” and a workshop on “Exploring Cancer through Genomic Sequence Comparison” sponsored
jointly by the NCI and the National Human Genome Research Institute (NHGRI) that brought together ~50 scientists for a two-day meeting in April 2004. The working group also benefited from discussions with various knowledgeable individuals.

The discussion below is intended to serve as a starting point. We recognize that the issues should be carefully re-examined in the course of planning and throughout a HCGP.

The following major issues are addressed: identification of genes that are frequent sites of somatic genomic alteration in tumors; identification of inherited genomic variants often found in cancer; the types of cancers to be studied; technologies for genome analysis; and the process of sample acquisition.

4.1 Identifying the sites of somatic genomic alteration. Somatic genomic alterations underlie the initiation and progression of cancer. These somatic changes in the tumor genome can alter the underlying DNA sequence in various ways, including point mutations (nucleotide substitution and small deletions/insertions); larger-scale loss and amplification (affecting regions in the range of 1 kb to 1 Mb); and chromosomal translocations and other rearrangement. Tumor genomes may also harbor aberrant methylation, which may silence or activate genes. Such abnormal methylation is formally an “epigenetic” change, but will be included here as a genomic alteration.

In principle, it is straightforward to identify all of the somatic alterations present in a tumor genome. One need only compare it with normal genome from non-tumor tissue from the same individual. Genomic differences between tumor and matched normal tissue necessarily represent somatic mutations. Rare genomic variants found in both the tumor and matched normal tissue represent novel polymorphisms, which may be informative for epidemiological studies. (It should be noted that epigenetic alterations may be harder to detect, because normal tissue may not serve as an adequate control.)

Identifying the subset of genomic alterations that are functionally important to the cancer is somewhat more complex. Some of the genomic alterations will be responsible for the initiation and progression of the cancer through the loss or gain of important cellular functions. However, most of the genomic alterations will simply reflect the high background rate of random mutation that occurs in tumors.

Recent studies suggest that tumor genomes may have a typical nucleotide substitution rate in the range of \(~1–2\) nucleotide substitution per Mb\(^1\) relative to the normal somatic genome. This corresponds to a total of \(~10,000\) mutations in a tumor genome. Of these, one would expect more than \(100\) that alter an amino acid in protein-coding regions or affect regulatory sites of genes. A typical gene might thus be mutated in perhaps \(0.5\)% of tumors, but only a minority of these changes will be functionally relevant in the cancer. Recognizing the functionally important genomic alterations thus requires overcoming this background noise. This can be accomplished by statistical analysis — that is, by examining a sufficient number of tumors to reliably detect changes that occur at a frequency significantly above the background noise.

Important functional changes will not be expected to occur in \(100\)% of tumors of a given type, but rather only in a subset. For example, mutations in the \(EGFR\) gene occur in \(~5–10\)% of lung cancers but play a crucial role in determining patient response to gefitinib. Similarly, amplification of the \(Her2\) gene is present in \(25\)% of ductal breast adenocarcinomas but is a key determinant of response to Herceptin.

Comprehensive identification of genomic alterations underlying cancer will thus require examining a substantial collection of tumors of each type to identify genomic alterations that occur at a significantly higher rate than the background mutation rate.

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\(^{1}\) The mutation rate is likely to vary among tumor types, especially those with different types of genomic instability.

\(^{2}\) Identification of functionally important genomic alterations may also be greatly aided by improved bioinformatics approaches to interpret the likely consequences of specific changes in nucleotide and protein sequences.
We propose the following threshold at least for planning purposes: **For each important cancer type, identify all genes in which the total frequency of genomic alterations exceeds 5%**.

How large a sample collection of tumors of a given type is required to detect all genes having genomic alterations in at least 5% of cases? A simple statistical analysis indicates that **a collection of ~250 tumors of any given cancer type should suffice**. Such a collection should be feasible for all important cancer types, making it possible to analyze each type individually. Moreover, additional power can be gained by searching for genomic alterations seen in multiple cancer types.

It should be emphasized that the evaluation of the genes that emerge from such analysis will need to draw on extensive biological insights gained from ongoing and future research. These will be needed to infer the likely mechanism of action of the genes, which will be crucial for clinical application. In addition, it will be valuable in assessing the importance of the less frequently occurring alterations.

**4.2 Issues in identification of inherited risk factors**. In addition to somatic mutations, inherited variation also plays an important role in cancer. The discovery of germline variants that influence cancer risk is currently the subject of intense research, building on i) family-based and population-based clinical collections of patients with cancer, ii) catalogs of the human genome sequence and its common variation in the population (SNP maps and haplotype maps), iii) rapidly improving technologies for detecting genotyping of SNPs in large patient samples, and iv) an emerging suite of analytic methods drawn from epidemiology, population and statistical genetics. These methods should make it practical in the coming years to comprehensively test common genetic variation in large patient samples, and they hold substantial promise to elucidate inherited risk factors that can be used to predict individual risk of cancer, direct screening paradigms, and most importantly, discover causal pathways that can then be targeted for prevention and therapy.

A Human Cancer Genome Project, as currently conceived, would not be designed to comprehensively identify all inherited risk factors for cancer. Rather, large epidemiological studies are required to detect variants that confer increased risk (for example, an allele present in 10% of people that increases risk by 10%). Such epidemiological studies exist in some cases and others are being planned. Nonetheless, a HCGP will contribute to such ongoing activity in a number of powerful and important ways.

First and most fundamentally, by illuminating causal pathways in cancer a HCGP will provide a framework for designing and interpreting future studies that aim to understand the inheritance of cancer. Pathways found to be causal in somatic studies would be targets for more intense study as candidate genes in population-based association studies. Even when technology allows association studies to expand beyond candidate genes to a whole-genome search, knowledge of cancer pathways will continue to be of great value for interpreting association data. It will inform both the statistical analysis (in terms of prior probabilities of association) and the biological analysis of potential risk factors.

Second, the current efforts in genetic epidemiology are largely focused on *common* genetic variants, with catalogs of such variants becoming increasingly complete and technologies for large-scale genotyping being developed. However, it is also important to consider the role of germline variants that are rare in the general population. By identifying the genetic variations (both somatic and germline) in

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3 Suppose that we wish to find the genes with genomic alterations in at least 5% of tumors of a given type in the presence of random genomic alterations occurring at a background rate of 0.5%. By studying \(N=250\) tumors, one can statistically expect to identify ~94% of all true-positive genes while having <1 false-positive signal out of 20,000 genes tested.

This is intended only as a simple analysis to indicate the approximate range needed to achieve high sensitivity and specificity. More sophisticated analyses should be performed; for example, to consider potential variation in mutation rate across tumor types, variation in mutation rates across genes, ways to use information about mutation types (such non-synonymous vs. synonymous changes), and so on.
tumors, we will obtain information about the aggregate frequency of rare inherited variants in each gene in cancer patients. With such information, it will be possible to test the frequency of such rare changes in cancer cases and controls by genotyping or resequencing in appropriately designed family and population-based studies.

Third, epidemiological studies are hampered by the heterogeneity of cancer. When multiple types of cancer are lumped together, the power to detect risk factors affecting one type is greatly diminished. As a HCGP allows scientists to classify tumors into more homogeneous groups based on underlying molecular pathophysiology, this knowledge can be applied to epidemiological studies.

**4.3 Cancers to be studied.** Defining the cancer types to be included in a HCGP is a complex question. Ideally, “cancer types” would correspond to biologically homogeneous groups. Unfortunately, no such taxonomy is available at present. Ultimately, the HCGP will greatly aid in clarifying the types of cancer. In the meanwhile, though, we must rely on available classifications.

**4.3.1 Human cancers.** Table 1 lists 34 major cancer types having combined incidence of ~1.4 million in the United States (with the individual types ranging from 230,000 to 1,500). Most of these clinical types can be further divided on the basis of histopathological or molecular properties into important subtypes; a few examples of subtypes are listed in Table 2. Although the precise definition of cancer types to be collected and analyzed by a Human Genome Cancer Project will need to be carefully considered, Table 1 provides a reasonable starting point. This suggests that the number of relevant cancer types may be in the range of ~50. Assuming ~250 samples of each type, this would imply an overall collection of ~12,500 samples.

For at least some of the cancers, it may be possible to make collections of both primary tumors and metastases. This would enable study of the characteristic genomic lesions associated with metastasis.

**4.3.2 Cell lines.** In addition to tumor samples from patients, it would also be important to include samples from cancer cell lines. Cancer cell lines are a key resource because they allow reproducible studies on the properties of cancer cells, including the derangement of cellular pathways, response to chemical and biological modulators and behavior in xenograft models. Although cancer cell lines are not perfectly representative of patient tumors (because they have undergone additional mutations ex vivo), studies have shown that most of the clonal alterations observed in such cell lines are also present in uncultured cells. Understanding the genomic alterations in widely available cancer cell lines would be an invaluable asset in the study of cancer.

The precise number of human cell lines to be included within a HCGP needs to be carefully considered. For planning purposes, we have estimated that it might be appropriate to include ~1,000 such cell lines.

**4.3.3 Mouse and other model systems.** We also believe that genomic analysis should be carried out on key animal models of cancer. The most important are mouse models, for which there are an increasing number of carefully constructed models with precisely defined genetic etiology. Understanding of the cancer genome in these mouse models will greatly assist in relating these powerful models to human cancer and thereby in developing their full potential to assist in the development of human therapies. In addition, there may be value in characterizing samples from larger models that develop spontaneous tumors (for example, dogs) in which therapeutics can be tested.

The precise number of tumor samples from mouse and other models to be included in a HCGP should be carefully considered. Because tumors from such model systems tend to be more homogeneous than human samples, many fewer samples (perhaps 20–50) should likely need to be analyzed. For planning purposes, we have estimated that it might be appropriate to include a total of ~1,000 samples.

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4.3.4 Total sample collection. Based on the considerations above, we estimate that the full sample collection might contain in the range of ~15,000 samples. Each would be represented by a high-quality well-annotated DNA sample in sufficient quantity to allow ongoing analyses of its genome by multiple groups.

4.4 Technologies for sample preparation and genomic characterization of tumors. Cancer samples would need to be analyzed with multiple technologies over the course of a HCGP, with the ultimate goal of identifying all significant genomic alterations.

Technologies for genome analysis have improved dramatically in terms of power and cost over the past decade, and progress is expected to continue the coming years. We discuss below the current state of technologies that would be required for a HCGP. In many cases, current technology is already adequate to make the project feasible — although further efficiencies would be desirable and appear to be in prospect. In some cases, current technology is not yet adequate to the task and new methods will need to be developed. In both cases, the HCGP itself would serve to propel technology improvement and development. The timing is thus right for the launch of a project.

The discussion below includes estimates of current costs and projection of likely future costs, to provide a baseline for project planning. These are intended to be only approximate.

We consider six technology areas. The first pertains to sample preparation and the remaining five concern genomic analysis.

4.4.1 Whole-genome amplification (WGA). It would be desirable to have effectively unlimited quantities of genomic DNA from each tumor sample. This would allow each sample to undergo many analyses by many groups over the course of a project. With the development of “whole-genome amplification” (WGA) methods, this increasingly appears to be feasible. Recent analyses indicate that WGA appears to yield an amplification of at least 5,000-fold, while maintaining a high degree of fidelity in terms of sequence accuracy and relative allelic representation. (Such results will, of course, need to be broadly confirmed.) With such techniques, it should be feasible to collect typical quantities of high-quality tumor samples and produce enough material to permit many analyses. (N.B. Current versions of WGA are not applicable to the study of epigenetic changes.)

4.4.2 Whole-genome loss and amplification analysis (WG-LAA). Various high-throughput and high-resolution techniques have been recently developed that make it possible to survey the entire genome to identify all regions of loss-of-heterozygosity and of amplification. One of the first techniques was array-CGH (in which tumor and normal DNA are hybridized to an array of large-insert clones). The most cost-efficient current techniques are array-based methods, known as Representational Oligonucleotide Analysis (ROMA) and Single Nucleotide Polymorphism genotyping (SNP-Chips). These can simultaneously assay loss and amplification at genomic locations at a density sufficient to detect deletions and loss-of-heterozygosity within the typical size range of a single gene. Future generations of these technologies should provide even greater resolution.

Such techniques could be used to identify those regions that are consistently lost or amplified in each type of cancer. These regions would be expected to harbor a gene (or genes) that is mutated in and plays an important role in cancer, which could subsequently be identified by gene resequencing (see below). Moreover, the pattern of loss and amplification would immediately help classify subtypes of the cancer.

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4 The costs are “fully loaded”, in that they reflect labor, reagents, equipment amortization and indirect costs. They assume a relatively high sample throughput, to allow efficient operation and full amortization of fixed costs. The costs, however, do not include sample acquisition or data analysis. The cost estimates were based on information from various laboratories, centers and manufacturers.
The current estimated cost of WG-LAA is ~$3,000–5,000 per tumor sample. Based on ongoing technology development, it is likely that these costs will fall by at least 5-fold in the coming 5 years.

**4.4.3 Chromosome rearrangement analysis.** Larger chromosomal rearrangements, such as translocations, can play an important role in the initiation and progression of cancer. A well-known example is the t(9;22) translocation that results in the BCR-ABL fusion gene in CML.

Technologies are available for systematic detection and precise genomic characterization of all chromosome rearrangements, but they are not well suited to the throughput and scale of a HCGP. Chromosomal rearrangements can be detected by multi-color fluorescent hybridization, but this technique requires whole-cell preparations (rather than just genomic DNA) and has relatively low resolution. In principle, chromosomal rearrangements can be detected by shotgun sequencing of paired ends from large DNA fragments prepared from a tumor, but this procedure is currently too costly for large-scale application (although this may well change with new sequencing technologies). It may be possible to develop effective techniques that do not require whole-cell preparation can be developed, but this will require focused efforts. It is thus not yet possible to give meaningful cost estimates.

**4.4.4 Large-scale resequencing of genes.** High-throughput resequencing of genes is becoming increasingly efficient. Exons can be readily amplified with flanking PCR primers, subjected to fluorescent dideoxy-sequencing and analyzed to identify mutations.

In the initial phases of a HCGP, we envisage two types of systematic resequencing efforts. 1) Genes whose function implicates them as potential targets for cancer-related mutations, including kinases, phosphatases, G-protein coupled receptors, transcription factors, non-tyrosine-kinase receptors, proteases, and others. A list of 1,000–2,000 high-priority candidates could be readily generated based on the known biology of cancer, to be resequenced in all cancers. 2) Genes across regions identified as lost or amplified in specific cancer types. Experience to date suggests that genes that are deleted or amplified in some human tumor samples are often a target for point mutation or epigenetic changes in other tumors. These genes would be resequenced in the cancer types that show consistent loss or amplification.

As sequencing technology continues to improve and costs fall, it should become possible to resequence all human genes in all samples. This would eliminate the bias of selecting specific sets of genes. (In the further future, it may someday become practical to resequence the entire genome of each sample. However, the launch of a HCGP should not wait for such advances in technology.)

The cost of resequencing is rapidly changing. At present, we estimate that the cost\(^5\) to resequence ~2,000 genes in a tumor sample would be less than $75,000. Various technologies are currently in development (involving single-molecule sequencing or related techniques) that seem likely to afford at least a 10-fold reduction within the next 5 years. This would make it possible to include all ~22,000 human genes at roughly the same cost.

**4.4.5 Genomic methylation analysis.** Efficient, high-throughput methods for the analysis of epigenetic changes are not yet broadly available, although there are growing efforts toward this goal. It is likely that the ROMA technique (applied with methylation-sensitive restriction enzymes) and new sequencing technologies (applied to bisulfite-treated DNA) will aid in this goal. Focused efforts will be required and it is not yet meaningful to estimate costs.

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\(^5\) This estimate assumes an average of ~10 exons per gene, double-stranded sequencing, and realistic failure rates. It does not include the cost of sequencing all of the genes in paired normal tissue; candidate mutations would thus need to be followed-up by targeted resequencing testing in normal tissue.
4.4.6 Genome-wide RNA expression analysis. The tumors collected and analyzed by a HCGP will be a crucial resource for understanding human cancer. Ideally, they should thus be characterized with additional genomic tools that would provide important information to elucidate the tumors’ biology.

RNA expression analysis is a particularly powerful approach that provides a near-complete picture of the genes active in the cell. This can provide valuable complementary information about the pathways activated and inactivated in tumors. RNA expression analysis has already been widely applied to cancer samples and has provided important insights, including revealing subtypes of cancer. Progress has been limited, however, by the lack of standardized methods and controls that would allow complete integration of RNA expression information produced in diverse laboratories (as, for example, can be readily done for DNA sequence information). Within a HCGP, close attention must be given to such standardization.

The current cost of comprehensive RNA expression analysis is in the range of ~$2,000 per tumor sample. Based on ongoing technology development, it is likely that these costs will fall by at least 5-fold in the coming 5 years.

4.4.7 Other technologies. It may be desirable to include additional methods for characterization of tumors (for example, proteomics), as they become available and affordable. These options should be considered on an ongoing basis by the project.

4.4.8 Technology summary. The discussion above indicates that it is already possible to perform extensive analysis of tumor genomes (including whole-genome loss and amplification analysis, systematic resequencing of 2,000 genes and expression analysis) at a fully loaded cost of less than $100,000 per sample. With reasonable assumptions about technology improvement and development over the next 5 years, it seems likely that comprehensive tumor analysis (including systematic analysis of all human genes, chromosomal rearrangement analysis and epigenetic analysis) will become feasible at roughly the same cost.

Assuming a comprehensive collection of ~15,000 samples, this would correspond to a total of ~$1.5B over perhaps a 10-year period to obtain comprehensive knowledge of the genetic basis of cancer. To put this in perspective, this would represent ~0.5% of the overall NIH budget.

4.5 Sample acquisition. The second critical component of a HCGP is the acquisition of suitable tumor samples to be analyzed.

4.5.1 Considerations in selecting samples. There are a number of important considerations in selecting samples:

Patient consent. It is essential that appropriate patient consent be obtained to allow multiple laboratories to perform comprehensive tests for genomic information from the tumor, to place the results (with usual identifiers removed) in a shared database for further analysis, and to report the results publicly. To the extent possible under HIPAA rules, NCI should develop uniform model consent forms that can be applied across institutions to meet these requirements for optimally effective use of the data.

Clinical annotation. The tumors to be analyzed should ideally be accompanied by detailed clinical information (including family history, medical history, onset and course of illness, nature and time of medical, surgical, and radiological treatments, responses to therapy, and outcome of disease) while being stripped of conventional identifying information (name, address, social security numbers and other unambiguous identifiers). Conditions for updating of information about living patients should be established.

Sample quality. The tumor samples to be analyzed should be of high quality. Multiple sections should be carefully evaluated by at least two certified pathologists, ideally including one who serves as coordinator for all samples of each tumor type. The pathological evaluation should include, at a
minimum, an estimate of the fraction of each sample composed of tumor cells, stromal cells, inflammatory cells, and vasculature. Especially in the cases of tissues or organs that give rise to multiple histological types of cancers, tests for appropriate developmental and differentiation markers should be conducted. In general, samples stored as paraffin blocks are unlikely to provide material of sufficient quality and quantity to permit a full range of analyses. Preference should be given to samples that have been quickly frozen after removal from the patient during surgery.

**Sample quantity.** Samples of adequate size will be required in order to permit enough material for the required genomic tests. Standards for the minimum amount of tissue to be collected will depend on the type of tumor, purity of the cell population in the tumor, and incidence of the tumor type (to meet the required number of tumors of each type to be analyzed in this project).

**Availability of matched normal DNA.** Samples of normal DNA (from blood samples, buccal smears, or normal tissue obtained at surgery) should be available from all patients whose tumors will be analyzed, so that it is possible to distinguish whether genomic variants are somatic mutations or newly discovered germline polymorphisms. This aspect of the study needs to be mentioned in the consent forms for the study, recognizing that germ-line mutations predisposing to cancer may occasionally be found and might be clinically important to cancer risk for the patients or their relatives.

**Ethnic diversity.** The tumors should ideally be selected to include representative samples from ethnically diverse populations. This may require focused sampling efforts to boost the number of cases from particular ethnic groups.

### 4.5.2 Logistics of sample collection

Sample collection should be coordinated by appropriate Cancer Sample Acquisition Centers.

In most cases, it will be necessary to collect new tissue samples that meet the requirements above. It will be necessary to establish guidelines for i) the protocols for collection, storage and DNA preparation to ensure uniformly high quality, ii) the clinical information to be obtained, and iii) the patient consent to be obtained. Such guidelines will need to be established in collaboration with knowledgeable physicians and scientists. The guidelines should be enforced by careful oversight of centers, with continued funding dependent on proper adherence. Such coordination will be particularly important because sample acquisition for many cancers may require multi-institutional efforts. Given the importance of patient consents, NCI will likely want to ensure that proposed Cancer Sample Acquisition Centers resolve key IRB issues before the commencement of funding.

In some cases, it may be possible to use existing clinical collections of tumor samples that have been systematically collected with both contemporaneous clinical annotation and subsequent patient outcome data. The availability of such patient outcome data would be advantageous, because it may immediately shed light on the prognostic power of genomic lesions identified. Such existing tumor collections will need to be carefully evaluated, however, to be sure that appropriate patient consent has been granted, that the tumors samples are of a suitable uniform standard and that the data derived can be made available without restriction to the entire scientific community.

DNA extracted from tumors will need to be distributed to project researchers under uniform access and distribution policies. This will likely require amplifying the genomic DNA by appropriate methods that ensure faithful representation of the genome. (It may also be possible to establish cell lines in some cases, but research would be required to determine whether such lines faithfully represent the genome.) It will need to be decided whether DNA distribution should be centralized. In any case, an ultimate repository of the DNA samples will be required. Because the Cancer Sample Acquisition Centers should not exist in perpetuity, long-term storage centers to house the primary DNA samples and the representations of the DNA will also need to be established.
4.6 Informatics. Medical informatics and bioinformatics will play a crucial role in a HCGP. There will be needs for:

- systems to manage collection, integration, storage and dissemination of samples and associated clinical data;
- systems to manage collection, integration, storage and dissemination of genomic information from the samples;
- new analytical tools to integrate and interpret experimental data about genomic alterations (including processing of raw data for statistical analysis and association of mutations with cancer types and clinical outcomes); and
- national database(s) to make the primary information and the scientific results broadly available to the biomedical community.

Informatics support will likely be needed in at least three forms: individual investigator grants to develop new analytical methods; components of center grants to develop and maintain production informatics systems; and national databases. In all case the support should be allocated based on competitive peer review.

5. Experience from the Human Genome Project

In planning a Human Cancer Genome Project, it may be useful to briefly consider the recent experience of the Human Genome Project.

One of the most important lessons is: **it is important to have a clear goal at the outset, but the operational definition of the goal, costs and timeline will likely need to be continually refined over the course of the project.** In the HGP, the degree of completeness and accuracy that could be achieved was not known in advance and only a rough estimate of the projected costs and timeline could be made. Some degree of ambiguity and uncertainty were tolerated, in order to take advantage of rapid technological change.

Other key lessons are:

- a program to achieve a focused goal should nonetheless include diverse scientific activities of different types and scales;
- funding should be awarded on the basis of rigorous peer review and should be subject to re-competition on a regular basis;
- rapid release of data before publication can greatly accelerate scientific progress;
- peer review is important for all components of the program;
- public policy issues raised by the science (as done by the ethical, legal and social issues component of the HGP) must be addressed; and
- involvement of multiple U.S. funding agencies and international funding agencies can improve the quality and effectiveness of a project;

Although the HGP is by no means a perfect analogy for the proposed project, these particular observations may well be applicable and are worth considering.

6. Initial Outline for a Human Cancer Genome Project

The working group recognizes that the ultimate design for a Human Genome Cancer Project will require further careful study and should continue to evolve over the course of the project. Here, we offer an initial outline as a starting point for further refinement.
6.1 Project goal. The project goal would be to **obtain a comprehensive description of the genetic basis of human cancer** by identifying all the sites of genomic alterations present at significant frequency in all major types of cancers.

6.2 Operational definition. The operational plan will need to be carefully considered. As discussed above, an initial plan would be to:

- Perform comprehensive genomic analysis of ~15,000 samples (including ~250 tumor samples from each of ~50 major cancer types, together with samples from cancer cell lines and appropriate animal models).
- Identify the comprehensive list of all somatic genomic alterations that occur with a frequency of at least 5% in any of the major cancer types (for which the samples should provide sufficient power).
- Capture information about the inherited genomic variations seen in patient samples, to provide information to be used in subsequent studies of cancer risk.

6.3 Project organization. The Human Genome Cancer Project would be largely carried out through an extramural network consisting of two kinds of centers:

- Cancer Sample Acquisition Centers, with the ability to collect samples from various tumor types with high quality and at appropriate scale.
- Cancer Genome Analysis Centers, with the ability to characterize tumor samples with high quality and at appropriate scale.

We envision a network consisting of multiple centers of each type. The appropriate support mechanism (e.g., grant vs. contract) will need to be considered. We note that the grant mechanisms may offer greater opportunity for innovation, while contract mechanisms may offer tighter accountability (which may be particularly important for sample collection). In either case, centers should be selected through rigorous peer review and funding should be contingent on the accomplishment of milestones. Centers should have sufficient size and stability to be able to efficiently accomplish their missions, but should have no expectation of permanent existence. Although existing NCI cancer centers or NHGRI genome centers may well prove excellent sites for some centers, the competition for centers should be open to any groups without preference.

The Human Genome Cancer Project should also include other mechanisms beyond production centers. These should include:

- Investigator-initiated research grants for the improvement and development of technologies (e.g., methods for characterization of chromosomal rearrangements or genomic methylation) and computational tools for cancer genome analysis, and
- Databases for maintaining information produced by the project.

Finally, a Human Genome Cancer Project should include a component to address ethical, educational, medical and regulatory issues (EEMRI). It is important to ensure that the health care system will be adequately prepared to deal with the changes that will be catalyzed by the project. An EEMRI program would study and (in coordination with other stakeholders, such as FDA) explore mechanisms that prepare patients, physicians, regulators, medical educators, health care agencies, biopharmaceutical companies, insurers and others for the consequences of systematic information about the genetic basis of cancer.

6.4. Data release. The Human Genome Cancer Project should adopt a policy that information about cancer genomes is rapidly released into the public domain without restriction on scientific use. The specific details of the data release policy will need to be worked out and may depend on the precise nature of the data.

The goal of the data release policy should be to protect the public interest in at least two important respects. The data release policy must ensure the protection of patient confidentiality. Also, it should
ensure that companies have freedom-to-operate with respect to the information to maximize commercial progress in clinical diagnostics and therapeutics. (This might involve such steps as having grantees file of statutory invention reports with the Patent and Trademark Office to put information into the public domain, as was done for the SNP Consortium.) Clear data release policies should be incorporated as a condition of each grant award.

6.5 Project management. The Human Cancer Genome Project should be jointly managed as an equal partnership by the National Cancer Institute (NCI) and the National Human Genome Research Institute (NHGRI). Such an arrangement would take advantage of the extraordinary depth of scientific and management expertise in these two sister institutes. Effective joint management will be best accomplished by ensuring that funding flows through both institutes.

In addition, a U.S. HCGP should encourage and cooperate with similarly directed efforts in other countries. Notably, the Wellcome Trust Sanger Institute in Cambridge, England, already has experience in analyzing cancer genomes.

6.6 Project timeline and costs. We believe that most of the ambitious goals of a HCGP could be accomplished within ~10 years of launch, based on current and projected technology.

Although the required project cost cannot be stated with certainty, our best judgment is that a HCGP could be accomplished with an average annual budget of ~$150M. (As discussed above, comprehensive characterization of tumor genomes would cost considerably more at current costs. However, we believe that continued improvements in technology will make it possible to accomplish the goal with this budget.)

The working group strongly believes that the long-term budget for a HCGP must come from increased funds appropriated by Congress, rather than from existing funds in the current NIH budget. Current projections show cuts or sub-inflationary increases in the NIH budget for at least the next several years. Without dedicated funding, a HCGP would require major cuts in existing programs. The working group, however, does support the immediate launch of pilot projects and recognizes that these will need to be funded from existing budgets. The recommended scope of such pilot projects is discussed below.

In relative terms, the projected cost of a HCGP would be modest given its broad impact across cancer research. The proposed average annual cost of ~$150M would correspond to an increase of ~3% in the combined annual budget of NCI and NHGRI. (As discussed below, the cost would begin at a lower level during a pilot phase and then increase to a higher level during full-scale implementation.)

In our judgment, such supplemental funding would seize the opportunity to create a permanent foundation of knowledge to transform the understanding and treatment of cancer. A compelling case can and should be made to Congress and the American people to support this project through the appropriation of new funds.

6.7 Related research. The information generated by a HCGP will propel progress in many areas. It will need to be followed up by studies in cancer biology (e.g., to analyze pathways biochemically or to construct animal models), in cancer epidemiology (e.g., to assess the attributable population risk of particular inherited genetic variants) and, of course, in cancer diagnostics and therapeutics. Although such follow-on studies fall outside the scope of the HCGP itself, they will surely require significant support from NIH sources, industry and public-private cooperation. This need should be incorporated into programmatic planning at NCI.

7. Assessing Success

How should the success of a Human Cancer Genome Project be assessed? In the short term, it will be important to drive the project with clear goals and milestones (such as samples collected, samples analyzed, technologies developed). In the long term, however, the ultimate measure of success must be
the impact on the lives of patients. It is important that the project design be continually optimized to maximize the likelihood and speed of such impact.

For diagnostics and prognostics, the project should aim to propel the development of routine “DNA biopsy” of tumors to supplement the current pathological practice of visual grading of tumors. DNA biopsies should require only a small sample from a patient’s tumor and should add useful prognostic information — including information about which cancers are likely to metastasize and should therefore be treated aggressively and which cancers are likely to respond to particular treatments.

For therapeutics, the project should aim to propel the development of new, targeted treatments that are more effective and less toxic than conventional chemotherapy. When coupled with long-term research on the biochemical pathways in which the discovered cancer genes participate, additional targets for cancer therapy will emerge. A clear picture of the underlying defects of cancer cells will provide a coherent framework for drug development and testing.

These benefits are already beginning to accrue and should accelerate long before the project itself is completed. Partial information about specific subsets of genes and specific cancer types has immediate value in propelling work in diagnostics and therapeutics across industry and academia.

The project should thus be designed to ensure that it bears early fruit. Moreover, it should be periodically reviewed to evaluate its impact on both basic science and clinical medicine.

8. Next Steps
The working group recommends that NCI and NHGRI take the next steps toward launching a Human Cancer Genome Project, even in advance of appropriation of new federal funds. Toward this end, we recommend concrete next steps and sketch an approximate timeline.

8.1 Initiation of management and oversight (2005).

8.1.1 Joint Working Group. A Joint Working Group (JWG) of experienced scientific staff from NCI and NHGRI should be established now to guide and coordinate the role of the funding agencies.

8.1.2 External Scientific Committee. An External Scientific Committee (ESC) should be established as soon as possible, consisting of ~5–8 senior scientific advisors to the HCGP.

The members of the ESC should have experience in implementing large-scale biomedical research projects and should span a broad range of expertise. They should primarily be scientists who use, in their own research, the kind of information that would come from this project.

The ESC would provide advice to program staff about the implementation of the HCGP — including initiation, specific areas of focus, assessment of progress and timing of scale-ups.

It would be advantageous if the ESC membership included at least one member on the National Cancer Advisory Board and at least one member was on the NHGRI Advisory Council.

8.1.3 ESC subgroups. The ESC would promptly establish subgroups to assist in developing the details of the project and provide appropriate input to program staff concerning solicitations for competitive awarding of funds for initial pilot projects. (NIH staff should do the actual preparation and writing of the solicitation.) We envisage four subgroups:

- **Sample selection subgroup.** This subgroup would consider: i) cancer types to be used in pilot phase and source of samples; ii) process for establishment of sample collection centers; and iii) sample types to be used for full project, including human cancers, cell lines and animal models (including decisions about metastases and sources of germline DNA).
• **Genomics subgroup.** This group would consider: i) initial genes to be prioritized in resequencing; ii) use of LOH information to guide selection of regions to be analyzed; and iii) priorities for technology development.

• **Bioinformatics subgroup.** This group would consider: i) storage and public access for project data and ii) data analyses that will be needed and mechanisms for catalyzing such work.

• **Ethical, educational, medical and regulatory issues (EEMRI) subgroup.** This group would consider: i) consent issues involved in carrying out the project and ii) unique intellectual property issues raised by the project.

8.2 Pilot phase (2006–2008). We envisage a pilot phase of ~3 years in duration, to be followed by full-scale production work. This phase would have three important components.

8.2.1 Sample collection. The primary goals of this work would be to provide ~1250 samples from five specific cancer types for the genomic analysis pilots (see below); provide a range of ~500 additional samples from a wider range of cancers for technology development projects (see below); create and validate general procedures for collection, characterization and maintenance of samples; and begin collection of larger sample collections for the full project. Decisions will need to be made about the appropriate mechanism for this solicitation, but it should be flexible enough that sample gathering can change to accommodate the needs of the technological applications, as those are discovered and refined through the life of the project.

**Timeline.** We suggest a solicitation for pilot sample collection centers, to be issued by summer 2005 and funded by February 2006. Initial samples would be collected and ready for distribution by mid-to-late 2006. Some tissue resources already exist and may be suitable for use in the pilot phase.

**Approximate cost.** Total of $3–4M/yr (including direct and indirect costs), across ~3–4 pilot sample collection centers.

8.2.2 Genomic analysis. The primary goals of this work would be to undertake initial genomic analysis by applying available technologies to an initial sample collection. The initial collection would consist of ~1,250 samples, with ~250 tumors from each of five cancer types. The available technologies consist of genome-wide LOH analysis, resequencing of ~2,000 genes and RNA expression analysis. This pilot work will allow an evaluation of the results and will also help drive significant gains in efficiency.

This work effort should be undertaken through cooperative agreements rather than contracts, because there are still many open scientific and technical questions. A contract mechanism is unlikely to have the flexibility to rapidly respond to new information or technical advances or to appreciably stimulate cost reductions during the time of the pilot project. Several awards (3–5) should be made to ensure competition, but should not be so many that coordination becomes unwieldy. Ideally, these efforts should be scalable over time.

**Timeline.** We suggest a solicitation for pilot genome analysis centers, to be issued by summer 2005 and funded by February 2006. Because pilot sample collection centers would not deliver projects samples until mid-to-late 2006, initial work would begin on a preliminary set of sample (which the JWG/ESC would need to identify and procure).

**Approximate cost.** Total of $40M/yr (including direct and indirect costs), across ~3–4 pilot genome analysis centers. (Assuming some gains in efficiency, this should allow resequencing of ~2000 genes and genome-wide LOH analysis in ~250 samples from each of five tumor types.)

8.2.3 Technology development. Truly comprehensive analysis of cancer genomes will require further technology development. The needs include optimizing existing technologies for the setting of
tumor samples; creating effective techniques for studying genomic rearrangements and epigenetic modifications; and improving the efficiency of methods for comprehensive resequencing.

We would propose that applications for technology development projects be solicited as soon as practical (once samples are available). Projects to optimize existing technologies would apply them to a variety of tumor types, to demonstrate feasibility and establish costs. If successful, such efforts could be scaled up. Projects to develop new technologies might involve substantial research components.

**Timeline.** We suggest a solicitation for applications (R01, R21, R21/R33) to be issued by summer 2005 and funded by February 2006.

*Approximate cost.* $5M in Year 1, growing to $15M in Years 2 and 3).

### 8.3 Full-scale implementation (2009–2014)

The pilot phase is intended to resolve open scientific and technological questions, including providing a clear picture of feasibility and cost. The ESC would be asked to evaluate these questions on a regular basis.

The HCGP should be ready for full-scale ramp-up by 2008. The project would involve a network of integrated or specialized centers, managed through cooperative agreements and/or contracts with a coordinating center.

*Timeline.* We project that the full-scale implementation could be completed over a period of ~5 years, with a budget of ~$200M/year. The details, including the number and structure of centers and other activities, should be defined by the JWG with advice from the ESC.

*Total cost.* The total cost of the project would thus be ~$1.35B over 9 years, corresponding to an average annual budget of ~$150M. This figure is an estimate, which should be revisited in the course of further project planning.

### 9. Conclusion

A major barrier in the fight against cancer has been the extraordinary complexity and heterogeneity of the disease. Scientific advances over the past decade have finally provided, in principle, the ability to gain a comprehensive picture of the genetic basis of cancer. Such systematic knowledge would lead to dramatic progress in the understanding, classification, detection, diagnosis and therapy of cancer, by accelerating research in thousands of laboratories throughout academia and industry. We owe it to generations of cancer patients to come to seize this opportunity.
### Table 1. Cancer Types and Subtypes

<table>
<thead>
<tr>
<th>Incidence in United States &gt;100,000 cases/yr</th>
<th>Incidence</th>
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<tbody>
<tr>
<td>Prostate cancer</td>
<td>230,110</td>
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<tr>
<td>Breast cancer</td>
<td>217,440</td>
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<tr>
<td>Lung cancer</td>
<td>173,770</td>
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<tr>
<td>Colon and rectal cancer</td>
<td>146,940</td>
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<tr>
<th>Incidence in United States &gt;10,000 cases/yr</th>
<th>Incidence</th>
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<tbody>
<tr>
<td>Bladder cancer</td>
<td>60,240</td>
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<tr>
<td>Melanoma</td>
<td>55,100</td>
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<tr>
<td>Non-Hodgkin’s lymphoma</td>
<td>54,370</td>
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<tr>
<td>Cancer of the uterus</td>
<td>40,320</td>
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<tr>
<td>Cancer of the head and neck</td>
<td>38,530</td>
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<tr>
<td>Kidney and renal pelvis</td>
<td>35,710</td>
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<tr>
<td>Cancer of the pancreas</td>
<td>31,860</td>
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<td>Cancer of the ovary</td>
<td>25,580</td>
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<td>Thyroid cancer</td>
<td>23,600</td>
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<tr>
<td>Cancer of the stomach</td>
<td>22,710</td>
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<tr>
<td>Liver and intrahepatic ductal cancer</td>
<td>18,920</td>
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<tr>
<td>CNS tumors</td>
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<tr>
<td>Multiple myeloma</td>
<td>15,270</td>
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<tr>
<td>Cancer of the esophagus</td>
<td>14,250</td>
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<tr>
<td>AML</td>
<td>11,920</td>
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<tr>
<td>Cancer of the cervix</td>
<td>10,520</td>
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<tr>
<td>Gallbladder and other biliary</td>
<td>6,950</td>
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<table>
<thead>
<tr>
<th>Incidence in United States &gt;1000 cases/yr</th>
<th>Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Testicular cancer</td>
<td>8,980</td>
</tr>
<tr>
<td>Soft-tissue sarcomas</td>
<td>8,680</td>
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<tr>
<td>CLL</td>
<td>8,190</td>
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<tr>
<td>Hodgkin’s disease</td>
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<tr>
<td>Cancer of the small intestine</td>
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<td>CML</td>
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<td>Anal cancer</td>
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<td>Cancer of the vulva</td>
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<td>ALL</td>
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<tr>
<td>Ureteral cancer</td>
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<tr>
<td>Sarcomas of the bone</td>
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<tr>
<td>Cancers of the eye and orbit</td>
<td>2,090</td>
</tr>
<tr>
<td>Cancer of the urethra and penis</td>
<td>1,570</td>
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### Table 2. Examples of Cancer Subtypes

<table>
<thead>
<tr>
<th>Cancer Type</th>
<th>Subtypes</th>
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<tbody>
<tr>
<td>Lung cancer:</td>
<td>Non-small cell, small cell</td>
</tr>
<tr>
<td>Breast cancer</td>
<td>Ductal, invasive, basaloid, estrogen receptor +/-, Her2 +/-</td>
</tr>
<tr>
<td>Cancer of the head and neck</td>
<td>Squamous cell, nasopharyngeal, adenoid cystic</td>
</tr>
<tr>
<td>Cancer of the uterus</td>
<td>Endometrioid, adenosquamous, papillary serous, clear cell</td>
</tr>
<tr>
<td>Cancer of the ovary</td>
<td>Serous, mucinous, endometrioid, clear cell</td>
</tr>
<tr>
<td>CNS tumors</td>
<td>Glioblastoma multiforme, anaplastic astocytoma, etc.</td>
</tr>
</tbody>
</table>
The Working Group on Biomedical Technology strongly recommends strategic improvements in the discovery and deployment of biomarkers in cancer research and treatment. For the purposes of this document, “biomarkers” are defined as endogenous molecules (such as proteins or metabolites) or injected agents (such as imaging agents) whose presence or state correlates with important physiological processes, disease outcomes and treatment response (including toxicity and efficacy).

More effective biomarkers for disease have the potential to significantly improve cancer survival through early disease detection, improve treatment by more accurate diagnosis and prognosis, and greatly enhance clinical trials by rapidly revealing therapeutic response. The power of biomarkers has become evident in recent years through DNA and RNA profiling of tumors and imaging technologies. However, the field is still at an early stage: many of the most powerful technologies (notably proteomics) are still maturing and have not yet been broadly applied to cancer. Most biomarkers are yet to be discovered.

It is clear that dramatic advances can be made by undertaking certain strategic initiatives including: organizing team science, establishing data standards, providing informatics support, acquiring reagents, employing mouse models of disease, promoting academic–industry collaboration and translating advances to patient care more rapidly. In this report, we recommend the creation of a standing NCI Biomarker Discovery Working Group to coordinate work across the institute on (i) discovery and validation of endogenous biomarkers of cancer in patient samples and (ii) creation and testing of imaging and other agents for in vivo monitoring of cancers and cancer therapeutics.

1. Effective Biomarkers Will Improve Patient Outcomes

Individuals at risk for cancer or with cancer would benefit enormously by better methods for (i) determining cancer risk, (ii) detecting and localizing cancer at its earliest stage, (iii) profiling for therapeutic decision making, and (iv) monitoring response to therapy in real time. It is already evident that molecular diagnostics can improve diagnosis and treatment. Genetic translocations or transcript array profiles allow stratifying many organ-specific cancers (breast, leukemia, lymphoma, sarcoma) into different subtypes that have distinctive therapeutic outcomes. For example, *Myc* gene amplification status predicts the outcome for childhood neuroblastoma (Bhattacharyya et al. 1997). The quantity of Bcr-Abl transcript predicts disease recurrence in chronic myelogenous leukemia long before clinical symptoms recur (Radich et al. 1995).

1.1 DNA biomarkers are not sufficient. The HCGP will deliver the ability to type cancer by alterations in the cancer genome, which will facilitate risk assessment, diagnosis, prognosis, and treatment of cancer. However, DNA biomarkers alone are not enough. For example, proteins are more diverse and therefore
carry more information than nucleic acids, since alternative splicing and more than 100 different posttranslational modifications result in 10–100 species of protein from each gene. Moreover, proteins are much more dynamic and reflective of cellular physiology — protein phosphorylation can signal the presence of a single double-strand break in DNA within seconds to minutes of the activating event. In addition, proteins may be more accessible in body fluids and may be more useful for molecular targeted imaging. Metabolites are another source of dynamic biomarkers. It is important, therefore, that efforts be made to identify and implement effective types of biomarkers.

1.2 Biomarkers will empower imaging technology. Many important characteristics of cancer require positional information as well as in situ physiological information. Where is the cancer located? How large is it? Is it confined? Is it hypoxic? What is its metabolism? The establishment of a number of NCI-supported imaging centers throughout the United States has brought significant resources, expertise and focus to the problem of improving molecular contrast reagents. The development of micro-imaging technology for many modalities of small animal imaging in combination with recent improvements in mouse models of cancer provides new opportunities for molecular imaging that are inducible, targeted to specific tissues and genes, and that more accurately portray human cancer.

Molecular imaging (the in vivo measurement, characterization, and quantification of biological processes at the cellular and subcellular level) completes the overall picture for the future of molecular medicine. The ability to see the molecular signatures of cancer is critical to fulfilling biologically based technologies’ promise of earlier detection and better disease management. Molecular imaging could one day be used throughout the cancer care pathway i) to detect early-stage alterations in gene expression, ii) to guide therapeutic choices, and iii) to evaluate and adjust treatment protocols. Ultimately, researchers envision molecular image-guided therapy systems to treat cancer as it is found.

Each of the major imaging modalities would be enhanced with molecularly targeted imaging agents that offer the opportunity not only to see where but also to see what is going on — to visualize apoptosis, proteolysis, angiogenesis, metabolism, cell surface expression patterns and metastasis.

A variety of different imaging modalities in current use all lend themselves to different forms of molecularly specific contrast agents. PET imaging is noteworthy because its high sensitivity translates to low doses. Improvements in magnetic resonance contrast agents are also resulting in reduced doses, approaching those in PET. These tracer amounts should lower the barriers to FDA approval, which is a significant problem for new contrast agents. Near-infrared imaging permits deep penetration into tissues and the ability to image multiple targets (or biological processes) simultaneously at different wavelengths.

Functional information about tumors can be achieved by using enzymatic substrates (e.g., protease substrates) that produce signal when cleaved or by tagging antibodies with contrast cargo specific for the proteins that are localized and functioning at the site of disease. Labeled ligands for cell surface proteins, such as somatostatin receptor, melanocortin receptor and integrins, are already available and more are being developed. With informative imaging agents, we could, for example, tell which cells are currently repairing DNA damage, distinguish cell division from apoptosis, and image the characteristically leaky blood vessels in tumors.

1.3 Biomarkers can improve cancer diagnosis. Accurate diagnosis of the hundreds of different types of cancer will permit more effective choice of therapy and will make clinical trials more effective. Cancer diagnosis can be improved through more accurate molecular and functional phenotyping. As therapies become more targeted to specific signal transduction and metabolic pathways, it is becoming of paramount importance to document the existence of those pathways in the target cancers. For example, targeting of breast cancers with herceptin is not indicated if the patient’s tumor cells do not over-express
Her-2/neu. Similarly, Gleevec is most effective against cancers that express the Bcr-Abl genotype. It is a reasonable goal that such molecular phenotyping can be expanded to include biomarkers for virtually all cancer subtypes, and that many of these can be accessible through non-invasive means, such as proteins in fluid samples or through imaging. Such information could improve the conduct of clinical trials, as segmentation of patients with biomarker-derived inclusion criteria will significantly reduce the numbers of patients required to achieve acceptable response rates.

1.4 Biomarkers can improve clinical trials. Better post-treatment diagnostics could greatly accelerate new drug development by shortening clinical trials, identifying responsive patients, and revealing toxic side effects. For example, one of the first trials approved with a molecular endpoint compares four treatments for chronic myelogenous leukemia and is currently underway. By using the endpoint of reduction in the DNA marker, Bcr-Abl, a trial that would have taken several years to complete will be reduced to 12 months.

The use of molecular markers can aid in the identification of a subset of patients that respond to therapy, thereby turning what would have been a failed clinical trial into a successful one. The remarkable response of some patients with gastrointestinal stromal tumors over-expressing the c-KIT kinase to the drug imatinib can be observed within days of treatment through PET imaging of glucose metabolism (Gayed et al. 2004). Similarly, response of breast cancer metastases to taxane therapies can also be observed with early changes in diffusion MRI signals (Theilmann et al. 2004, in press). Despite these notable successes, imaging is not used in most clinical trials to achieve rapid and specific assessment of response. This is due in part to the fact that few agents are being translated into the clinic to date and few agents are being accepted by the FDA.

1.5 Biomarkers can improve therapies. If we could routinely follow a patient’s response to therapy in real time, both dosing and agent selection could be individualized. Currently some chemotherapeutic agents are individualized by adjusting dose to the patient’s individual metabolic characteristics. Moreover, a series of agents could be tested on the same patient in a matter of weeks. A key factor in such a test is to optimize the negative predictive value and dynamic range of responses, so that non-responding patients can be accurately identified. Defining modalities appropriate for such tests will benefit from appropriate pre-clinical imaging of animal models.

Therapeutic strategies can also directly benefit from an understanding of the proteins that are prominent in each type of cancer. A search for these sentinels of disease would enable a whole industry of new molecularly targeted therapeutic approaches. Many of the broadly toxic agents could become cancer-specific reagents if coupled to targeting moieties (e.g., antibodies, engineered ligands) or other vehicles that deliver them specifically to the cancer cells. There is at least one FDA-approved targeted therapy of this type and many more are in development. The FDA-approved therapy, Myelotarg, couples an antibody specific for tumor cells with a toxic reagent, calicheamicin. Such targeting will be required for effective internal radiotherapies.

Short of prevention, improved diagnostics to detect cancer at an early, curable stage would provide the greatest benefit for cancer patients. For most cancers, 5-year and even 10-year survival is often near 90% for cancer detected at stage one, while it may be only 10% or less for cancer detected at stage four (Etzioni et al. 2003). We have, of course, known for a long time that if we could detect cancer earlier, we could save more lives. The Pap smear strongly reduces mortality through early detection of cervical cancer as does colonoscopy for colon cancer. Furthermore, both tests have been embraced by the community despite their significant inconvenience, cost and requirement in clinical expertise. These successful screening examples have created a social environment that should lead to the rapid application
of new tests. What we need are affordable and effective diagnostic tests for more types of cancer. A recent success is the finding that DNA markers are more effective than histologic analysis at detecting those patients with Barrett’s esophagus who are likely to progress to cancer. Placing these high-risk patients under intensive surveillance for early detection has been shown to increase 5-year survival from less than 10% to more than 80% (B.J. Reid, personal communication).

The risk of cancer recurrence is high in patients who have previously had cancer, even for those who have been in remission for 5 or more years. Cancer survivors constitute a high-risk group that is most likely to be the first beneficiaries of improved tests for early detection of disease. Monitoring CML patients during Gleevec therapy and in the post-transplant setting for the persistence of the Bcr-Abl translocation is already an effective technique.

1.6 Biomarkers may contribute to risk assessment. Screening individuals for early cancer detection will be more cost-effective and efficacious if we can segment the population into smaller groups at increased risk for specific cancers. Success in identifying individuals at increased risk has, of course, been achieved for many cancers through epidemiological studies that identify strong environmental or behavioral risk factors and by genetic studies that identify mutations underlying rare inherited cancer syndromes. With a few exceptions, such as serum PSA, the use of molecular markers in the assessment of risk for sporadic malignant disease remains largely unexplored.

Epidemiologic studies indicate that lifestyle, diet and environmental exposures significantly affect the risk for sporadic disease, but little advance has been made in identifying markers reflective of the stable, cumulative molecular changes associated with, or mediating, this risk. Stochastic genetic alterations occur infrequently and are difficult to detect, but there is increasing interest in more common, stable genetic and epigenetic changes in histologically normal or pre-malignant tissue, reflective of deleterious exposure, and associated with increased risk for malignant progression. In Barrett’s esophagus, DNA mutation, methylation, and ploidy changes are highly correlated with increased risk for cancer (also see Zöchbauer-Müller et al. 2003). Another epigenetic risk marker is the loss of imprinting of IGF2 in peripheral blood lymphocytes in subjects at risk for colorectal cancer.

It should be possible to identify individuals at risk by functional tests for cellular processes that protect against cancer; for example, the effectiveness of DNA repair. Most familial cancer-prone syndromes are due to defects in DNA repair. A study by Scott and Roberts revealed that about 40% of breast cancer patients, prior to treatment, exhibit a defect in DNA double-strand break repair in their white blood cells (Scott et al. 1999). Cell-based and biochemical tests have been developed for about ten different pathways that participate in DNA repair, many of which would likely contribute to cancer risk if defective. There are also a number of case-control molecular epidemiology studies that apply functional assays of DNA repair capacity as potential risk factors for sporadic cancers, although these data have not been validated in prospective studies. In general, more effort is required to understand risk stratification based on various cancer-related phenotypes.

2. Biomarker Discovery Can Be Improved

2.1 Many advances in fundamental knowledge are not being translated into molecular diagnostics. During the last 40 years, we have achieved an impressive understanding of the molecular fundamentals of cancer. We now understand that cancer arises in a single cell as a result of genetic changes that alter a number of cellular processes — growth control, immortality, apoptosis, somatic evolution, angiogenesis, metastasis — and many cancers appear to have activated a wound healing genetic expression program (Chang et al. 2004). These changes are driven by abnormal methylation or a high rate of mutation. The
proteins that function in each of these cellular circuits provide not only potential drug targets, but also signals that may allow us to non-invasively visualize and monitor physiology.

Moreover, new advances continue at an astonishing rate. In just the last few years we have seen: the sequencing of the human genome, providing a catalogue of all human genes; the development of RNAi technology, permitting the sophisticated loss of function analysis of human cells, and the identification of cancer stem cells, defining a potential new paradigm for cancer etiology.

Such recent advances, however, have been translated into effective diagnostics in only a few cases to date— for example, imaging agents that detect DNA replication, apoptosis, or proteolysis. In some respects, the discovery of new biomarkers appears to have been undervalued and under-funded relative to drug discovery. For example, the the NCI Early Detection Research Network (EDRN), charged with discovering and validating new biomarkers, has not yet brought new agents to patient care.

It is time to unleash the diagnostic and informational content of our knowledge of altered molecular circuits into improved diagnostic agents for cancer patients.

2.2 Technologies for identifying protein biomarkers are being ineffectively utilized. There are many different approaches to discovering biomarkers for cancer. The variables include the type of technology approach, the cancer site, the source of tissue for candidate discovery, the choice of biological pathway or class of molecule to examine. The discovery can be made more rational. Rather than sift randomly through thousands of proteins in disease vs. non-disease looking for rare differences, one could interrogate proteins enriched in tumor tissue, in fluids near cancer cells, or secreted by human cancer cells in culture or in xenograft capsules. In addition, one could develop strategies to look in blood specifically for the ~1,000 proteins known to play roles in cancer (e.g., angiogenesis, apoptosis, cell cycle, etc.) by a variety of approaches, including antibody enrichment. Special attention might be given to the identification of cell surface proteins and the preparation of reagents for detecting them, which would allow for sorting cells belonging to developmental lineages within tissues and tumor.

2.3 DNA methylation markers are promising but under-explored. Altered DNA methylation patterns provide one promising platform for cancer biomarker development, because these changes are pervasive in cancer, appear to be detectable in free, tumor-derived DNA in bodily fluids of cancer patients, and are based on a chemically and biologically stable analyte. The successful development and implementation of DNA methylation-based biomarkers has thus far suffered from the following four impediments:

- Lack of a comprehensive, genome-wide description of baseline methylation patterns in normal tissues. A Human Epigenome Project is underway in Europe, although it is still at an early stage and there is no comparable effort in the US.
- Lack of a coordinated and comprehensive approach to methylation marker identification. Only about 1% of known CpG islands and fewer than 10% of anonymous CpG islands have been evaluated to any extent for their tumor-specific methylation behavior.
- Lack of standardized technology for DNA methylation analysis. This inhibits cross-platform comparisons and cross-validation studies. Genome-wide marker identification approaches rely mostly on methylation-sensitive restriction enzyme digestion, while sensitive detection technologies useful in clinical tests rely largely on bisulfite-based methylation-specific PCR.
- Lack of a systematic optimization of sample processing to maximize detection sensitivity. Such mundane, non-innovative but necessary technology optimization is difficult to fund through investigator-initiated funding mechanisms.

These impediments result from insufficient coordination, communication and standardization.
2.4 Few new imaging agents are being applied to patients. Cancer diagnostics and therapeutics requires the ability to locate incipient disease, determine its extent, and monitor response to therapy. At present, we can image larger cancers by cross-sectioning imaging techniques such as CT, MRI, and PET/SPECT and by optical techniques such as endoscopy or intravital microscopy. In order to use imaging to pinpoint early cancers and pre-neoplasia (often only a few millimeters in size), we will need higher resolution technologies. This size range is below the detection threshold for most state-of-the-art CT, MRI, and PET. One example of in vivo high-resolution imaging is fiberoptic confocal microscopy performed during endoscopy. This technology could be particularly well suited for surveying epithelial surfaces at cellular resolution.

A clear strength of imaging approaches is the high connectivity between pre-clinical and human use. For example, most equipment manufacturers (e.g., GE, Siemens, Phillips) are developing human and animal imaging platforms with common interfaces to facilitate the translation from animal to human. Nonetheless, testing new agents in patients is challenging due to regulatory (FDA) and reimbursement (CMS) issues, the lack of incorporating imaging endpoints into therapeutic trials, and high costs for perceived small markets. Also, pharmaceutical companies are not making significant investments to develop imaging in concert with drug development and, as a result, imaging agent development often lags 2–3 years behind drug development for a given target. Finally, another limitation is the need for more creative chemistry to design and synthesize informative probes.

3. How to Improve Biomarker Discovery

3.1 The need for team science. A consistent theme that emerged from focus group sessions was the need for more team science. While much fundamental discovery in cancer research is best pursued through individual investigator awards, many of the important goals discussed here require collaboration. The NCI should bring together the strengths within and across academic institutions into a highly interactive network of contributing laboratories. A systematic and integrative approach will be required with teams of investigators sharing and aggregating data.

Achieving the goals will require bringing together expertise in genomics and proteomics, small and large animal studies, and clinical and epidemiological studies. Informatics support will be needed for data extraction, data transfer and data storage, and standard algorithms for data analysis that work across platforms and enable common resources for universal access to the successes and failed efforts of other investigators. Chemistry, radiopharmacy, engineering and bioengineering expertise can improve imaging and biomarker discovery. Basic and clinical scientists need to be included to aid in identifying questions of biologic significance and facilitate the translation of discovery to therapy. Expertise in outcomes research is needed to demonstrate the clinical and economic value of evolving approaches to screening cancer patients, at risk individuals, and healthy populations.

Because of the complexity of approaches that can and should be pursued both in biomarker discovery and the development of imaging agents, an effective search for these sentinels of cancer will require a team effort – including many labs working on the same samples, sharing data, developing standards, and comparing information. Sharing data across labs will require an informatics platform that can support these coordinated activities — something that does not currently exist in the academic sector.

Moreover, because of the variety of disciplinary expertise required, there will be an ever-increasing need for cross-trained scientists. Indeed the shortage of cross-trained scientists is a major impediment to more rapid development of validated imaging approaches.
3.2 The need for data standards. Currently, it is impossible to compare performance across different laboratories for most fields of biomarker discovery and molecularly targeted imaging due to the lack of uniform standards for reporting data and the use of different samples and technologies for analysis. There is an urgent need for communities of scientists working with each analytic approach to meet and establish data standards that will facilitate comparing data across laboratories and instruments. In some cases this can best be accomplished by incorporating known molecular standards in each sample analyzed or including a sample containing standards in each experiment. Current funding mechanisms tend not to support work to ensure reproducibility because it is often not considered “innovative”.

3.3 The need for an informatics platform. Each laboratory and imaging center typically maintains its own database and generally finds it impractical to aggregate its data with that from other sites. Moreover, analysis software is typically written by individual centers or is proprietary. It will be impossible to exchange data across laboratories and compare results quantitatively until standard analysis tools are readily available and widely shared. The field of biomarker discovery needs highly functional databases, data transfer standards, a variety of analysis and comparison tools, and the ability to aggregate data from many sources. If highly functional systems were readily available, it would be the first choice for most investigators in the field and would assure a uniformity of data acquisition across many discovery laboratories.

3.4 The need for reagents. A common complaint among investigators is the lack of reagents necessary for biomarker discovery. It is difficult for any single laboratory to obtain the diverse array of reagents needed, and the development of reagents independently by different laboratories increases the lack of reproducibility in data. Reagents are needed in the form of tissue and blood samples, chemical libraries, peptide standards and antibodies. Initial evaluation of biomarkers will require large numbers (hundreds) of clinically annotated plasma (and solid tissue) samples that could be collected and stored for many cancer sites. To evaluate early detection capability, collection of plasma from early stage patients is needed (together with stored tissue) as well as pre-symptomatic blood samples from individuals later diagnosed with cancer. To evaluate clinical response, plasma obtained from well-controlled clinical trials with clinical outcomes is essential. For protein biomarker discovery it is essential to have access to many antibodies for detection of candidates in low concentration. It would be straightforward to draw up a list of at least 1,000 proteins known to be involved in cancer-related processes, such as apoptosis, angiogenesis, and metastasis, that are all potential candidate biomarkers. While the cost of individual laboratories producing antibodies against these proteins is prohibitive, it would be an modest investment by the NCI to do so. Such an investment would be justified by its potential to empower the entire research community with accessible and standard reagents. A similar situation exists for chemical libraries for developing contrast agents for imaging. Efforts are needed to create libraries with chemistries that are favorable for imaging agent development.

Finally, validation of early detection markers will require large cohort studies in which samples are obtained and stored from healthy people prior to disease onset. This resource will be needed within a couple of years, making the initiation of such a collection imperative.

3.5 The need to implement new technology improvements. Technology improvement is also crucial to advance the field. Examples of recent technologies that could dramatically improve biomarker discovery are proximity-based oligonucleotide coupling that links antibodies to DNA tags for PCR-based signal amplification, and recombinant antibodies produced using yeast surface display. Technology
improvement should be considered in imaging modalities, combinatorial synthesis of contrast agents, mass spectrometry, protein arrays, protein fractionation, protein detection, protein quantitation, DNA methylation analysis, new detector technologies and other appropriate methodologies.

Molecular probes will require a variety of pharmacological profiles and half-lives, as well as continued development of “smart” imaging reagents whose signal depends on biochemical activities. Desirable performance enhancements include decreasing the time and barrier required to conduct imaging tests to make them more feasible for large-scale trials and clinical implementation, multiplexing contrast agents to compare several biochemical and physiological process at the same time, and developing better transducers to support three-dimensional imaging.

A number of existing and developing imaging approaches do not rely on exogenous molecularly specific contrast reagents yet retain high specificity for aspects of tumor behavior, such as vessel permeability, cellularity, metabolism and organization. These should be developed in parallel with molecularly specific reagents and biomarkers to generate complete pictures of tumor behavior.

4. General Recommendations

Based on the analysis above, the working group makes a number of general recommendations concerning the directions needed to advance work on biomarker discovery. The next section discusses how to ensure their implementation.

4.1 Foster team science. The NCI should create new models for funding team science that will assure that promote collaboration in biomarker discovery, by encouraging groups of investigators with critical mass and diverse expertise to work together on key problems.

4.2 Establish data standards. The NCI should bring scientists together to develop data standards for each technology platform (imaging modalities, proteomics, DNA markers, metabolomics, etc) and to improve reproducibility across laboratories on a specific imaging modality. Such an effort will likely require the development and dissemination of uniform reference standards that can be used by laboratories to confirm results for existing, newly developed or proposed biomarkers.

One or more technology assessment centers should be funded to compare different technologies head-to-head on the same samples to establish methods for best performance.

4.3 Build informatics platforms. The NCI should create a centralized and publicly available database for technology platforms in which investigators can aggregate data across studies on a common tumor type. For contrast reagents, tracked information should include formulation, source, biodistribution, chemical structure, pharmacokinetics, and in vivo stability. For endogenous approaches, tracked information should include profiles and variance of normal tissues, acquisition and analysis conditions.

4.4 Provide reagents to the community. The NCI should support production of common reagents needed for each technology platform—such as molecular imaging probes, small-molecule libraries as sources of new imaging probes, antibodies against cancer-related proteins, isotopically labeled peptides for mass spectrometry and other reagents as needed.

4.5 Development new technologies. The NCI should support the development of new technologies, methodologies and approaches within discovery programs. Mechanisms could include pilot grant programs to encourage the development of improved technologies, reagents and procedures. Where
appropriate, efforts to automate of technologies for higher throughput and greater reproducibility should be supported.

4.6 Employ mouse models of cancer. The NCI should take maximal advantage of the power of mouse models for both technology improvement and biomarker discovery. Animal models provide controlled experimental conditions and an opportunity for reproducibility that cannot be achieved with human subjects. Variables that can be controlled include genotype, environment, precise cancer type and disease stage. Initial development and evaluation of technologies for biomarker discovery may be best performed on highly uniform animal samples rather than on human samples. The NCI mouse models of human cancer consortium (MMHCC) has created mouse models of many different human cancers, and these provide an important resource for this work.

4.7 Promote academia-industry collaboration. The NCI should promote appropriate collaborations between academia and industry. Since an effective discovery of biomarkers is of great benefit to both academia and industry, it should be possible to collaborate across industry–academic partnerships to facilitate the process. Such collaborations should bring together pharmaceutical, image acquisition and biotech companies with molecular probe development and biomarker discovery efforts. Biomarker endpoints should be developed at the earliest stage of drug discovery, to connect drug actions to a specific biomarker endpoint at all stages of development through the clinic.

4.8 Translate advances to patient care. The NCI should encourage rapid translation of biomarkers to the clinic. Endpoint based on biomarker (including endogenous proteins and imaging readouts) should be incorporated into therapeutic trials. One way to encourage this would be to create imaging cores and/or centers focused on tumor response assessment in cancer centers. Another step would be to ensure the participation of biomarker scientists in the protocol review and startup phase at individual cancer centers. Positive single-trial results should be confirmed with multi-center tests. ACRIN is available for radiology-based trials, and oncology groups are available for therapeutic trials; however, there is no current mechanism in place to disseminate therapy trials that include an imaging endpoint.

Clear guidelines for IRB and FDA approval for human use should be established to provide a framework within which imaging approaches and agents can be more readily approved for human trials. This should also include clear guidelines for acceptance of INDs.

4.9 Promote work on standards for approval and reimbursement of biomarkers. The NCI should promote broad discussions concerning guidelines for approvability of new biomarkers by the FDA and utility of the biomarkers in a clinical setting. In addition, the NCI should support scholarship in areas related to reimbursement for the clinical use of biomarkers. Because the effective use of biomarkers may well decrease procedures, it is important to explore the benefits of ‘outcome-based’ rather than ‘activity-based’ models of reimbursement to ensure that reimbursement policies do not create disincentives for the use of biomarkers.

4.10 Promote work on public understanding of biomarkers. The NCI should promote patient and physician education related to biomarkers, because probabilistic risk assessments will create challenges for both groups. In addition, the NCI should promote work to understand the potential for discrimination based on information about biomarkers.
5. Specific Recommendation

Biomarkers hold tremendous promise for improving the detection, diagnosis and treatment of cancer. In the previous section, we have outlined a number of general recommendations concerning how to advance progress on the development and validation of biomarkers. The remaining issue is how best to ensure the implementation of these steps.

We are not recommending the creation of organized large-scale projects – for example, an effort to discover serum biomarkers for all common cancers. The technologies for biomarkers discovery (beyond the DNA level) are not yet well enough developed to make such focused goals feasible. At present, the key issues are to advance the state of the art of the technology (including through the development of standards, tools and approaches) and to achieve some dramatic successful to serve as models (including the identification of endogenous biomarkers for a few cancers and the development of some new types of imaging agents). Such progress may set the stage for large-scale efforts at a later date.

We are also not recommending the creation of a specific new NCI program for biomarker discovery. There are currently nearly 20 programs or initiatives within NCI relevant to this area (listed in Section 6). The creation of yet another program would not suffice to accomplish the important goals outlines above.

Instead, the NCI needs to take a more comprehensive approach to this crucial area by evaluating the success of existing efforts relative to overall goals, identifying key areas that are not being addressed and modifying or creating programs to address them.

Accordingly, we recommend the creation of a standing NCI Biomarker Discovery Working Group to coordinate work across the institute on (i) discovery and validation of endogenous biomarkers of cancer in patient samples and (ii) creation and testing of imaging and other agents for in vivo monitoring of cancers and cancer therapeutics. The working group should report, on an annual basis, to both the NCI Director and the Board of Scientific Advisors. Its charge would be to:

i) evaluate the extent to which the recommendations are already being addressed through one or more of the existing programs;

ii) determine the extent to which different programs are successful in their goals and the extent to which they may have redundant elements;

iii) propose steps to improve coordination of activities across programs;

iv) ensure that each of the recommendations above has an appropriate programmatic home, either through an existing program or through the creation of a new effort;

v) determine whether current funding is adequate to ensure rapid implementation of the recommendations;

vi) propose new funding, where existing funding is inadequate to achieve the goals; and

vii) prepare an annual assessment of progress on these recommendations.

It is clear that achieving the goals set forth here will require additional funding for biomarker discovery. This is particularly the case with respect to mechanisms to encourage team science, provision of community reagents (such as antibodies and chemical libraries of imaging agents), technology assessment mechanisms, and development of informatics platforms.
6. Appendix

Some of the NCI programs related to biomarker discovery are:

- Early Detection Research Network (EDRN)
- In Vivo Cellular and Molecular Imaging Centers (ICMICs)
- Small Animal Imaging Resource Program (SAIRPs)
- Mouse Models of Human Cancers Consortium (MMHCC)
- Imaging Working Group, which aims to enhance collaborations between SAIRPs and MMHCC
- Development of Clinical Imaging Drugs and Enhancers (DCIDE) program, which aims to provide funds for pre-clinical testing for submission to the FDA
- Contract program to validate imaging methodologies for pre-clinical testing of new drugs
- Unconventional Innovations Program (UIP), which aims to stimulate development of radically new technologies in cancer care
- caBIG initiative, which works with cancer centers in developing access to key bioinformatics platforms
- Specialized Programs of Research Excellence (SPOREs), which aims to speed bi-directional exchange between basic and clinical science focused on specific cancer sites
- Innovative Molecular Analysis Technologies (IMAT) program, which supports research projects to develop and carry out pilot applications of novel technologies for the molecular analysis of cancer
- Clinical Trials Cooperative Group program, which is designed to promote and support clinical trials of new cancer treatments, explore methods of cancer prevention and early detection
- Small Business Innovation Research (SBIR) grants, which aims to support to small business for innovations in cancer
- NCI Alliance for Nanotechnology in Cancer, which will establish Centers for Cancer Nanotechnology Excellence to design and test nanomaterials and nanodevices, with the aim of introducing novel diagnostic tools and techniques to combat cancer processes
- NIH Roadmap initiatives, including the Molecular Imaging and Contrast Agent Database (MICAD);
- Interagency Oncology Task Force (NCI-FDA IOTF)
- Clinical Proteomics and Biomarker Discovery, a new program currently under consideration at NCI
7. References


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