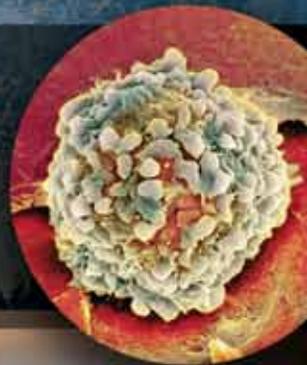


# THE NATIONAL CANCER PROGRAM

MANAGING THE NATION'S RESEARCH PORTFOLIO

AN ANNUAL PLAN AND BUDGET PROPOSAL FOR FISCAL YEAR **2013**





# The National Cancer Program

## MANAGING THE NATION'S RESEARCH PORTFOLIO

This year marks the 75th anniversary of the founding of the National Cancer Institute, the first so-called “categorical institute” of what has become the National Institutes of Health, with its 27 Institutes and Centers. Over the years, the Congress and the public have generously supported the NCI—and the NIH generally—with sustained budgetary increases. This was especially true for the NCI during the rapid expansion of its budget following the National Cancer Act of 1971 and for the NIH, including the NCI, during the 5-year doubling of its budget, launched in 1998. Both of these eras of rapid growth were remarkably fruitful. The first launched the pursuit of cancer genes and the molecular basis of oncogenesis, laying the foundation for the transformation of clinical oncology that is now occurring. The latter accelerated the completion of the human genome project that now guides the study and control of all diseases, including cancers. Since 2003, however, the budgets of the NCI and the NIH have grown minimally, with their buying power shrinking by about 20 percent as a consequence of inflation.

**This decade-long hiatus in financial growth has come, ironically, at a time of unmatched promise in the oncological sciences and at a time when the world of cancer research has expanded in talent, facilities, and ideas.**

This decade-long hiatus in financial growth has come, ironically, at a time of unmatched promise in the oncological sciences and at a time when the world of cancer research has expanded in talent, facilities, and ideas. Progress in molecular biology, especially in the deciphering of cancer genomes and the probing of the signaling pathways that govern normal and malignant cell growth, has transformed our ability to understand the broken parts of a cancer cell; to develop new and more precise therapeutic strategies; to begin to reformulate diagnostic categories; and to imagine screening for and prevention of some cancers in more powerful ways. In just the past few years, NCI-supported science has delivered a remarkable collection of genetic information about several types of cancers, a number of new targeted therapies for various cancers, compelling examples of successful immunologically based-therapies, persuasive evidence that radiographic screening can reduce lung cancer mortality, and many new observations about the genesis of cancer cells, their development, their behavior, and their microenvironment.

One of the goals of this annual report is to summarize some of these findings and their practical consequences, so that the NCI's many supporters and beneficiaries can better appreciate the significance of the NCI and the argument for the enhanced support that we request in the "by-pass budget." We provide this summary in two ways: by describing some of the NCI's broad research programs that address a wide range of cancers and their underlying biological properties and by discussing several specific types of cancers (five this year) that exemplify the various strategies and the variable rates of progress on the different diseases that we are working to control. The latter disease-specific presentations also help to acquaint the report's readers with some important fundamental principles: **first, that different types of cancers are often united by common themes, but also characterized by inherent differences in epidemiological factors, molecular mechanisms, and clinical features; and second, that studies of each cancer type are strongly influenced by work on other types of cancer.** These notions have implications with respect to the way we use the public funds we receive from Congress. We must, and we do, balance our knowledge about the public health burden of each cancer type against a consistent historical message: The sources of our greatest advances are difficult to predict and often emerge from unexpected places. So scientific opportunity, the richness of experimental ideas, and the talent of investigators must be taken into account, along with the toll taken by individual cancer types, if we are to spend our funds wisely and earn public trust, especially at a time of fiscal restraint.

When the National Cancer Act was signed in 1971, the NCI Director was deemed to be the leader of the National Cancer Program, the totality of the nation's efforts to combat cancer. We now recognize that efforts to control cancer and its effects—through science, medicine, and social programs—are now so vast, conducted by so many people, and funded by so many organizations that leadership in any strict sense is not possible. Still, the NCI and its Director have enormous potential to lead the nation's efforts through the NCI's "convening power"—the ability to bring people together from all sectors working on cancer and to think cooperatively about how to solve our most difficult problems.

In that spirit, the NCI makes frequent use of its many well-established external committees—the National Cancer Advisory Board, the Board of Scientific Advisors, the Clinical and Translational Advisory Committee, the Director's Consumer Liaison Group, and others—to discuss new programs and obstacles to progress. In addition, especially over the past 2 years, the NCI has been convening a large number of workshops and creating new advisory groups to seek broad counsel on a variety of important topics. Most numerous among these have been the Provocative

Questions workshops, designed to solicit ideas from a diversity of scientists and clinicians about important research opportunities that have been comparatively neglected (see p. 4). Other gatherings have been convened to explore ways to accelerate the improvements in medical practice, best called “precision medicine,” in the era of genetically informed cancer care that we are now entering (see p. 13). The NCI also has new means for obtaining specialized advice about critical components of its scientific program: the National Frederick Advisory Committee for oversight of the Frederick National Laboratory for Cancer Research (see p. 50) and outside advisors for the National Cancer Informatics Program, (see p. 78) and for two new centers at the NCI: the Center for Cancer Genomics (see p. 8) and the Center for Global Health (see p. 66). Still other discussion groups have been assembled to consider the pending reorganization of the NCI’s Clinical Trials Cooperative Groups and the increasing recognition of the centrality of “team science” in cancer research.

Such group events inevitably illustrate the strength, size, and diversity of the organizations that share the NCI’s goals and work with us in various ways to reach those goals. Those organizations include private pharmaceutical and biotechnology firms; scientific and medical societies; disease advocacy organizations and other voluntary groups; state-based research programs; and a variety of research institutions, universities, and medical schools, especially the NCI-designated cancer centers.

Connected by financial ties that may be loose or tight, these organizations are joined solidly to the NCI by a fierce determination to make progress against the complex set of diseases that we group together as cancer. In many ways, the interactions between these groups—convened, organized, and led by the NCI—constitute the backbone of the National Cancer Program. This report inevitably focuses on the specific contributions that the NCI makes to this complex national effort; our achievements constitute a reliable barometer of the National Cancer Program’s progress and promise. For that reason, the NCI offers this report as an account of how the entire nation is faring in its efforts to control a world-wide scourge.

Harold Varmus, M.D.  
*Director, NCI*

# Provocative Questions

IF YOU DO NOT KNOW HOW TO ASK THE RIGHT QUESTION, YOU DISCOVER NOTHING.

— W. Edwards Deming,  
American statistician and expert on innovation

One of the ways NCI exercises its leadership of the National Cancer Program is by helping define for the research community the most important research questions that will lead to the greatest advances against cancer. Readers of last year's report will recall that NCI launched in late 2010 a Provocative Questions initiative to identify important but non-obvious questions, the answers to which will surely drive progress against cancer. Since then, the Provocative Questions website has listed more than 100 questions and has been visited by more than 35,000 scientists worldwide. NCI issued a request for applications that focused on a selected list of 24 questions. More than 750 applications were reviewed by panels assembled by NCI, and 56 applications totaling just under \$21.5 million were funded.



During the past year and a half, recognizing that most good research begins with a good question, NCI has brought together diverse groups of researchers—many who have never met before—to propose, craft, and debate what they consider to be critical questions in cancer research. Questions that are outside the usual sphere of focus and that could lead to important discoveries are the basis for NCI’s Provocative Questions initiative.

NCI launched the initiative late in 2010, seeking to go beyond the questions that are self-evident or that have been studied for many years. We asked investigators to propose intriguing questions that need attention but might not otherwise get it or that have stumped us in the past but may be answered by new technologies. The initiative, which elicited a strong and exciting response from the research community, has recently funded its first 56 investigators.

Seventeen workshops included clinical and translational investigators, basic scientists, behavioral researchers, epidemiologists, evolutionary biologists, drug developers, communications experts, and more. In every workshop, new and thought-provoking questions emerged. Researchers showed great enthusiasm for helping to set the agenda.

To extend this exercise well beyond the relatively small number of people who could be invited to the workshops, NCI created an interactive website ([provocativequestions.nci.nih.gov](http://provocativequestions.nci.nih.gov)). Visitors to the website had the opportunity to learn more about the Provocative Questions initiative, review the recommendations of workshops already conducted, propose additional questions, and comment on questions proposed at workshops or on the website.

From the hundreds of questions that were submitted during workshops and online, 24 were chosen for solicitation of grant applications. These questions build on specific advances in our understanding of cancer and cancer control, they address broad issues in the biology of



Colorectal cancer cell.

cancer that have proven difficult to resolve, and they take into consideration the likelihood of progress in the foreseeable future. Answers to these questions could help to overcome obstacles to the control of cancer.

To initiate research focused on these 24 questions, NCI issued a request for applications and received more than 750 applications that were reviewed by panels assembled by NCI. Fifty-six applications totaling just under \$21.5 million were funded. Because the Provocative Questions exercise intends to focus our attention largely on understudied areas, study sections were asked to judge the relative value of applications by considering the power of the ideas proposed to answer the questions, rather than by evaluating preliminary data or the reputation of an applicant. The initiative does not replace NCI's longtime and essential emphasis on funding investigator-initiated research, but rather it represents a compromise between investigator-initiated projects and NCI-directed programs.

#### PROVOCATIVE QUESTIONS

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

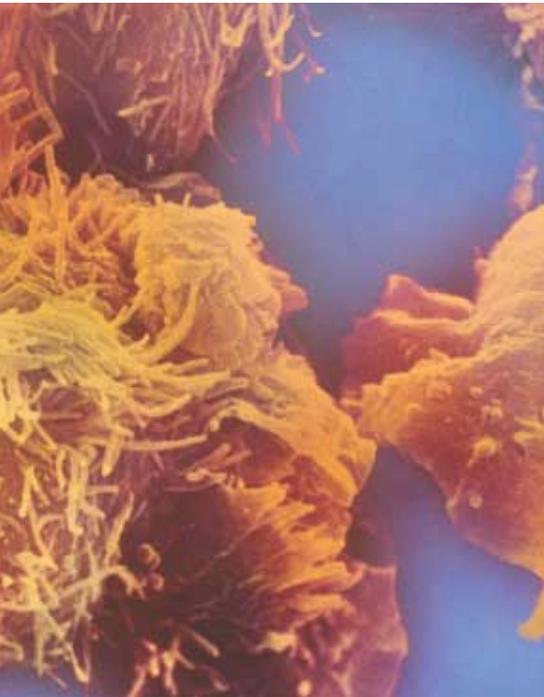
Certain modifiable behaviors, such as tobacco use, ultraviolet light exposure, and sexual behaviors, are linked to increased risk of some cancers. By understanding basic mechanisms of executive control, emotion, and motivation, we might be better able to understand why people fail to alter behavioral patterns, and then be able to help them reduce their resistance to change. Recent advances in behavioral and neurological studies can help advance understanding of whether defects—in the delivery of messages or in the efforts to change behavior—affect an individual's ability to avoid risky behavior. Reductions in behavior that increase risk would have an enormous impact on the incidence of cancer.



Reflecting the involvement of experts from many disciplines, the Provocative Questions cover numerous areas. For example: How does obesity contribute to the incidence and mortality of cancer? Why do some commonly used drugs, such as aspirin, appear to reduce the risk of cancer? How do changes in RNA processing contribute to tumor development? How do some neurological diseases, such as Parkinson’s disease, reduce the incidence of some cancers? The boxes below contain detailed descriptions of several of the Provocative Questions.

The Provocative Questions initiative is an experiment in its own right, one that asks several questions about the research process. The first clear result is that the research community has responded. Soon we will know whether the questions will incite “provocative results.” There’s more to learn, of course. How do we best use good questions to paint the landscape of what we know and what we want to know about cancer? Will interesting answers lead to sustained research programs that expand the pursuit of additional answers?

NCI plans to expand the list of questions through additional workshops and the website, to invite applications in response to the RFA annually for at least another 2 years, and to consider whether to expand the initiative in the more distant future.



Scanning electron micrograph of human cancer cells.

#### PROVOCATIVE QUESTIONS

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

One of the most disappointing features of the development of new, targeted therapeutics is how routinely drug resistance emerges. Evolutionary theory may provide answers to that conundrum. Strong selection, one theory suggests, will always result in the emergence of resistant populations, as long as some portion of the stressed population can adjust to the selective pressure. Similar theories suggest that lessening the selective pressure to a level that merely holds the population in check may succeed for extended periods of time. Developing and using drugs that are not solely designed to kill cells may help establish a balance that results in tumor stasis, rather than strong selection for drug resistance. Ultimately, this may not produce a cure for a particular cancer but rather a method to treat cancer as a chronic disease. There may be situations in which living longer with a non-regressing tumor is preferable to rapid tumor regression followed by an almost certain drug-resistant relapse.

# Center for Cancer Genomics

Pursuing the genetic foundations of many cancers is a vital component of NCI's current research, and such genetic and genomic studies comprise a great proportion of the institute's research portfolio. Our principal task in the years ahead—for NCI and for the entire cancer research enterprise—will be managing huge volumes of data; standardizing how tissue samples are collected, sequenced, and analyzed; and encouraging donations of tissue samples from patients.

The discoveries of genetic conditions associated with cancer, along with the molecular abnormalities identified in tumors, are now beginning to drive improvements in cancer screening, diagnosis, and care. By studying the structure and function of entire genomes sampled from humans and other organisms, as well as studying the molecular make-up of individual patients' tumor cells, researchers have already pointed to many genes involved in cancer that are informing drug development, knowledge of biologic function, and DNA-based diagnostics. These findings all lead toward "precision medicine," an approach in which diagnoses are refined and treatments are custom-tailored based on the molecular make-up of an individual tumor. For some cancers, including leukemias and lung and breast carcinomas, targeted treatments developed based on these findings are already helping patients.

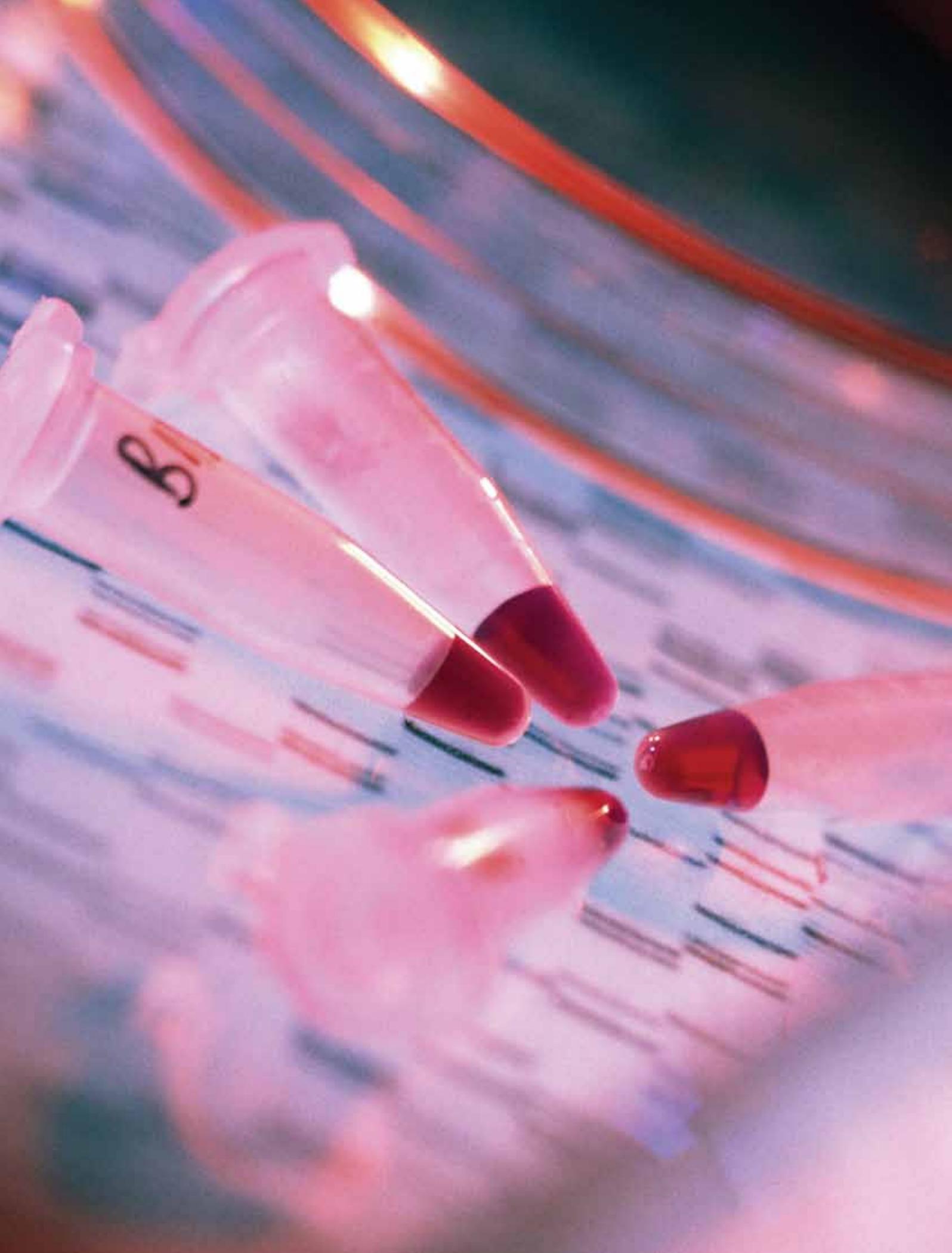
Recognizing the power of genomics, NCI recently established a Center for Cancer Genomics, with the mission of developing and applying genome science to better diagnose and treat cancer patients. NCI is supporting research to identify the genetic drivers of cancer, to advance adoption of precise tumor diagnosis and treatment, to prepare patients and their doctors for the changes in medical care influenced by genomics, and to protect privacy without blocking progress in cancer treatment or research.

The center was headed during its first year by renowned geneticist Barbara Wold, Ph.D., from the California Institute of Technology (Caltech). During her leave from Caltech (she joined NCI in September 2011), Wold worked to build the new organization. The center's flagship program, The Cancer Genome Atlas (TCGA),



Arul Chinnaiyan, M.D., Ph.D., and colleague at the University of Michigan Medical School, explore the practical aspects of genomic sequencing in clinical practice.

Microtubes containing purple solutions of DNA lying on top of an autoradiogram. The bands on the autoradiogram represent the sequences of genetic code of these DNA samples (right).



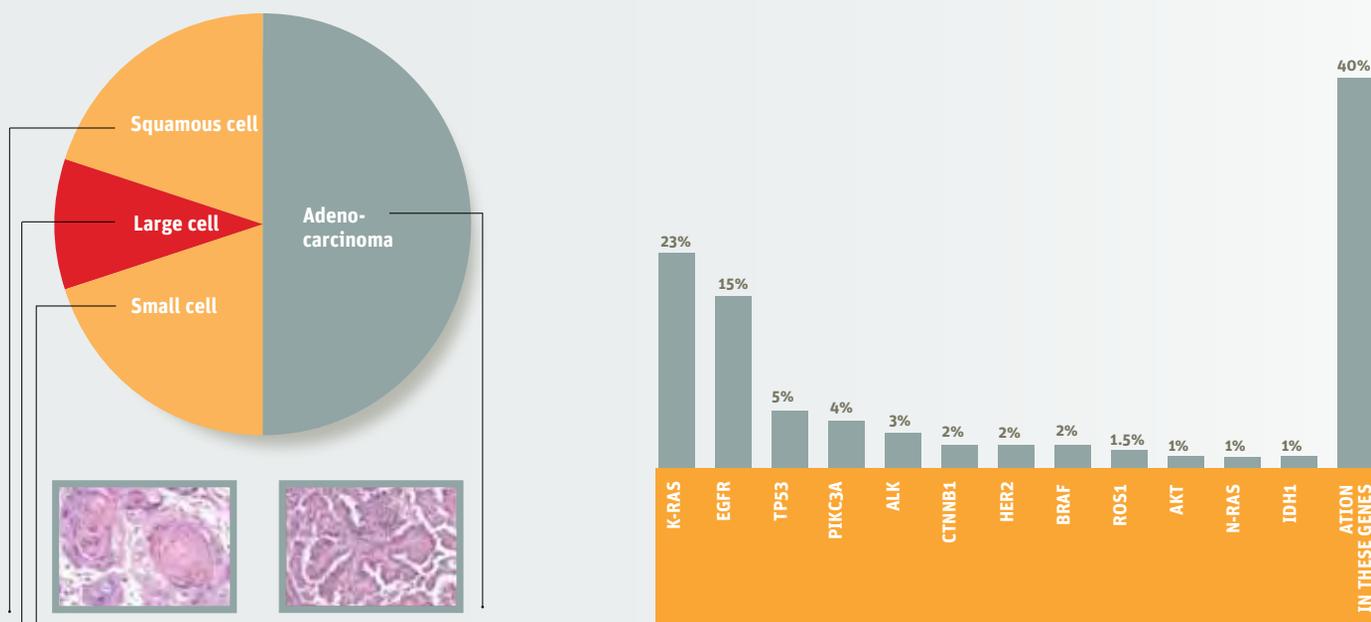
is a joint initiative of NCI and the National Human Genome Research Institute (NHGRI). TCGA is currently collecting and analyzing thousands of samples—as many as several hundred for each of more than 20 different cancers—to identify genetic and epigenetic features that drive the initiation and progression of cancer. The center will incorporate many other NCI-sponsored genomics initiatives, such as the Therapeutically Applicable Research to Generate Effective Treatments (TARGET) program, which aims to identify useful genetic markers in childhood cancers; the Cancer Genetic Markers of Susceptibility (CGEMS) project, a collaboration with NCI’s Division of Cancer Epidemiology and Genetics to use genome-wide association studies to identify inherited genetic susceptibility to prostate, breast, pancreatic, lung, and bladder cancers; and the Cancer Target Discovery and Development (CTD<sup>2</sup>) Network, which aims to bridge the gap between the enormous volumes of data generated by the comprehensive molecular characterization of various cancer types and the ability to use these data to develop human cancer therapeutics.

The Center for Cancer Genomics promotes opportunities to work with other agencies and with community physicians to usher in a modern era of prevention, diagnosis, and treatment based on the study of genomes, gene expression, proteomics, and other technologies. Right now, NCI is working with the cancer research community to ask: What are the key scientific opportunities? What is the best and speediest path to the clinic? Where are the bottlenecks in discovery, trial design, and standard of care? How can we best exploit the genomic sequencing of tumors in clinical practice to drive further discovery?

Discoveries based on genomics will lead to molecular diagnostics and drug development. In turn, clinical data from application of these new findings will be fed back into the system for continued discovery. “Complete understanding of cancer will come,” Wold said, “if we can harness data obtained in the clinic from patients and use it to inform and improve diagnosis and treatment in a cyclic way.”



Barbara Wold, Ph.D.



For decades, lung cancers have been categorized into four types based on the size and appearance of the malignant cells seen under a microscope. But genomic studies suggest that these types of lung cancers, such as adenocarcinoma, may be classified — and in some cases treated more effectively — by identifying the mutations present in patients’ cancer cells. Source: Levi Garraway, Dana-Farber Cancer Institute.

## Cancer Genomics Research: The Cancer Genome Atlas

Begun as a pilot project by NCI and NHGRI in 2006, The Cancer Genome Atlas (TCGA) established a research infrastructure and focused initially on the genomic characterization of three cancers: glioblastoma multiforme, ovarian cancer, and lung cancer. As one of the NIH’s signature programs under the American Recovery and Reinvestment Act, NCI and NHGRI expanded TCGA to characterize 20 cancer types in detail by 2014. By November 2011, TCGA had collected tissue samples (tumor tissue as well as normal tissue) from patients with most of those 20 cancers. A number have reached their 500-sample goal, and others are rapidly heading toward it. At the time of this writing, about a quarter of TCGA’s findings have been published, another quarter are being analyzed, and the remaining half are still in the data-collection stage.

In June 2011, TCGA researchers published as an open-access article—that is, a peer-reviewed article posted online and accessible to everyone, free of charge—the largest cancer genome study to date: an analysis of genome changes in ovarian cancer. They reported sequencing the whole exome

(examining all the protein-coding regions of the genome) on an unprecedented 316 ovarian tumors. The study confirmed that mutations in a single gene, *TP53*—a tumor protein involved in cell cycle arrest, apoptosis, senescence, and DNA repair—are present in more than 96 percent of the tumors. TCGA also identified a multitude of less-frequent mutations in other genes.

NCI and NHGRI are now using the capacity that has been built for these large efforts to sequence genomes of rare tumors that were not the original focus of TCGA or TARGET. Fewer samples, perhaps 50 rather than several hundred, will be sequenced. Through the NCI Center to Reduce Cancer Health Disparities, NCI is also working to obtain more samples from minority populations (see p. 44).

Meanwhile, researchers are starting to introduce complex molecular diagnostics into clinical trials and the care of individual patients. In a recent pilot test of so-called clinical sequencing, Arul Chinnaiyan, M.D., Ph.D., and colleagues at the University of Michigan Medical School, explored the practical aspects of genomic sequencing in clinical practice as part of a study funded by NCI and the Prostate Cancer Foundation. For an initial two patients—one with metastatic colorectal cancer and one with metastatic melanoma—they used a combination of sequencing technologies to identify and cross-validate classes of mutations and other genetic abnormalities that were common in these cancers. Moreover, they completed this project in less than a month and at a cost of just \$3,500. Now the University of Michigan researchers are setting up clinical protocols to match patients' genetic changes to clinical trials to demonstrate patient benefits.

### High-Quality Tissue Samples

In operating rooms around the country, tissue collected from patients is usually preserved in formaldehyde at room temperature and then embedded in paraffin. Later, it can be sliced for microscopic examination. These formaldehyde-fixed, paraffin-embedded (FFPE) samples are widely available, but the tissue is often not of high enough quality for genomic studies.

**“Forty years ago, cancer was a black box. We had essentially no understanding of how cancer cells differ from normal cells. Today we have a remarkably deep understanding of this process. Investment in basic research has paid off significantly, with effective new drugs based entirely on these discoveries. But this is just the beginning. I predict that over the next few decades we’ll see many more examples of currently difficult-to-control cancers coming under control, based on our sophisticated understanding of the inner workings of cancer cells, as well as powerful new technologies. It is important to point out that 40 years is a blink in time when one considers a disease that’s affected humanity since its beginnings,”** said Tyler Jacks, Ph.D., cancer researcher and director of the Koch Institute for Integrative Cancer Research at MIT.

## Precision Medicine

In November 2011, the National Academy of Sciences (NAS) released an important report, *Toward Precision Medicine: Building a Knowledge Network for Biomedical Research and a New Taxonomy of Disease*. The committee wrote that “realizing the full promise of precision medicine, whose goal is to provide the best available care for each individual, requires that researchers and health-care providers have access to very large sets of health and disease-related data linked to individual patients.”

That’s a lofty goal that requires much better integration of research and data from patient visits and patient care than exists today. The idea is to get information directly from patient populations treated at community settings—patients not enrolled in clinical trials—and feed it into the knowledge network used by researchers and clinicians.

To speed improvements in the control of disease, the committee called for a knowledge network that contains—and more importantly, integrates—all disease-relevant information, akin to a biomedical Google. Clinical care has improved for certain cancers because of genetic knowledge, but the pace could be faster. There is an abundance of disease-relevant data, but it’s not always carefully collected or made available in a usable form. The NAS committee envisioned marrying insights from basic and clinical research with data from patient care settings to enable discovery and lead to what they refer to as “precision medicine.”

Charles Sawyers, M.D., chair of the Human Oncology and Pathogenesis Program at Memorial Sloan-Kettering Cancer Center, and Tom Misteli, Ph.D., a senior investigator at NCI’s Center for Cancer Research who studies genome organization, were part of the NAS committee. Both described how a knowledge network would advance their work. Sawyers said he would like to see the clinical infrastructure adopt genomic profiling on a more routine basis to characterize tumors arising in all patients, especially the relatively small proportion of patients who are involved in clinical trials. It should become part of the baseline characterization of a cancer patient, he said, like getting a complete blood count or chemistry panel.

Basic scientists like Misteli could use the knowledge network as a new discovery tool. “A knowledge network—an interface between patient data and basic research—would allow us to mine the data in an unbiased way to

develop hypotheses and answer important questions,” Misteli explained.

### Protecting Privacy while Supporting Research

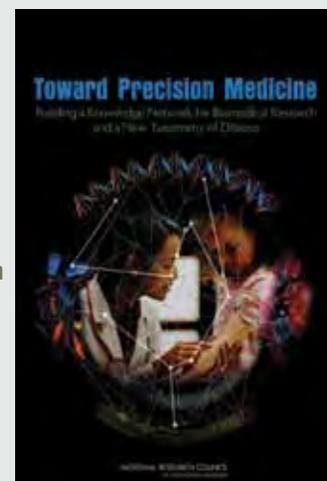
Obtaining and sharing data from patients will require an evolution in patient privacy rules. “If properly informed,” Sawyers said, “more patients are willing to share the data that emerge from studies of their tissues.

The opportunities for benefits today are much more obviously tangible, so it’s time for a rethinking of privacy rules.” With key legislation in place, particularly the Genetic Information Nondiscrimination Act, which prohibits discrimination in health insurance and employment based on genetic information, there is an opportunity to modify the strictness of current privacy rules.

“We need to get national consensus on patient consents,” said NAS committee member Isaac Kohane, M.D., Ph.D., the director of Children’s Hospital Informatics Program and Henderson Professor of Pediatrics and Health Sciences and Technology at Harvard Medical School. “Advocacy groups are very much in favor of sharing patient data for research. There are mechanisms that we can implement to allow patients to opt in or opt out of data sharing.”

Kohane directs a unit called Informatics for Integrating Biology and the Bedside, an NIH-funded National Center for Biomedical Computing site based at Partners HealthCare System in Boston. The center’s studies have shown that health care systems can be used to conduct genomic research and discovery research using the informational byproducts and the biological products of health care delivery. It also works to include minorities, who are often underrepresented in cohort studies but are frequent users of local, community-based medical centers.

The NAS committee recommended pilot projects to establish large databases over years or decades, to be mined by all interested parties in an open-source way. “Pilots should be done at point of care,” Sawyers said. “That should be the new model for learning in the future.”





Rigorous genomic studies like TCGA need the highest quality tissue samples available. Consequently, researchers have been limited to using tumor samples that were plunged directly into liquid nitrogen in the operating room before storage. This method offers high-quality samples, but it is costly and difficult to implement at a broad community level. Recently, however, new technology is making possible the comprehensive analysis of FFPE samples.

A histology technician in the NCI Department of Laboratory Pathology cuts paraffin blocks of tumor tissue into slices 3 to 4 microns deep.

Paul Mickey Williams, Ph.D., at NCI's Frederick National Laboratory for Cancer Research, compared gene expression profiling of tumor samples from patients with diffuse large B-cell lymphoma that were preserved via FFPE with those preserved via the rapid freezing method. Using material from 45 patients, he was able to accurately amplify and sequence RNA from both samples with 97.7 percent accuracy.

“If we are moving into a world of new and powerful diagnostic tests, we need to be certain that every patient has a specimen that is going to be of adequate quality,” Williams said.



## Old Specimens through a New Lens

Historically, tumor samples have been preserved in formalin and encased in paraffin wax blocks, a process called FFPE (“formalin-fixed and paraffin embedded”) that rendered them worthless for genomic study by then existing methods. But advances in technology have overcome this barrier and may soon open vast libraries of older samples to genomic scrutiny.

Researchers from the Huntsman Cancer Institute at the University of Utah recently used this new approach to analyze changes in the genome of Ewing sarcoma tumors, many of which were collected a decade or more earlier and preserved in paraffin. Ewing sarcoma is a rare cancer that strikes children, teenagers, and young adults; only 300 to 400 cases are diagnosed in the United States each year.

“The rarity of Ewing sarcoma poses a problem for cancer research,” said Huntsman’s Joshua Schiffman, M.D. “Because there are so few cases, it has been difficult in the past to find enough tissue samples to conduct valid studies of the genetics and biology of this disease.” Further complicating matters, most of the samples scientists have access to have been FFPE preserved.

“FFPE has been the standard technique for preserving pathology samples for decades,” said Schiffman. “But until recently, genomics technology has not been available to make use of the huge resource these samples represent.”

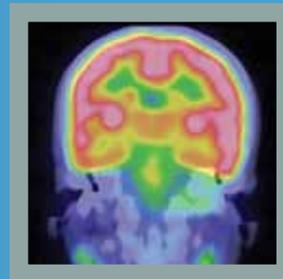
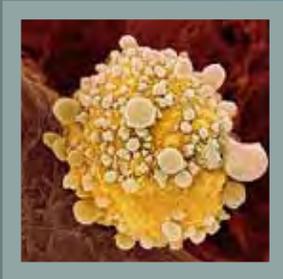


Using the new tool, however, the Huntsman team analyzed 40 FFPE samples of primary tumors from Ewing sarcoma patients who were treated at Primary Children’s Medical Center in Salt Lake City during the past 12 years. “This doesn’t sound like a large sample, but for this rare cancer, it reflects 10 percent of all cases diagnosed in a given year, so the quantity is significant,” he added.

The researchers recently published their findings about the genome of Ewing sarcoma in *Cancer Genetics*, where they reported finding a previously unknown sarcoma subtype, genetic factors related to long-term survival, and identification of a genetic change between the primary and metastatic stages of the disease that could lead to better, more targeted treatment for patients who have Ewing sarcoma.

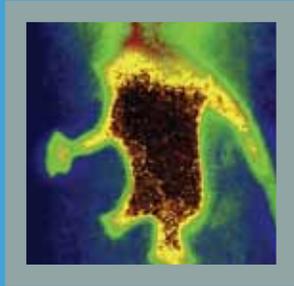
“Our results will have to be validated with a larger number of samples, but this gives us the tool to do that on clinically archived samples,” said Schiffman. “Clearly, learning more about FFPE-preserved tumor samples with these genomic factors will be essential to finding new treatments that will improve overall survival among all Ewing sarcoma patients.”

# Introduction to Cancer Profiles



The disease we call cancer is, in actuality, a collection of diseases, each of which poses a different set of questions for the researchers who search for causes, mechanisms, and commonalities that will inform better prevention, detection, diagnosis, and treatment. The pages that follow present profiles of five cancers, which represent a small slice of NCI’s extensive research portfolio. For some of these cancers, we’re able to tell a story of important and recent progress in controlling them. Other cancers we profile remain resilient and difficult to treat, despite our research efforts, but our growing understanding of the basic cancer biology in these cancers offers promise for effective intervention.

For the vast majority of cancers, it takes years—often decades—for the complement of mutations necessary to drive the disease to occur. This is why three-quarters of all cancers in the United States are diagnosed in people who are 55 years of age or older. For some cancers, such as colorectal cancer, many of the molecular steps that silently accumulate during the cancer’s quiescent stages have been identified, and

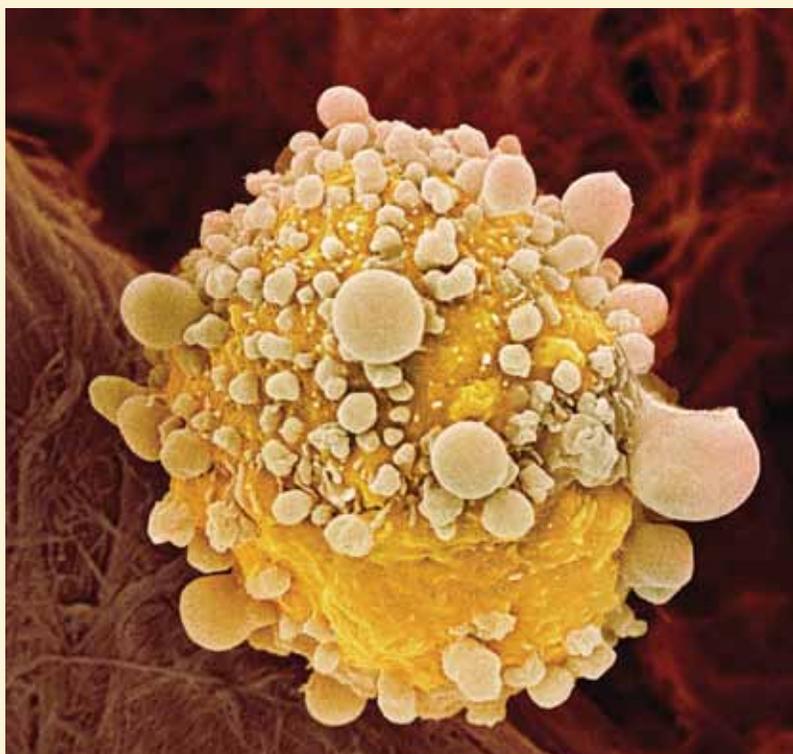


improved screening methods—which offer the best control for colorectal cancer—have been developed. For renal cancer, studies of highly affected families have provided insight into the genetic underpinnings of not only inherited forms of the disease but also of sporadic, or non-inherited, forms. Comprehensive genomic analysis is also facilitating classification of diseases such as B-cell lymphoma, which should inform research and lead to individualized treatments. For some cancers, such as those of the pancreas, a better understanding of the tumor microenvironment and host factors may help achieve the improvements in patient outcomes that have been elusive to date. Targeted therapies, such as imatinib (Gleevec®) in gastrointestinal stromal tumors, illustrate the potential power of therapies directed at genetic targets.

NCI is committed to answering the most pressing questions for each cancer type and continuing to pursue fundamental knowledge about the inner workings of cancer cells, building upon past discoveries, so that we can eventually control cancers of all types.

## PANCREATIC DUCTAL ADENOCARCINOMA

Because pancreatic cancer is often diagnosed at a late stage, surgical removal of the tumor or the organ is often difficult, if not impossible. Pancreatic ductal adenocarcinoma, or PDAC, is by far the most common type of pancreatic malignancy. PDAC is distinct from other cancers due to the biological barrier the tumor builds around itself. Patients whose disease is caught at an early stage have a better chance of long-term survival, but the pancreas emits few known clues to signal that the carcinogenic process has begun, so there are currently no early detection tests. For more than 30 years, NCI-supported laboratory scientists have been studying a gene called *KRAS*, the genetic driver of pancreatic cancer initiation and progression. However, at this time, no therapeutic solutions to *KRAS* mutations have been developed. Pancreatic cancer is the fourth leading cancer killer in the United States. Overall, just 6 percent of patients survive 5 years after diagnosis. In 2012, it is estimated that there will be 43,920 new diagnoses of pancreatic cancer and 37,390 deaths will be attributed to it. Further identifying risk factors and genetic changes, achieving greater understanding of the metastatic process, and developing better methods of early detection and treatment offer the means of better controlling PDAC.



Pancreatic cancer cell. Colored scanning electron micrograph (SEM) of a pancreatic cancer cell.

The pancreas contains two types of tissue that have distinct jobs. Pancreatic endocrine tissue, which gives rise to pancreatic neuroendocrine tumors, is responsible for making hormones, such as insulin, that help regulate blood sugar levels. Pancreatic exocrine tissue produces enzymes that aid in digestion. Pancreatic ductal adenocarcinoma, or PDAC, arises in exocrine tissue, specifically in the cells comprising the ducts that carry pancreatic digestive enzymes to the small intestine. PDAC accounts for more than 90 percent of all pancreatic cancers. It is these tumors, which are most often fatal, that are the focus of this profile.

### Mouse Models Help Reveal Tumor Defense

In 2003, Sunil Hingorani, M.D., Ph.D., and colleagues at the University of Pennsylvania, with funding from NCI's Mouse Models of Human Cancer Consortium, engineered a mouse model of human PDAC and were able to watch the disease unfold step by step. Similar to PDAC tumors in humans, the tumors in these mice are surrounded by a dense cellular matrix, or stroma, that forms a shield around the tumor mass, like the shell around a walnut. This shell causes increased fluid pressure within the tumor microenvironment that compresses existing blood vessels, thereby limiting the blood supply to the tumor. Consequently, when a chemotherapy drug is administered, the restricted blood flow prevents sufficient amounts of the drug from reaching the tumor.

The precise mechanisms that cause this restricted blood flow are not fully understood. However, mouse models are proving to be an invaluable tool in the

search for answers to this question and questions about many types of human cancer, as well as in devising new therapeutic options for patients. In 2009, Kenneth Olive, Ph.D., and others at the Cambridge Research Institute in London used mouse models of human PDAC to show that an experimental drug that inhibits an intracellular signaling pathway linked to several cancers (known to researchers as the “Hedgehog” pathway) caused regression of the stromal barrier surrounding pancreatic tumors, subsequently leading to the expansion of tumor blood vessels. The reopening of the vasculature permitted increased delivery of the chemotherapy drug gemcitabine to the tumors, resulting in inhibition of tumor growth. This discovery suggests that inefficient drug delivery may be one reason that pancreatic tumors do not respond well to chemotherapy.

Hedgehog pathway inhibitors have since been tested in clinical trials of pancreatic cancer, with mixed results, but other approaches to breaking down the stromal barrier are also being investigated. Two teams—one led by Hingorani at the Fred Hutchinson Cancer Research Center in Seattle, and the other led by David Tuveson, M.D., Ph.D., then at the Cambridge Research Institute in the United Kingdom—recently reported that an enzyme called PEGPH20, which targets a molecule called hyaluronan, improves delivery of the drug gemcitabine to mouse pancreatic tumors. Hyaluronan, or hyaluronic acid (HA), is a complex sugar that occurs naturally in the body and is a major component of the stromal matrix surrounding pancreatic tumors. Like the Hedgehog inhibitors, PEGPH20 caused alterations to the stroma and vasculature of mouse PDAC, permitting high concentrations of gemcitabine to

spread throughout the tumors. The result was a significant increase in the survival time of mice treated with gemcitabine plus PEGPH20 compared with mice treated with gemcitabine alone. An early-phase clinical trial is under way to test the combination of PEGPH20 and gemcitabine in people with metastatic pancreatic cancer.

### Risk Factors

To learn more about the role of inherited genes in predisposing people to pancreatic cancer, the NCI-supported Pancreatic Cancer Cohort Consortium conducted two genome-wide association studies. These types of studies, which involve the rapid scanning of DNA markers across the complete genomes of many people, seek to identify genetic variations associated with a particular disease. The researchers discovered four novel regions in the genome that are associated with risk for pancreatic adenocarcinoma, and they are now investigating these associations by examining the functions of genes in the four regions.

As with many other cancers, lifestyle and comorbid conditions may play a role in pancreatic cancer. Until recently, however, only two factors were known to increase pancreatic cancer risk: cigarette smoking and diabetes. Studies by researchers, including investigators in NCI’s Division of Cancer Epidemiology and Genetics, have now revealed that several additional factors may increase pancreatic cancer risk, including intake of foods high in fat (particularly from processed and animal sources), heavy alcohol use, being overweight or obese in young adulthood, and older age. (The link between obesity and cancer is being addressed in NCI’s Provocative Questions initiative, page 4.) Approximately one-quarter of pancreatic cancers

are attributable to an “unhealthy lifestyle,” according to the findings. New efforts are under way to clarify the mechanisms underlying these associations.

Research on many cancer risk factors, including diet, stress, inflammation, and environmental exposures, will be significantly enabled by a new experimental population research resource.

### Uncovering New Drivers of Pancreatic Cancer through Rapid Autopsy

Past analyses of malignant pancreatic tumors have revealed that virtually all of them harbor mutations in the *KRAS* gene. Other commonly mutated genes have been known for some time to include the tumor suppressors *p16*, *p53*, and *SMAD4*. More recently, researchers have begun trying to uncover the mechanisms of PDAC metastasis. As part of this effort, Christine Iacobuzio-Donahue, M.D., Bert Vogelstein, M.D., and their colleagues at Johns Hopkins University studied samples of primary tumor tissue and metastatic tissue from the lungs, liver, and other organs of patients who had undergone a procedure known as rapid autopsy.

In rapid autopsy, which represents a new approach in pancreatic cancer research, tissue is collected within a few hours of a patient’s death. Because DNA, RNA, and other molecules within cells begin to degrade shortly after death, rapid autopsy allows researchers to collect tissue samples that will yield clearer insights into the biological processes that contribute to pancreatic cancer and other diseases.

The Johns Hopkins University team sequenced every gene in rapid autopsy specimens from seven patients to compare the genetic mutations in metastatic lesions versus the primary tumor. Some of the mutations they found were present in most or all of the primary tumor cells, suggesting that they occurred before the development of metastasis. However, in each patient, a set of progressor mutations was also identified. Progressor mutations are genetic changes that are present in one or more of metastases examined, as well as in pockets of cells within the primary tumor. Overall, the Hopkins team's data indicate that cells within the primary tumor, which all descended from a single cell, accumulate additional mutations over time, giving rise to subpopulations of cells, some of which are able to leave the pancreas and take root in other parts of the body. Further analysis of the affected genes should help elucidate the cellular pathways that contribute to pancreatic cancer progression and metastasis.

Rapid autopsy programs have now been established at the Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins University and the University of Nebraska Medical Center's Eppley Institute for Research in Cancer and Allied Diseases. To date, these two centers have conducted more than 100 rapid autopsies of patients with pancreatic cancer who died despite aggressive treatment.

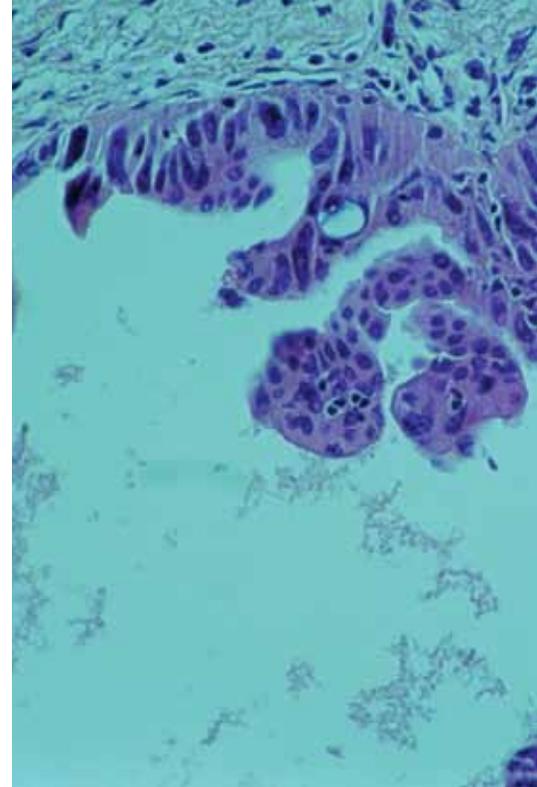
In addition, there is growing evidence that the tumor microenvironment plays an important role in conferring drug resistance and in tumor recurrence. The NCI Tumor Microenvironment Network (TMEN) consortium is addressing this important area of research with multiple human cancers, including PDAC, using

tissues from rapid autopsy to delineate the mechanism of tumor stroma-conferred resistance.

#### Detection is Key

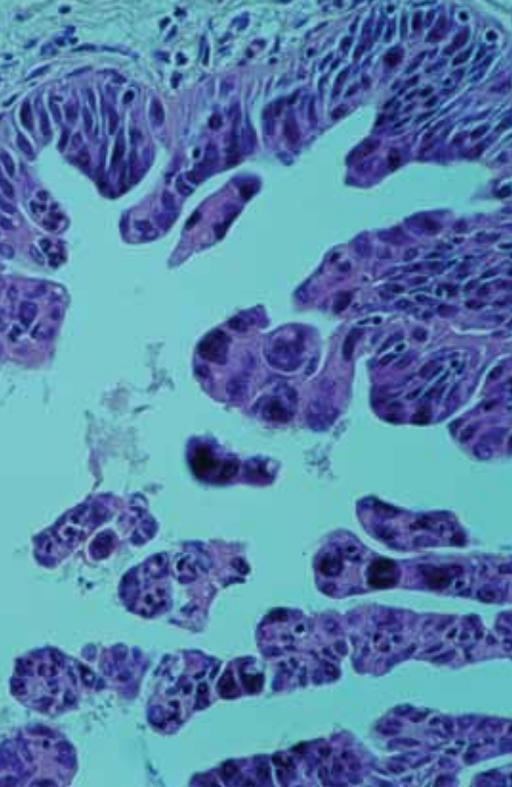
The American Cancer of the Pancreas Screening (CAPS) Consortium, established by Marcia Canto, M.D., at Johns Hopkins University and researchers at four other U.S. institutions, is developing approaches to detect and selectively treat asymptomatic high-grade precancerous lesions of the pancreas, which are more likely to respond to treatment than advanced pancreatic tumors. NCI and the Lustgarten Foundation, a nonprofit organization focused on advancing pancreatic cancer research, funded a recently completed CAPS study. The CAPS team used three common imaging modalities—computed tomography (CT), magnetic resonance imaging (MRI), and endoscopic ultrasound (EUS)—to screen individuals at high risk of developing pancreatic cancer because of a strong family history of the disease or the presence of a predisposing genetic mutation, such as a *BRCA2*, *p16/CDKN2A*, or *STK11* gene mutation.

About 42 percent of the symptom-free CAPS study participants were found to have at least one pancreatic mass, and many had multiple lesions. Most of the masses were small cysts that warranted only continued monitoring, but a small number of participants were found to have noninvasive high-grade lesions, which were subsequently removed surgically. The results of the study revealed that MRI and EUS are better than CT for detecting pancreatic lesions. However, more research is needed to better identify individuals for whom this kind of screening is appropriate and to guide decisions about next steps when lesions are found, since many lesions may pose no threat to the patient. CAPS



researchers are continuing to address these issues in another clinical trial that is already under way and in a planned international collaboration involving researchers from 10 countries on four continents.

Although imaging may offer visual clues about the presence of pancreatic cancer and its precursors, biomarkers may provide different or complementary information for early detection. With funding support from the NCI Mouse Models of Human Cancers Consortium and the institute's Early Detection Research Network, Samir Hanash, M.D., Ph.D., and others at the Fred Hutchinson Cancer Research Center joined forces with investigators at Harvard Medical School and the University of Michigan to conduct an in-depth analysis of the proteins in the plasma of a genetically engineered mouse model of pancreatic cancer. Based on samples from mice with early-stage disease, similar to the PDAC precursors detected in the CAPS study, the team identified a panel of five biomarkers that were elevated in diseased mice compared with their healthy counterparts. The team is now studying whether the candidate biomarkers, when



Light micrograph of a section through an adenocarcinoma of the ducts of a human pancreas.

measured in blood samples taken from individuals at high risk of cancer, are able to distinguish those who would subsequently be diagnosed with pancreatic cancer from those who would not.

Another team at the University of Nebraska Medical Center's Eppley Institute for Research in Cancer and Allied Diseases has been working to develop a test that harnesses the body's immune response to pancreatic cancer cells to aid in detection and diagnosis. In a recent study, the Eppley team looked at all of the genes expressed in peripheral blood mononuclear cells (immune cells including monocytes, T lymphocytes, B lymphocytes, and natural killer cells) from 26 patients with pancreatic cancer and 33 healthy control subjects. They found a number of genes that were expressed at different levels in the two groups and identified a "predictor set" of eight genes that was able to distinguish between

those with pancreatic cancer and those without the disease with considerable accuracy. Moreover, there is some evidence that premalignant pancreatic lesions also induce immune system changes, suggesting that it might be possible to exploit these changes to detect noninvasive pancreatic lesions before they become invasive cancers.

To be useful, early detection methods for pancreatic cancer should be able—at a minimum—to identify disease before it has metastasized outside the pancreas. However, scientists still do not understand the process by which tumor cells leave the pancreas and take root in other places in the body. The Johns Hopkins team that sequenced DNA from primary tumors and metastases used mathematical modeling and clinical histories to estimate how long it took for the identified mutations to accumulate. They concluded that, on average, it took more than 11 years for a "mature" tumor to form after the occurrence of the first cancer-related mutation in a pancreatic cell, and that it took an additional 6 years before cells from the primary tumor gave rise to a metastatic lesion at another location. A follow-up modeling study involving a larger number of rapid autopsy patients illustrated the heterogeneity of the metastatic process: Some patients with tumors smaller than 1 centimeter in size will have metastases while a small percentage of patients with larger tumors will be metastasis-free. The possibility of early metastases was demonstrated in the laboratory of Ben Stanger, M.D., Ph.D., at the Abramson Cancer Center of the University of Pennsylvania, where pancreatic tumor cells were found to enter the bloodstream of a mouse model of pancreatic cancer even before an overt tumor could be found in the pancreas.

### Innovative Funding Strategies

NCI is working with a group of organizations, including the Pancreatic Cancer Action Network, the Lustgarten Foundation, and the National Pancreas Foundation, to explore cooperative strategies for funding pancreatic cancer research. These funding strategies would allow meritorious grant applications to be passed from one organization to another for funding support.

Each organization continues to support branches of research most vital to its goals, such as improved mouse models of pancreatic cancer. These models allow researchers in many institutions to study how cancer arises via a constellation of mutations that are known from the analysis of tumors. Mouse models also provide researchers with a common platform for drug testing at many of the NCI-designated cancer centers. In addition, the Lustgarten Foundation is completing a pancreatic cancer biomarkers initiative aimed at identifying substances in the blood, body fluids, or tissue that signal a risk of cancer or its presence at very early stages. The Lustgarten Foundation also identified and funded research groups working to develop antibodies to the biomarkers identified through the initiative, with the stipulation that all antibodies would be deposited with the NCI Early Detection Research Network and made freely available to the cancer research community.

## COLORECTAL CANCER

Colorectal cancer originates in the mucosal tissue that lines the inside of the colon and rectum. It is thought that most cases of colorectal cancer develop progressively from small abnormal growths called polyps. Ninety percent of colorectal polyps are classified as hyperplastic polyps, growths that generally do not become cancerous. The remaining 10 percent of colorectal polyps are classified as adenomatous polyps, or adenomas, and research has shown that these lesions give rise to virtually all cases of colorectal cancer. Because there is evidence that it takes approximately 10 years for an adenomatous polyp less than 1 centimeter in size to transform into an invasive colorectal tumor, most of these polyps should be detectable by screening—and removed—before they can become cancerous. Therefore, regular screening, especially with flexible sigmoidoscopy or colonoscopy, is probably the single most important tool in the medical toolbox for colorectal cancer, since finding and removing precancerous polyps and early cancers is the best way to reduce morbidity and mortality from this disease. Over the years, clinical implementation of these insights has already saved tens of thousands of lives, with a reduction in colorectal cancer deaths by approximately 3 percent per year from 1999 through 2008—a decrease of around 30 percent. Still, in 2012 it is estimated that more than 143,000 Americans will be diagnosed with colorectal cancer and more than 51,000 will die from the disease.



Colon cancer. Colored X-ray showing cancer (green) of the colon. The colon, together with the much smaller rectum, forms the large intestine.

The first step in virtually all colorectal cancers is the runaway proliferation of cells in the mucosal epithelium of the colon or rectum that begins with mutation of a tumor suppressor gene. Such mutations are rarely hereditary and most are believed to be related to lifestyle factors, including diet, although a family history of colorectal cancer is a risk factor for the disease.

This excessive cell proliferation can almost always be traced back to problems in the Wnt signaling pathway, a network of proteins that plays a role in embryonic development, cell differentiation, and many other critical cellular processes. Alterations or aberrations in this pathway are also linked to the initiation and progression of many kinds of cancer, as tumorigenesis is a likely result when the Wnt pathway goes awry.

One way the Wnt signaling pathway has been implicated in colon and rectal cancers is through mutation of the tumor suppressor gene *APC*. This gene normally suppresses Wnt signaling, and thus suppresses tumorigenesis. After mutation of one copy of *APC*, however, silencing of the cell's other copy by a second molecular event is sufficient to allow for uncontrolled cell proliferation, leading to the formation of an early adenoma. Progression from an early adenoma to invasive carcinoma is thought to involve the acquisition of additional mutations in other genes.

To date, scientists have identified a number of mutations that contribute to the initiation and progression of colorectal cancer. In addition to *APC*, in

those cases in which *APC* is not mutated, other genes mutated in colorectal cancer include *KRAS*, *PIK3CA*, *TP53*, *SMAD4*, *PTEN*, *BRAF*, and *FBXW7*. Moreover, mutations in genes involved in DNA repair (mismatch repair genes), such as *MSH2*, *MLH1*, *MSH6*, and *PMS2*, have been associated with one of the well-known types of inherited predisposition to the development of colorectal cancer. The discovery of these genes and the way they work represents a milestone in cancer research and understanding. Many of these same genes have been shown to play a role in other tumor types, such as those of the breast, pancreas, brain, stomach, lung, and prostate.

Researchers supported through NCI's Integrated Cancer Biology Program and using data generated through The Cancer Genome Atlas project (see p. 11) are beginning to explore how the complex interplay of known genetic alterations, both driver and passenger mutations, interact during the development of colorectal cancer. Using sophisticated computational tools, these approaches will help uncover new targets for diagnosis and intervention.

These are not simply intellectual triumphs. They have important implications for reducing the morbidity and mortality from colorectal cancer. Through molecular, epidemiologic, and mathematical studies of colorectal cancer, we now know that it takes an average of 30 years for a patient to die following the molecular event—often a mutation in the *APC* gene—that initiated his or her tumor. The final stage, metastasis, begins an average of 27 years after the initial event. Importantly, up until the metastatic stage, virtually all colorectal tumors, whether benign or malignant, can be cured

by surgery alone, without the need for any additional therapy. Put another way, a death from colorectal cancer today will most likely occur because the cancer or its precursor adenoma was not detected during the preceding 27 years.

### Hereditary Forms of Colorectal Cancer

Although hereditary forms of the disease account for only about 10 percent of the total number of colorectal cancers diagnosed in the United States, the affected families are often decimated by cancer, with parents, siblings, and extended relatives developing the disease at an early age, often in the prime of life (30s and 40s) and sometimes even younger. However, these cases have also offered some of the best clues about the initiation and progression of colorectal cancer. Many hereditary colorectal cancer syndromes have been recognized for decades, but the molecular basis for them was unknown. Scientists now know the genomic basis for every one of these syndromes. Familial Adenomatous Polyposis, Hereditary Non-Polyposis Colorectal Cancer (HNPCC, or Lynch syndrome), Attenuated Polyposis, Peutz-Jeghers syndrome, Juvenile Polyposis Syndrome, and others are each caused by a hereditary mutation in one or more genes.

These discoveries have completely changed the management of disease in families with these syndromes. Tests for detecting the relevant mutations are now commercially available, and members of these families can determine in childhood whether they have inherited a mutated gene or not. Those who have only normal copies of the genes can be reassured that their colorectal cancer risk is no higher than average. Conversely, those who have inherited a mutated gene may undergo surveillance for

colorectal polyps or tumors earlier and more frequently and have lesions removed when they are still benign. Some patients may require removal of some or all of the colon. With appropriate genetic counseling and surveillance measures, most patients with hereditary colorectal cancer syndromes can have life expectancies similar to those of the general population.

### DNA Mismatch Repair

HNPCC, or Lynch syndrome, is the most common form of inherited colorectal cancer and is characterized by defects in a DNA repair mechanism called mismatch repair (MMR). The defects are caused by hereditary, or germline (affecting every cell in the body), mutations in the MMR genes *MLH1*, *MSH2*, *MSH6*, and *PMS2*. These genes encode proteins that act as proofreaders that identify and correct errors that naturally occur when cells replicate their DNA content during cell division. When mutations inactivate both copies of an MMR gene, other mutations start accumulating throughout the genome because cells are now unable to properly repair “mismatches” that occur during DNA replication. Some of the mutations that would have been repaired under normal circumstances can now potentially contribute to the development of cancer. In addition, MMR proteins are thought to play a role in other processes that help suppress carcinogenesis: DNA damage surveillance and the prevention of recombination between two non-identical DNA sequences. Proper MMR function is vital to cellular health and function. People with Lynch syndrome have an increased risk of developing not only colorectal cancer, but also endometrial, ovarian, stomach, liver, urinary tract, brain, and skin cancers.

Because the cell's replication machinery makes mistakes more frequently on repetitive sequences, MMR-defective cells often display variability in the length of DNA segments known as microsatellites, which are comprised of short (two to six bases), tandemly repeated sequences. This variability in microsatellite DNA length is called microsatellite instability. Genes that contain microsatellites in their coding regions have an increased risk of mutation. Compared to cells with a normal MMR system, cancer cells with a defective MMR system are more prone to acquiring and retaining new mutations in cancer-associated genes, such as *TGF-βRII*, *TCF4*, *IGF2R*, and *BAX*. It is estimated that MMR-defective cells have mutation rates 100 to 1,000 times higher than normal cells. MMR defects occur in approximately 15 percent of non-hereditary colorectal tumors, as well as in some other cancers, such as endometrial cancer and gastric cancer. The mechanism of how these defects arise is different: MMR genes are silenced through an epigenetic mechanism called DNA methylation, rather than genetic mutation, as in patients with Lynch syndrome.

### Therapy

The prognosis for patients with metastatic colorectal cancer has improved significantly in the past decade. Surgery is curative for most patients during the first stage of the disease. Additional improvement has been realized, in part, because of the unprecedented way in which these cancers can and have been studied as they grow—the same techniques that make them good targets for prevention make them easy to study in patients. But progress also has come through painstaking research into the best conventional chemotherapy drug combinations, advances in

imaging and radiotherapy, and the development of new antibody therapies such as cetuximab and panitumumab, which both target a protein called the epidermal growth factor receptor. As a result, more than 50 percent of patients with metastatic colorectal cancer can expect to live longer than 5 years, far longer than expected in the past.

### More Effective Screening

The practical implications of this knowledge are clear: One important way to reduce the suffering and death from colorectal cancer is to detect it before it occurs or metastasizes. Recent studies show that the removal of polyps helps reduce colorectal cancer deaths by up to 50 percent. Increasing the prevalence of colorectal cancer screening might result in an even greater reduction in the future.

There are several effective screening options. Colonoscopy is a procedure in which a flexible tube with a tiny camera (called an endoscope) is inserted through the rectum and allows visualization of the entire colon. If a polyp is found, it can be removed during the procedure. Sigmoidoscopy also uses a flexible endoscope and allows polyp removal during the procedure, but less of the colon is visualized than with colonoscopy. Fecal occult blood tests check for blood in stool specimens. NCI is also funding a study of “virtual colonoscopies,” which allow the detection of polyps without the insertion of tubes into the colon or rigorous bowel preparation procedures. Additionally, NCI-funded investigators are engaged in developing blood-based and stool-based tests that can detect abnormal genes or other biomarkers that could improve early detection.

Public health specialists will have to determine the optimal ways to ensure compliance with evidence-based screening guidelines in appropriate populations, as well as to ensure greater uptake of preventive measures, such as diet and lifestyle changes.

## NCI's Cancer Genome Atlas Yields Insights Into Colorectal Cancers

The Cancer Genome Atlas project this summer provided the most recent elucidation of just how critical the new era of genomically informed medicine will be for colon and rectal cancers. (See related story on TCGA on p. 11.)

Initially, the TCGA Research Network studied colon tumors as if they were distinct from rectal tumors. However, according to TCGA's large-scale genetic analysis of colon and rectal cancer tissue specimens, the pattern of genomic alterations in colon and rectal tissues is the same, regardless of anatomic location or origin within the colon or the rectum. Therefore, these two cancer types can be grouped as one.

Other findings from the TCGA colorectal study point to additional treatment options. There is a known association between the aggressiveness of colorectal tumors and the phenomenon of hypermutation, in which the rate of genetic mutation is abnormally high because normal DNA repair mechanisms are disrupted. In the TCGA study, 16 percent of the specimens were found to be hypermutated. Three-fourths of these cases exhibited microsatellite instability, which often is an indicator of better prognosis. Microsatellites are repetitive sections of DNA in the genome. If mutations occur in the genes responsible for maintaining those regions of the genome, the microsatellites may become longer or shorter.

The investigators observed that 24 genes were mutated in a significant number of the 224 colorectal cancer specimens examined. In addition to genes found through prior research efforts (e.g., *APC*, *ARID1A*, *FAM123B/WTX*, *TP53*, *SMAD4*, *PIK3CA*, and *KRAS*), the scientists identified three other genes (*ARID1A*, *SOX9*, and *FAM123B/WTX*) as potential drivers of this cancer when mutated. It is only through a study of this scale that these three genes could be implicated in this disease.

The research network also identified the genes *ERBB2* and *IGF2* as mutated or overexpressed in colorectal cancer and, therefore, as potential drug targets. These genes are involved in regulating cell proliferation and were observed to be frequently overexpressed in colorectal tumors. This finding points to a potential drug therapy strategy in which inhibition of the products of these genes would slow progression of the cancer.

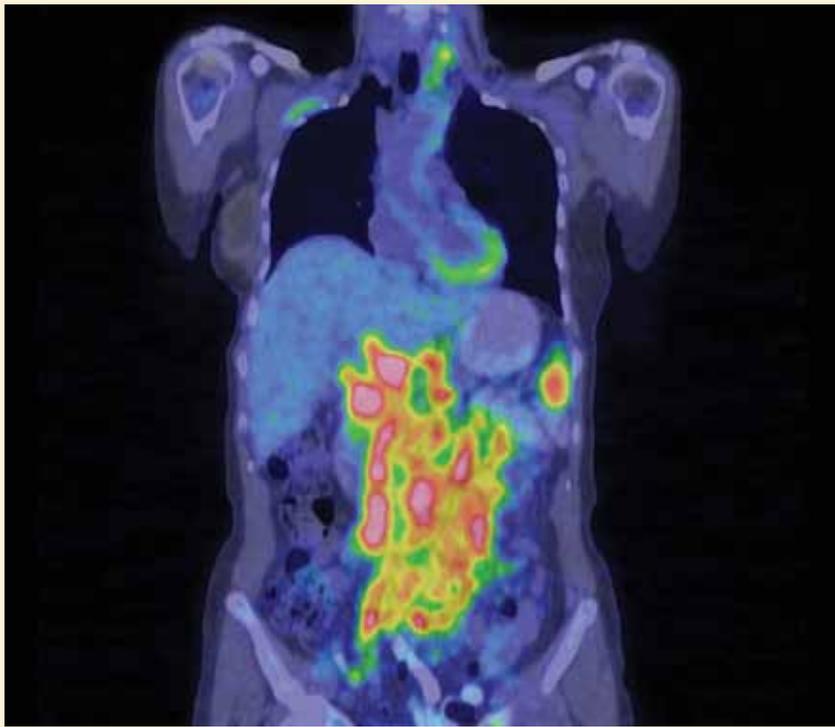
A key part of this study was the analysis of signaling pathways. Among their many functions, signaling pathways control gene activity during cell development and regulate the interactions between cells as they form organs or tissues. Among other findings, the TCGA Research Network identified new mutations in the Wnt pathway, which is altered in more than 95 percent of colorectal cancers. According to the researchers, this finding will improve development of Wnt

signaling inhibitors, which show initial promise as a class of drugs that could benefit colorectal cancer patients.

In addition to examining the Wnt pathway, the investigators identified RTK/RAS and AKT-PI3K as pathways that are altered in a substantial set of colorectal tumors, which therefore may show promise for developing targeted therapies for colorectal cancer. Because of these findings, drug developers may now be able to narrow their scope of investigation with an expectation of producing more focused therapeutic approaches.

## B-CELL LYMPHOMA

Lymphomas are cancers that arise from lymphoid cells, which are part of the immune system. The World Health Organization currently recognizes about 70 different types of lymphoma and divides them into four major groups: mature B-cell neoplasms, mature T-cell and natural killer cell neoplasms, Hodgkin lymphoma, and immunodeficiency-associated lymphoproliferative disorders. Although Hodgkin lymphoma is a B-cell malignancy, it is characterized by an abnormal type of cell known as the Reed-Sternberg cell, which is not found in other types of B-cell lymphoma. Collectively, lymphomas represent about 5 percent of all cancers diagnosed in the United States. In 2012, it is estimated that 79,000 Americans will be diagnosed with lymphoma and 20,100 will die from the disease. Although lymphoma incidence rates have been stable over the past decade, lymphoma death rates have been declining steadily. These declines in mortality can be attributed to improvements in treatment. Today, the 5-year relative survival rate for all patients diagnosed with lymphoma is approximately 71 percent; for patients diagnosed with Hodgkin lymphoma, it's about 85 percent. Indeed, Hodgkin lymphoma is now considered one of the most curable forms of cancer. Treatments for lymphoma include surgery, watchful waiting, chemotherapy, radiation therapy, and targeted therapy. The choice of treatment depends on the type and grade of the lymphoma, the stage of the disease, and the age and general health of the patient.



FDG-PET/CT fusion image of the body, frontal section, showing B-cell (type B) non-Hodgkin lymphoma with abdominal lymph node localization and splenic involvement.

©Centre Jean Perrin

The cells that give rise to lymphomas are the progeny, or offspring, of blood stem cells, which are multipotent cells that divide to produce myeloid cells and lymphoid cells. Myeloid cells include red blood cells and white blood cells known as granulocytes (eosinophils, neutrophils, and basophils). Lymphoid cells include T cells, B cells, and natural killer cells. Lymphoma is a disease of lymphoid cells, with B-cell cancers representing up to 80 percent of all lymphomas diagnosed in adults. This profile focuses on a B-cell lymphoma known as diffuse large B-cell lymphoma, or DLBCL.

### Not Just a Single Disease

B cells are an integral part of the adaptive immune system, which is also known as the specific immune system. This part of the immune system is activated in response to invading pathogens, such as bacteria and viruses, and it has the ability to remember previous contacts with foreign invaders, mounting stronger responses to them each time they are encountered. A portion of activated B cells will develop into antibody-producing plasma cells. Others will become “memory cells” that can be activated in response to future attacks.

Over the past decade, Louis M. Staudt, M.D., Ph.D., chief of NCI’s Molecular Biology of Lymphoid Malignancies Section, has been a leader in the effort to classify B-cell lymphomas based on their molecular underpinnings. He and his colleagues study gene mutations linked to cancer development and changes in gene activity that are associated with particular tumor types. Using DNA microarrays and gene expression profiling, Staudt and his colleagues have identified new forms of B-cell lymphoma that

are indistinguishable by diagnostic methods currently in widespread use. For example, they found that DLBCL, which oncologists previously thought was the most common type of lymphoma, is actually three distinct diseases—germinal center B-cell-like (GCB) DLBCL, activated B-cell-like (ABC) DLBCL, and primary mediastinal B-cell lymphoma—each of which responds differently to therapy.

For example, genetic analyses performed by Staudt and his colleagues revealed that mutation of a gene called *MYD88* in ABC DLBCL tumors can lead to chronic activation of a signaling pathway known as the nuclear factor kappa B (NF- $\kappa$ B) pathway, which promotes cancer cell survival. “We found that

if you can interrupt this survival pathway,” Staudt said, “you can kill the lymphoma cells.”

Moreover, Staudt and his colleagues identified mutations in two additional genes in ABC DLBCL tumors that appear to contribute to lymphoma development: *CD79* and *CARD11*. Now, they are looking for drugs that counteract the effects of these three mutations.

“We understand many of these cancers, from a biological perspective, much better than we did a decade ago,” said Wyndham Wilson, M.D., Ph.D., head of NCI’s Lymphoma Therapeutics Section. “And what’s important is that the biological understanding leads to new targets for drugs.”

### Drugs for Every Tumor

Basic scientific research can lead to unexpected discoveries, and discoveries applied to the treatment of one type of cancer can often be applied to another. This storyline is playing out in B-cell lymphoma, as Staudt and Wilson are successfully applying a strategy that had first been applied to treat multiple myeloma, a cancer of bone marrow cells.

Wyndham Wilson, M.D., Ph.D., (left) and Louis M. Staudt, M.D., Ph.D., of the National Cancer Institute.



Decades of sustained funding by NCI and other NIH institutes have provided a clear picture of how proteins are normally broken down, or degraded, inside cells in structures called proteasomes. This understanding ultimately led to the development, and FDA approval in 2003 for certain other cancers, of the drug bortezomib (Velcade), which blocks the degradation of numerous proteins, including many that regulate the cell cycle and cell death (apoptosis).

Staudt and colleagues found that bortezomib inhibits the NF- $\kappa$ B signaling pathway, which is chronically activated in most cases of ABC DLBCL, whether due to *MYD88* gene mutation or another mechanism. This knowledge led Staudt and Wilson to begin testing the drug, in combination with standard chemotherapy, in patients with B-cell lymphoma. They found that the bortezomib–chemotherapy combination produced complete or partial remissions in 10 of the 12 ABC DLBCL patients they tested. This subtype of DLBCL has historically been very difficult to treat. Bortezomib in combination with standard chemotherapy to treat patients with DLBCL is now being tested in a large-scale, international phase 3 clinical trial.

“This is a baby step,” Staudt said. “Bortezomib works, but it affects many pathways within cells and causes side effects that limit its use. We want to find something that has a more targeted role in the cell and is more tolerated by patients.”



One such promising agent is a drug called ibrutinib, which inhibits a signaling protein inside B cells called Bruton’s tyrosine kinase, or BTK. Ibrutinib was first found to be active against chronic lymphocytic leukemia, and it was approved for this use by the FDA in March 2012. Research by Staudt, Wilson, and their collaborators has demonstrated that chronic activation of a protein called the B-cell receptor on the surface of B cells is another pathogenic mechanism in ABC DLBCL. Signals from activated B-cell receptors are received by BTK, which, in turn, relays them to NF- $\kappa$ B, which ultimately acts to promote cell survival. “BTK is a critical link between the cell surface and signaling in the nucleus,” said Staudt, whose team is in the very early stages of studying that link.

Burkitt lymphoma, shown in the lower portion of the frame, beneath the skin.

One patient that Staudt treated with ibrutinib had such a large tumor in her abdomen that she couldn’t eat. The tumor had not responded to conventional chemotherapy. Nevertheless, after 1 week on ibrutinib, taken orally each day, she no longer felt any discomfort and imaging confirmed that the tumor had shrunk. She was able to eat again and returned home. Another patient had ABC DLBCL that had responded twice to chemotherapy but eventually recurred each time. Her tumor had a mutation in the B-cell receptor, suggesting that the receptor might be chronically “on,” delivering signals that could be blocked by ibrutinib. She began to feel better within the first week of treatment, and, by 8 weeks, her cancer was in complete remission. She remained cancer-free 15 months later, taking only this one

drug daily. Although these are exceptional cases, they point to future promise from drugs that target similar signaling pathways.

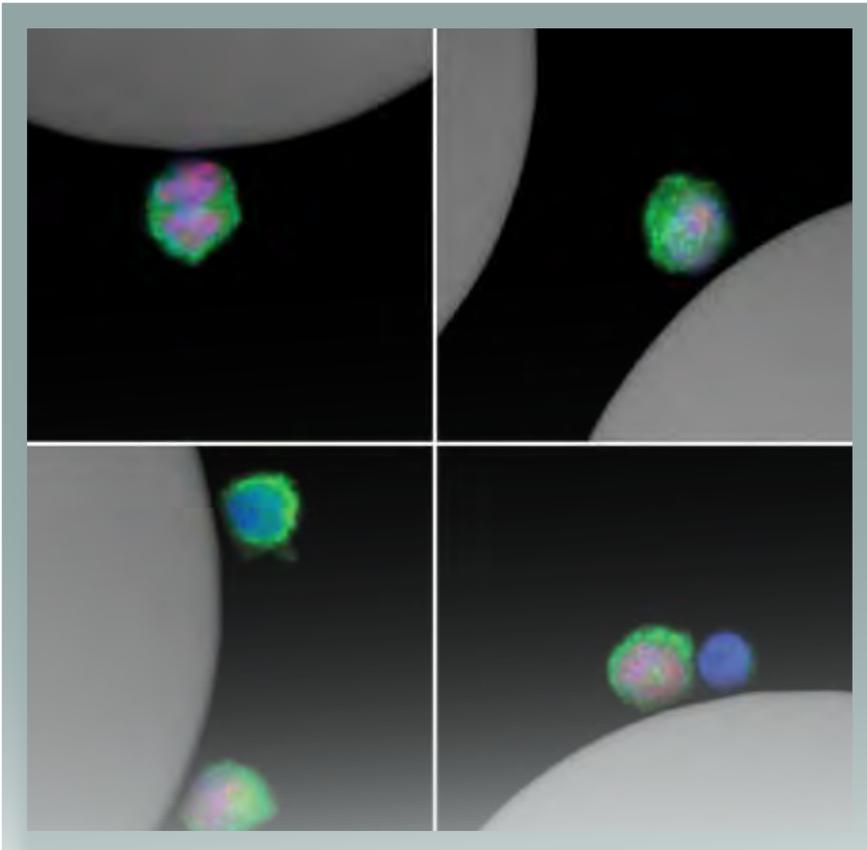
Unlike conventional chemotherapy, treatment with ibrutinib causes minimal side effects, if any. Ongoing studies of this drug are assessing the frequency and the duration of the tumor responses. The methods that Staudt identified to assign lymphomas to the ABC molecular subtype are allowing his team to determine which tumors will respond to this BTK inhibitor—a textbook example of precision medicine.

Other researchers are also trying to discern the molecular features of DLBCL. For example, Todd Golub, M.D., of the Broad Institute of MIT and Harvard has sequenced the protein-coding regions of the genomes of tumor samples from 55 patients with DLBCL and paired samples of normal tissue, and he identified a number of new mutations not previously associated with DLBCL. The newly identified mutations will provide further insights into the development of DLBCL, as well as new targets for drug development.

Although the sophisticated tools required to do these analyses are available at NCI's laboratories in Maryland, they are not yet available at most clinics around the country. By bringing these advanced technologies to patients around the world, doctors will be able to diagnose

lymphoma types based on their gene expression patterns.

Staudt is leading an NCI initiative to develop easy and inexpensive ways for doctors to analyze B-cell lymphoma samples genetically. "This will allow our knowledge of which treatments work against which genetic mutations to have a more widespread impact," he said. The Lymphoma-Leukemia Molecular Profiling Project involves researchers from around the United States, Canada, and Europe. They have developed a DNA microarray, called a "lymphochip," that defines gene expression profiles to distinguish lymphoma subtypes. "We have all this knowledge now," Staudt said. "But this has not yet penetrated the broader community. That's our next goal."

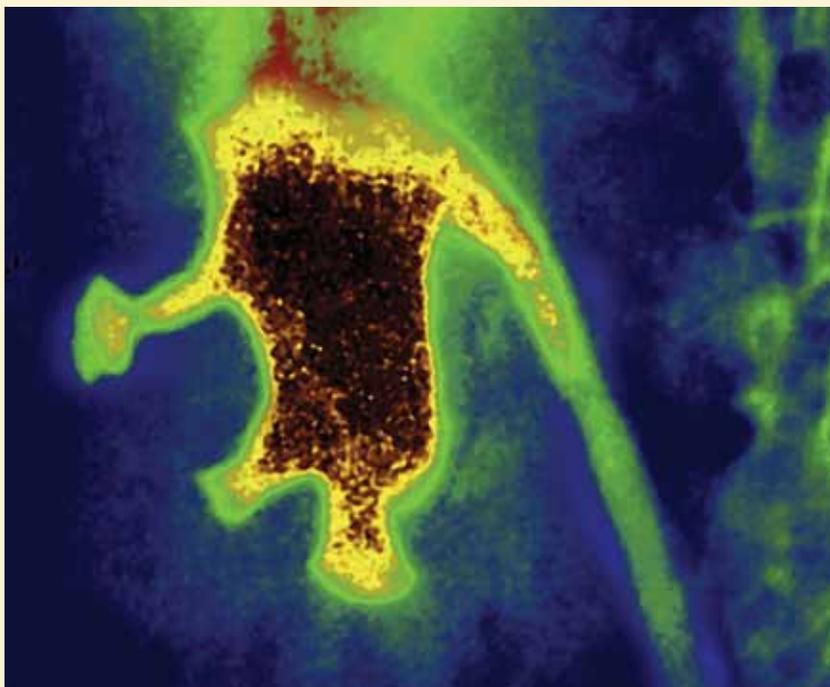


Circulating tumor cells captured from a sample of whole blood.

[Image courtesy of S. Stott; © Science/AAAS]

## RENAL CELL (KIDNEY) CANCER

The most common type of kidney cancer is renal cell carcinoma (RCC), which arises in the renal parenchyma (the part of the kidney that makes urine). RCC accounts for more than 90 percent of kidney cancers. Nearly three-quarters of RCCs are classified as clear cell carcinomas because of their pale appearance when examined under a microscope. The other major type of RCC is called papillary carcinoma. In addition to RCC, other cancers that occur in the kidney are transitional cell carcinomas of the renal pelvis (the part of the kidney where urine collects and drains to the ureters and the bladder), sarcomas, and Wilms tumors, a rare type that occurs almost exclusively in children. Cigarette smoking, obesity, and hypertension appear to contribute to the risk of RCC. In addition, mutations in more than 15 genes have been associated with RCC, both in the inherited and sporadic forms, but they provide only a partial picture of the complex processes of this disease. Kidney cancer incidence has increased steadily over the past several decades, a rise attributed in part to increased detection of early-stage disease. Moreover, kidney cancer mortality rates have improved little in the past 20 years. This year in the United States, it is estimated that more than 64,000 people will be diagnosed with kidney cancer and about 13,000 will die from it. Greater understanding, gleaned from laboratory research on the molecular underpinnings of RCC, has yielded new strategies for its treatment, including the first generation of molecularly targeted therapies, many of which deplete tumor cells of nutrients and oxygen by blocking the growth of blood vessels.



Renal carcinoma of the right kidney, shown on an intravenous pyelogram, or IVP.

Credit: BSIP / Science Source

Current understanding of the molecular genetics of RCC stems largely from studies of families with inherited predispositions for the disease. Over the past two decades, five forms of familial RCC have been identified, each associated with specific genetic mutations. The most common of these familial disorders is von Hippel-Lindau (VHL) syndrome, which increases risk for tumors of the eye, pancreas, brain, and kidneys. Studies of VHL families showed that virtually all members carry mutations in a gene on chromosome 3. The gene, which is also called *VHL*, was identified by researchers in the NCI intramural program in 1993, and its protein product acts as a tumor suppressor. When *VHL* is inactivated, cells behave as though they lack sufficient oxygen and nutrients. As a result, the cells ramp up a number of survival pathways, including those that promote the growth and recruitment of new blood vessels—a classic tumor characteristic. As with most other mutated genes identified in inherited kidney cancer, *VHL* is mutated in sporadic kidney cancers, too. (Sporadic kidney cancers arise in patients who do not have an inherited predisposition.) A recent study estimated that in more than 90 percent of sporadic clear cell RCCs, *VHL* is inactivated by mutation or other changes that reduce its expression.

In total, mutations in more than 15 genes have been associated with inherited and/or sporadic RCC. However, the genes identified to date, although important, provide only a partial picture of the complex processes that lead to RCC. This point is illustrated

by the findings of NCI-funded geneticist Kimryn Rathmell, M.D., Ph.D., who leads a research team at the University of North Carolina at Chapel Hill and uses a variety of models to study RCC. Rathmell engineered mice with mutations in *VHL* but found that the mice did not develop RCC until she treated them with a drug that causes additional random mutations throughout the genome. These results suggest that, although the loss of *VHL* function is an important event, other still-unknown mutations or aberrations also play a role.

### Angiogenesis

Over the past decade, several targeted therapies have been developed and approved for the treatment of RCC. Some interfere with pathways that are altered when *VHL* is mutated, including pathways involved in increased blood vessel formation. The strategy is to block the growth of these blood vessels and kill tumor cells by depleting them of nutrients and oxygen.

Kimryn Rathmell, M.D., Ph.D.  
University of North Carolina at  
Chapel Hill.

When tumors grow to approximately 2 cubic millimeters in size, about the size of a raindrop, they start to form their own network of blood vessels by inducing the outgrowth of sprouts from pre-existing blood vessels in a process known as angiogenesis. Tumors depend on this new blood vessel network to supply the oxygen and nutrients necessary for survival, growth, and spread.

In a healthy person, the growth of new blood vessels is kept in check by a balance of proangiogenic and antiangiogenic chemical signals. But tumor cells—together with cells in the tumor's immediate surroundings, or microenvironment—release an abundance of proangiogenic signals, upsetting the normal balance. These signals coax cells called endothelial cells to migrate and develop into new blood vessels for the tumor. Unlike normal blood vessels, tumor blood vessels are frequently disorganized, uneven in size and shape, and leaky.

**Genomic Research.** The Cancer Genome Atlas project (see p. 11) holds promise to help generate additional information about the genetic patterns that characterize RCC. As part of this effort, 500 RCC tumors (both clear cell and papillary carcinomas) are undergoing comprehensive genomic analysis. The findings, it is hoped, will help define subgroups of clear cell and papillary RCC, which should better guide research and treatment of these diseases.

Over the past two decades, a number of natural and synthetic agents have been discovered to block angiogenesis and thereby slow or stop tumor growth and spread. The FDA has approved several drugs that inhibit angiogenesis for the treatment of cancer, including breast, colon, lung, kidney, liver, and brain cancer, as well as neuroendocrine tumors and gastrointestinal stromal tumors.



Unfortunately, most patients experience only a temporary benefit from currently available angiogenesis inhibitors. Over time, tumors become resistant to this treatment and start growing or spreading again. One strategy to decrease resistance to antiangiogenic inhibitors is to target multiple pathways at the same time, using a single inhibitor or a combination of inhibitors. Clinical trials are currently testing combinations of antiangiogenic therapy and other treatments that target blood vessels, such as tumor vascular-disrupting agents that target already established tumor blood vessel networks. Angiogenesis inhibitors, like most cancer therapies, are not without side effects. In addition to testing new angiogenesis inhibitors and combinations of treatments, efforts are under way to reduce toxicities associated with angiogenesis inhibitors, such as bleeding, hypertension, and blood clots that may lead to a stroke or heart attack.

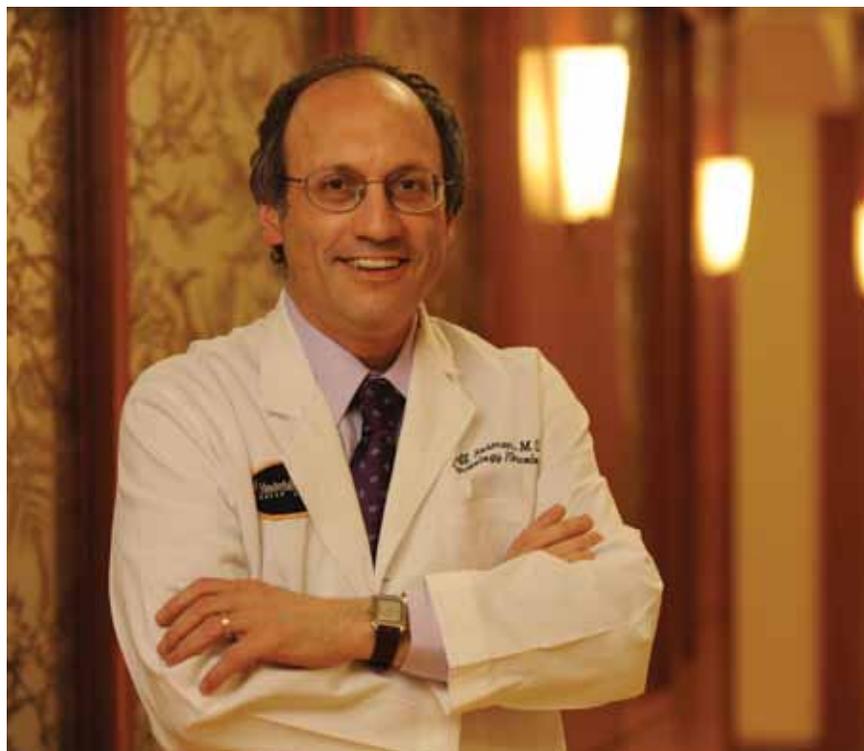
### Other Clinical Approaches

“We need a new approach to go after the heart of these cancers,” said W. Marston Linehan, M.D., chief of NCI’s Urologic Oncology Branch. Linehan noted that all of the genes identified in familial RCC, including *VHL*, are involved in cellular metabolism: They are responsible for monitoring and responding to changes in available energy, nutrients, iron, and oxygen. It may be possible to improve on or complement current RCC treatment strategies by targeting the metabolic defects that occur in this disease. Linehan’s laboratory has found that the diabetes drug metformin, which alters how cells respond to energy needs, can have a profound effect on RCC cells in tissue culture. Whether this finding will lead to a treatment strategy to help patients with RCC remains to be seen.

Jeffrey Sosman, M.D., at Vanderbilt-Ingram Cancer Center in Nashville, is among scientists

trying another approach to stop RCC: coaxing the body’s immune system into attacking cancer cells more effectively. It is an approach that is being explored in many types of cancer, and one drug that enables enhanced immune responses against cancer, ipilimumab (Yervoy), has already been approved as a treatment for advanced melanoma. A new drug, called MDX-1106, works in a way similar to that of ipilimumab. MDX-1106 is an antibody that binds to and blocks the activity of a protein on immune cells called PD1. PD1’s job is to keep immune responses in check, preventing runaway responses that might damage the body’s normal tissues. But there is evidence that tumors can take advantage of PD1 and prevent immune cells from fighting RCC and other cancers. In an initial clinical trial of MDX-1106, it shrank tumors in a quarter of patients. The drug is now being tested in large-scale international clinical trials.

Jeffrey Sosman, M.D.,  
Vanderbilt-Ingram  
Cancer Center.



## Judah Folkman, “Grandfather” of Angiogenesis

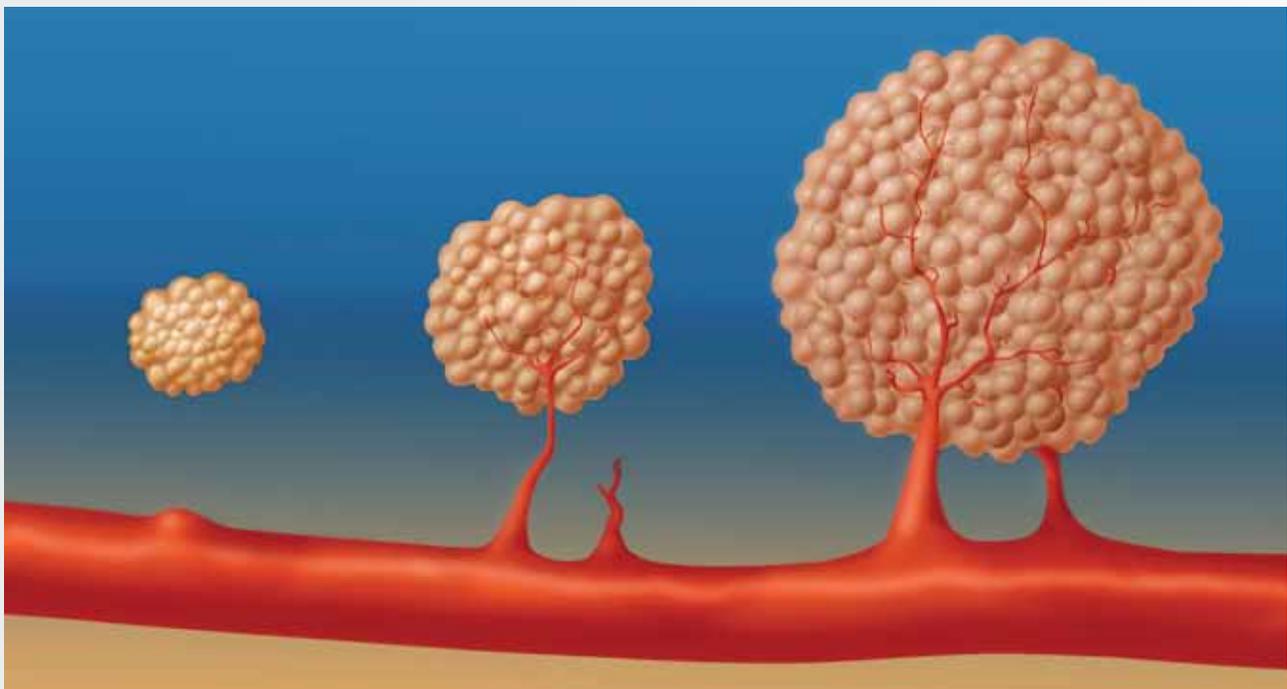
The scientist most responsible for the field of angiogenesis research was the late Judah Folkman, M.D., of Harvard University. As a young Navy doctor, Folkman studied blood vessel growth at the National Naval Medical Center. It was during his Navy career that he invented an implantable device that allowed the timed release of fertility drugs, and he donated it patent-free to the World Population Council. This is the device now known as Norplant, and it marked Folkman’s first legacy in the biomedical research community.

In 1971, after returning to his alma mater, Harvard, he used his familiarity with the vascular system to postulate, in a landmark *New England Journal of Medicine* article, that all cancerous tumors depend on the initiation and

maintenance of a new vascular supply to support their rapid growth and development. If this blood supply could be cut off, he proposed, the tumor would wither and die.

Initially disregarded by many cancer researchers, his views on angiogenesis have become mainstream orthodoxy, leading to the use of angiogenesis-blocking drugs as a mainstay of therapy for many kinds of cancers. The list includes such drugs as bevacizumab (Avastin), sorafenib (Nexavar), sunitinib (Sutent), pazopanid (Votrient), and everolimus (Afinitor), some of which were already known to affect cancer cell signaling and growth, as well as vascularization. More than 50 angiogenesis inhibitors have entered clinical trials for cancers as wide-

ranging, morphologically, as lung cancer, prostate cancer, breast cancer, and liver cancer. While antiangiogenesis therapy hasn’t proven to be quite the “silver bullet” Folkman predicted it would be, it remains one of the most effective approaches to controlling cancer.



Progression of angiogenesis. This is a physiological process involving the growth of new blood vessels from pre-existing vessels, occurring in the transition of tumors from a dormant state to a malignant state.

## GI STROMAL CANCER

Gastrointestinal stromal tumors (GISTs) are uncommon tumors that form in the wall of the gastrointestinal tract from cells known as ICCs, or interstitial cells of Cajal. ICCs are sometimes called gastrointestinal pacemaker cells because they help transmit signals from the autonomic nervous system to the smooth muscles of the gastrointestinal wall, stimulating waves of contraction (peristalsis) that help propel food and waste products through the digestive system. GIST can begin anywhere in the gastrointestinal tract; 60 percent of tumors originate in the stomach, and another 30 percent in the small intestine. Other sites of origin include the esophagus, colon, rectum, and anus. GIST affects about 4,000 to 5,000 people in the United States each year. GIST treatment in adults has been greatly improved by the development of several highly effective targeted therapies. In children, however, the story is very different.



Three-dimensional computed tomographic reconstruction scan of the small intestine showing a gastrointestinal stromal tumor (GIST), seen as a red spot in the jejunum.

Until the 1990s, any sarcoma that developed in the walls of the gastrointestinal tract was called a gastrointestinal sarcoma. With the emergence of technologies that allowed researchers to classify tumors based on their molecular characteristics, it became clear that these tumors are not all the same. Among the subgroups that emerged was GIST.

In 1998, Seiichi Hirota, M.D., Ph.D., of Osaka University Medical School in Japan found that the tumor DNA from five of six tested GIST patients had a mutation in a gene called *KIT*. Since then, other researchers have determined that approximately 85 percent of all GISTs have a *KIT* mutation and that 5 to 8 percent have a mutation in another gene called platelet-derived growth factor receptor alpha (*PDGFRA*). The discovery of *KIT* mutations, which are not found in other gastrointestinal tumors, offered an easy way to genetically distinguish most GISTs, and it led to the development of targeted treatments for the disease.

Both *KIT* and *PDGFRA* encode cell-surface receptor proteins. The portion of each molecule that sits on the cell surface acts as a receptor for specific growth factors; the portion of each protein that is located inside the cell has tyrosine kinase enzyme activity. When the appropriate growth factors bind to these receptors, the tyrosine kinase portions become activated and start transmitting signals to the cell nucleus, thereby promoting cell proliferation and survival. The mutations identified in *KIT* and *PDGFRA* in GIST lead to the production of receptor proteins that are activated all of the time—that is, the tyrosine kinases are continuously transmitting signals that promote cell proliferation

and survival, even in the absence of growth factors.

Tyrosine kinases are enzymes that transfer a phosphate group from a molecule called adenosine triphosphate, or ATP, to specific proteins. As a result, proteins that receive these phosphate groups, which are linked to tyrosine amino acids in the proteins, are either turned “on” or turned “off.” Cells use tyrosine kinases—both those that are part of cell-surface receptor proteins and those that are located exclusively inside cells—to control many vital functions, including the cell cycle, metabolism, proliferation, differentiation, and survival. Altogether, 90 tyrosine kinases have been identified in human cells, and activating mutations in a number of these kinases have been shown to play a role in human cancer.

Another example of tyrosine kinase activation in human cancer involves a protein called ABL, which is an intracellular tyrosine kinase. Constitutive activation of this kinase is the cause of chronic myelogenous leukemia (CML). In CML, part of the gene that encodes ABL becomes joined with part of another gene called *BCR*, producing a fused gene known as *BCR-ABL*. The product of this fused gene is a protein, BCR-ABL, in which the ABL tyrosine kinase is constitutively active. Once this was discovered, researchers began searching for a drug that would block the activity of the BCR-ABL tyrosine kinase. This search ultimately led the development of a drug called imatinib (Gleevec), which is highly effective in the treatment of CML. In 2001, the FDA approved imatinib for the treatment of CML. Even before that approval, however, researchers were trying to determine whether imatinib could block the activity



of other tyrosine kinases. In 2000, laboratory scientists demonstrated that imatinib could also block the activity of *KIT* and *PDGFRA*. Shortly thereafter, North American and European research teams launched a series of clinical trials to determine whether imatinib would work against GIST.

“We hoped that it would yield just some benefit,” said George Demetri, M.D., an oncologist at the Dana-Farber Cancer Institute in Boston. “We had no idea just how incredibly beneficial it would end up being.”

Although fewer than 5 percent of GIST patients benefit from standard chemotherapy, more than 50 percent responded to imatinib in the original study. Some patients from the initial trial of imatinib are still in remission more than a decade later, said Demetri. In 2002, the FDA approved imatinib for GIST patients whose tumors have

George Demetri, M.D., (left) of the Dana-Farber Cancer Institute and Jonathan A. Fletcher, M.D., of the Brigham and Women’s Hospital.

mutations in *KIT*, and it has rapidly become the standard of care for metastatic GIST. However, some patients develop resistance to this drug and have to turn to second-line treatments as their tumors accumulate new gene mutations. A second-line drug, sunitinib (Sutent), which also targets the KIT protein, has been approved for patients who develop resistance to imatinib. The duration of the clinical benefit from sunitinib depends on the mutations in the patient’s GIST and its metastases. Approximately 20 percent of patients taking sunitinib have stable disease for 2 years or longer.

“But, we’re still not curing anyone,” noted Demetri. Patients must remain on treatment or their tumor will begin to grow again. Demetri recently discovered that cells in the area around GISTs produce signaling molecules that keep the tumor alive during treatment with imatinib. Blocking these signals, he said, could make the tumor cells die. He has already identified some of the molecules, and now he is piecing together their functions and learning how to block them.

Compared with many other cancers, GIST appears to have a relatively stable genome, and only a small number of driving genetic mutations have been found in these tumors thus far. For this reason, GIST is being used to explore general questions about cancer development and metastasis in the hope that the knowledge gained can be applied to other cancer types. By studying GIST biology, researchers may learn more about how tumors of all types grow and spread.

For example, studies of early GIST might reveal what makes a cancer aggressive. Some small GISTs grow very slowly, even though they appear to have the same driving genetic changes as those that grow rapidly. Researchers in Japan have found millimeter-sized GISTs in the gastrointestinal tracts of around 40 percent of people who died from other causes. “There are these tiny GIST freckles,” said Demetri, “but they never turn into larger tumors, even though they have the same driving mutations.” This study in Japan suggests that other events—perhaps additional mutations or changes in the tumor microenvironment—are required to turn these GIST tumors into aggressively growing cancers.

### **Pediatric GIST: A Very Different Disease**

Pediatric GIST is very rare, even by rare cancer standards, representing only 1 to 2 percent of all GIST cases (approximately 60 cases per year in the United States). It is also very different from its adult counterpart. Whereas 85 percent of GISTs in adults harbor mutations in one of two genes, *KIT* or *PDGFRA*, the opposite is true in children with GIST—85 percent have no detectable mutation in either gene. The events that trigger these pediatric tumors are unknown, and the tumors do not respond to imatinib or sunitinib, the drugs that have made such a difference for adults with GIST.

For children and youth who develop GIST, NCI and the Eunice Kennedy Shriver National Institute of Child Health and Human Development have partnered with members of GIST Support International and the LifeRaft Group to organize a consortium of pediatric GIST researchers to field a program



Lee Helman, M.D.,  
National Cancer Institute.

at the NIH Clinical Research Center aimed at designing innovative treatment protocols. Within the past 4 years, 60 to 80 patients with pediatric GIST have been evaluated at NIH, explains Lee Helman, M.D., from NCI's Pediatric Oncology Branch.

Su Young Kim, M.D., Ph.D., formerly an NCI postdoctoral fellow, led the clinical team in Helman's lab, which includes geneticists, medical oncologists, pediatric oncologists, pediatric surgeons, nutritionists, and pain specialists. The research team has learned about the clinical and molecular features of this disease, which distinguish it from GIST in adults. They found that the disease is usually slow-growing in children, occurs overwhelmingly in girls, and almost always occurs in the stomach, whereas adult GIST occurs equally in both genders and occurs often in the small intestine as well as in the stomach. In addition, in contrast with adult GIST, pediatric GIST often presents as multifocal disease, meaning that there are multiple, distinct tumor foci within the affected anatomic region.

Pediatric GIST can arise in the context of a hereditary cancer syndrome called the Carney-Stratakis syndrome. This syndrome predisposes affected individuals to GIST and to paraganglioma, a rare tumor of the peripheral nervous system (nerves outside of the brain and spinal cord). Carney-Stratakis syndrome is caused by an inherited mutation in a gene that produces a protein called succinate dehydrogenase (SDH),



Pediatric oncologist Katherine Janeway, M.D., Dana-Farber Cancer Institute.

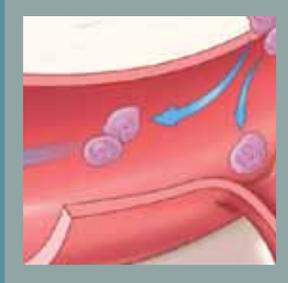
which is involved in cellular respiration. Last year, a Dana-Farber research team led by pediatric oncologist Katherine Janeway, M.D., reported that five of 34 patients (15 percent) with so-called wild-type GIST (no *KIT* or *PDGFRA* mutations) who were 22 years of age or younger and who had no personal or family history of paraganglioma (that is, they were not affected by Carney-Stratakis syndrome) had tumors with an *SDH* gene mutation. This finding suggested that *SDH* mutations might play a role not only in GISTs associated with Carney-Stratakis syndrome but also in non-hereditary forms of the disease. Janeway and her team then showed that all pediatric GISTs tested, including those with and without *SDH* gene mutations, lacked expression of the SDH protein. They are now looking for mutations in other genes or epigenetic changes—alterations that affect gene expression but do not involve changes to the

DNA sequence of genes—to explain the absence of SDH protein in pediatric GISTs. A deficiency in SDH protein leads to the accumulation of succinate in cells and subsequent increased production of vascular endothelial growth factor and insulin-like growth factor 1 receptor. Drugs that target these molecules may help GIST patients who have an SDH deficiency.

The patients described in Janeway's study attended the NIH GIST clinic, and the genetic testing of their tumors took place there.

“We are now beginning to define the disease more by molecular drivers, which is always a good thing,” Helman said. Identifying molecules or changes that drive tumor development is the first step in developing new targeted therapies.

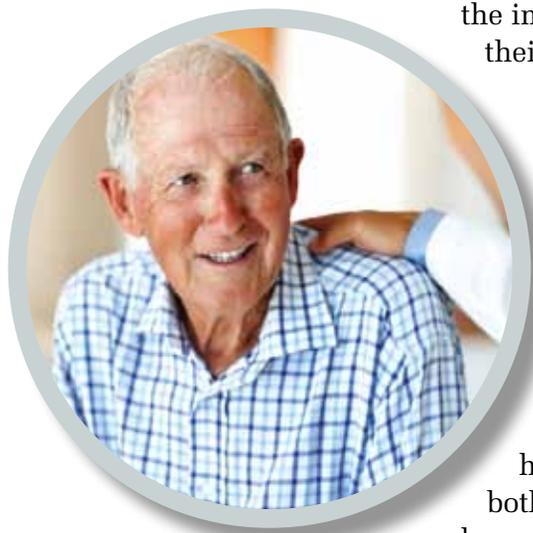
# Research Focus



In this section we provide a snapshot of three important research areas that affect many types of cancers. In the first section, on comorbidities, we discuss our growing understanding of the ways that health conditions such as heart disease, diabetes, and obesity complicate the treatment of many cancers. In the next section, on circulating tumor cells, we highlight a new approach to understanding how tumors metastasize. In the third section, on reducing cancer health disparities, we show how NCI is working to understand and address the disproportionate burden of cancer among various racial and ethnic groups.

## Research Focus: Comorbidities

Sixty percent of cancer patients and survivors are age 65 or older. With age comes increased risk for other health conditions such as heart disease, diabetes, and dementia. Growing rates of obesity and physical inactivity, problems pervasive in the U.S. population, also increase the risk for many chronic conditions. Based on National Health Interview Survey data, among cancer patients age 65 and older, 36 percent reported at least one additional illness—referred to as a comorbidity—and 16 percent reported two or more comorbidities. When people with cancer have one or more comorbidities, what is the impact on the care that they receive? And, in turn, how does their cancer treatment affect their other conditions?



Older age, comorbidities, and functional limitations should not automatically deprive a patient of treatment. Often, older patients can tolerate chemotherapy as well as younger patients. For example, postoperative, or adjuvant, chemotherapy for colorectal cancer in patients age 70 and older is as effective as it is in younger patients, and harmful side effects can be reduced if certain drugs (oxaliplatin, for example) are avoided. But questions exist as to which treatments and which comorbidities interact. For example, how do heart disease drugs interact with cancer drugs when both may affect cardiac function? And many people with diabetes have peripheral neuropathy, nerve damage that causes numbness or pain in the hands and feet. But some chemotherapy drugs have the same side effects. Do the two together make the condition worse? Many of these questions need to be explored. And most importantly, can we remediate some of the age-associated comorbidities so older patients with cancer can derive the full benefits of cancer treatment?

Comorbidities affect a patient's ability to participate in clinical research, as well, according to Julia Rowland, Ph.D., director of NCI's Office of Cancer Survivorship. Older patients are more likely than younger ones to be excluded from treatment studies because they have other chronic health problems. For example, individuals with a history of diabetes or heart disease often have changes in their kidney, liver, or heart function tests that require their

exclusion from drug trials. This means that most treatments, as they move through clinical testing, are not tested in patients with comorbidities. So, although we have a growing population of older patients who will need to be treated for cancer, we don't have the data to know what is safe and effective for them, Rowland explained. To address these questions, NCI has funded several new grants that specifically consider comorbidities in cancer patients.

Siran Koroukian, Ph.D., at Case Western Reserve University School of Medicine, has been studying comorbidities among elderly cancer patients in Ohio. With funding through the NIH Clinical and Translational Science Awards program, her group has linked data from the Ohio Cancer Incidence Surveillance System with Medicare data and the home health care Outcome and Assessment Information Set to explore the prevalence and impact of multimorbidity, defined as having one or more comorbidities, functional limitations, or geriatric syndromes. As many as 88 percent of Ohio residents with breast, prostate, or colorectal cancer who were admitted to home health care in the 30-day window after cancer diagnosis had one of the multimorbidity conditions or some combination of the three. The most common comorbid conditions were hypertension, cardiovascular disease, diabetes, and arthritis.

In a 2011 NCI-funded study, Koroukian's group examined the effects of multimorbidity on treatment and survival outcomes in older patients with local and regional breast or colorectal cancer. Patients with multimorbidity were less likely to receive standard therapy and more likely to experience poor survival outcomes. What remains unclear is the degree to which these poorer outcomes resulted from the patients' poor general health or from their inability to tolerate standard therapy.

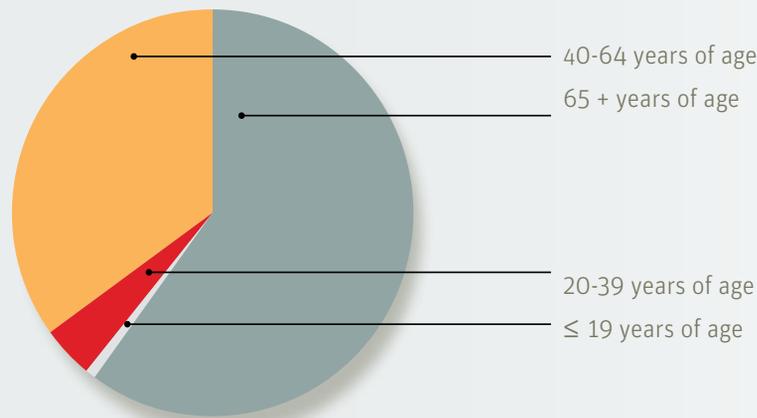
### Preparing for a Boom in Older Cancer Survivors

In the not-too-distant future, the United States can expect a sizable increase in the number of older citizens who have survived cancer. Although some believe that the term "survivor" refers to someone who has been "cured," NCI defines a survivor as anyone who is living with

**"Now that we are moving toward molecularly targeted therapeutics, our two big questions are: How do we apply this modern science to treatments in clinical trials, and then how do we export what we learn at the cancer center to benefit the patients in our region? That is our biggest challenge. We'll need regional networks, partners who treat patients within communities—including minority communities—who can provide tumor samples so we can do molecular analyses and determine whether a patient is best suited for standard therapy or targeted therapy. We need to have minority patients in genomics studies now to answer questions in the most scientifically sound way," said Max Wicha, M.D., cancer researcher and founding director of the University of Michigan Comprehensive Cancer Center.**



**Estimated Number of Persons Alive in the U.S. Diagnosed with Cancer on January 1, 2008 by Current Age**



Source: SEER Cancer Statistics Review, 1975–2008.

a cancer diagnosis, regardless of the present status of his or her cancer. In a 2011 study, NCI investigators predicted a 42 percent increase in the number of cancer survivors 65 years of age and older—from about 8 million to more than 11 million—between 2010 and 2020.

The study, led by Rowland, is the first in a planned series of annual reports on the booming—and aging—population of cancer survivors in the United States.

“We often think of cancer survivors as young people,” Rowland said. “But the reality is that most are older adults.” Among all cancer types, 60 percent of survivors are age 65 and older (see pie chart). For colorectal cancer, 73 percent of survivors are in that older age range.

Although clinicians are doing a better job at diagnosing cancer and a better job of controlling disease, their patients, who are living longer, often suffer adverse effects from treatment, some of which are long-term or delayed. “None of our treatments is benign. To realize the goal of reducing the national burden of cancer, we need to focus research on this older survivor population in addition to the younger survivor population,” Rowland said.

Cancer care does not end once treatment of the disease is completed. It also includes consideration of the effects of survivors’ health behaviors and medical follow-up care on cancer-related morbidity and mortality. People are now living longer, but many struggle with quality-of-life issues. Attending to these issues, including comorbidities, will be important. “We really don’t know some of the interactions between cancer and other chronic problems in the older survivor population,” says Rowland. “Nor do we fully appreciate the impact of cancer and its treatment on the processes of aging.” In the coming years, the Office of Cancer Survivorship plans to focus attention on the rapidly expanding population of older survivors.

## Research Focus: Circulating Tumor Cells

Cancer is most treatable when it is contained, before it has a chance to spread to distant parts of the body. Metastasis is often the beginning of cancer's deadly path. Metastatic tumors can spring from a very small number of cells that break off from a primary, or original, tumor and find their way to distant sites in the body. At those sites, the metastatic cells can advance quickly or stay dormant for years. Finding the most dangerous of these metastatic cells will be a crucial element in preventing and combating advanced cancer.

When a patient has cancer, a small number of cancer cells can shed from the primary tumor and enter the bloodstream. The presence of these circulating tumor cells (CTCs) displays one of the routes by which some cancers spread to distant parts of the body. It also offers the possibility of developing blood tests that can diagnose cancer, guide treatment, predict whether the tumor will spread, and follow the course of a disease. The possibilities are vast, but they depend on an understanding of the biology of CTCs that science has not yet achieved.

Daniel Haber, M.D., Ph.D., of Harvard Medical School and the Massachusetts General Hospital, is among several NCI-funded scientists who are trying to get at the root of what CTCs are and how they can be used in the clinic. Their results, for now, are limited by the technology that detects CTCs. Current techniques for separating CTCs from blood cells often yield too few tumor cells to do complete analysis of their properties.

The platform that is most widely used is the Veridex CellSearch system. When magnetic nanoparticles carrying antibodies specific for a protein found on cancer cells are mixed with a small sample of a patient's blood, the antibodies attach to CTCs. A magnet is used to pull the nanoparticle–antibody–CTC complexes out of the blood, the cells are stained, and then they are analyzed under a microscope to ensure that they are truly tumor cells—which are shaped differently from normal blood cells—and to count them.

“Right now we know that if you have circulating tumor cells that are detectable in the blood, then you have a worse cancer than if we can’t detect cells,” says Haber. “But until we can get to the genetics of these cells, we’re not taking full advantage of this technology.”

The FDA has approved the Veridex CellSearch system to test blood samples for the presence CTCs in patients with metastatic breast cancer, metastatic colorectal cancer, and metastatic prostate cancer, and some cancer centers are using it to predict disease outcomes. Tracking the numbers of CTCs before and after chemotherapy can be used to predict survival time and recurrence rates among patients. But the test is based only on numbers of CTCs rather than the genetics or other qualities of the cells.

“The problem with the existing method is that it fixes the cells in order to separate them, so they’re dead,” says Robert Kinders, Ph.D., head of the Pharmacodynamics Assay Development Laboratory at the Frederick National Laboratory for Cancer Research. Kinders is leading a collaboration between NCI and industry to create a new platform, tailored to NCI’s research needs, that can pull live CTCs from blood (see related story p. 63).

Daniel Haber, M.D., Ph.D., (left) and Mehmet Toner, Ph.D., of the Massachusetts General Hospital Cancer Center and the Harvard Medical School.



## Research Focus: Reducing Cancer Health Disparities

A troubling truth about cancer is that its burden is not shared equally among Americans. African American men, for example, are twice as likely as their white counterparts to die of prostate cancer. While Hispanics have lower rates of incidence and death from all cancers combined when compared with non-Hispanic whites, they are more likely to develop certain cancers, including cancers of the stomach, cervix, or liver. NCI is pursuing research on many fronts to understand and address these disparities—whether due to genetic or other biological factors, influenced by diet or lifestyle, or perhaps most tragically, as a result of poorer access to preventive care, screening, and high-quality treatment.

Overcoming cancer health disparities among subsets of our citizens is a moral and ethical obligation, as well as a scientific challenge. Through its Center to Reduce Cancer Health Disparities (CRCHD), NCI supports research to identify and understand the factors that contribute to disparities in the incidence and mortality of cancer, and to develop and disseminate appropriate interventions that are culturally relevant. Much of this work, described on the following pages, occurs within a network of community-based partnerships that NCI has established across the nation.

Along with its portfolio of community-based clinical research and training programs and in conjunction with other NCI activities, CRCHD supports basic research that reveals a complex picture of the roots of cancer disparities. Genetic and other biological factors contribute to differences in cancer incidence and outcomes among U.S. population groups.

To gather more information about the molecular basis of cancer, for example, the Center for Cancer Genomics is expanding the participation of racially and ethnically diverse and underserved populations in programs such as The Cancer Genome Atlas (TCGA, see p. 11), the Therapeutically Applicable Research to Generate Effective Treatments initiative, and other genetic studies (see p. 8).



To increase the rate of collection of high-quality biospecimens from under-represented groups, NCI is launching The National Biospecimen Awareness and Collection Campaign. The ultimate goal of this campaign is to develop and advance our ability to diagnose, treat, and prevent cancer among all people, as well as reduce cancer disparities among specific population groups. Breast and prostate cancer will be the initial priorities of the joint effort with TCGA, although tissue samples of all cancer types are being acquired.

Complementary activities are under way in NCI's Geographic Management of Cancer Health Disparities Program and Biospecimen/Biobanking Geographic Management Program to develop culturally relevant patient education modules on biospecimens and biorepositories, which will expand on patient education materials developed in recent years by collaborations between the Cancer Information Service and Community Networks Programs across the nation.

Additional efforts focus on the influence of comorbidities (see p. 39), such as diabetes and obesity, on cancer health disparities. NCI also funds programs to increase the number of investigators who undertake cancer health disparities research, as well as the number of researchers from under-represented backgrounds who pursue cancer research in general.

### Community Networks Program Centers

CRCHD also supports community-based participatory research, education, and training to reduce the cancer burden in minority and underserved communities. Leaders from several of these centers recently co-authored a paper that provides examples to primary care physicians of ways to enhance life after cancer in diverse populations.

Several NCI grantees study cancer prevention in American Indian communities. Jeffrey Henderson, M.D., M.P.H.—a Lakota, enrolled in the Cheyenne River Sioux Tribe—founded the Black Hills Center for American Indian Health in Rapid City, South Dakota. As part of the Regional Native American Community Network Program, Henderson is studying lifestyle and behavioral risk factors, such as tobacco use, that are associated with cancer—particularly lung cancer—among Native Americans.

A team led by Stevens Smith, Ph.D., and Leah Arndt, Ph.D., at the University of Wisconsin, is nearing completion of a 3-year smoking cessation study of American Indians. The goal of the Menominee Smoking Cessation trial—the first tribal-sponsored clinical trial in the nation—is to test a culturally tailored treatment versus standard treatment in adult American Indian smokers at the Menominee Tribal Clinic. The research team collaborated with the Spirit of Eagles, an NCI-supported Community Network Program (CNP) that works to improve

## Bringing Genomics to Native Americans

Just 10 years ago, Phyllis Pettit Nassi—enrolled in the Otoe-Missouri Tribe and a member of the Cherokee Nation—couldn't even use the word “cancer” among Native American populations. Traditional cultural beliefs held that if you speak of illnesses or negative happenings, you bring them to the listener. She set out to increase awareness, demystify cancer, and remove the fear of the word itself.

“Today, we can talk about cancer,” said Pettit Nassi, who is manager of special populations at Huntsman Cancer Institute in Salt Lake City. She spends most of her time on the road, traveling across Utah and 17 other states, including Idaho, New Mexico, Montana, Arizona, Wyoming, and Alaska. Her goal is to help Native American populations understand the importance of early detection for cancer and participation in research. She accepted NCI's charge to increase tribal participation in clinical trials. After much consulting with interested tribes, she has increased clinical trial participation from zero to 12 people this past year.

She has most recently added genomics to the important topics she discusses. “I decided this year that we need to leap forward,” said Pettit Nassi, who is a member of NCI's Director's Consumer Liaison Group. Since July 2011, she has spoken to more than 50,000 tribal members in small group meetings or

while staffing a booth at Native American events. “In these conversations, I mention genomics and share my belief that our tribal members and our health care providers must begin to get information on personalized medicine and genetically targeted therapies,” she said. “It's so very important that we don't get left behind.”

In January, Pettit Nassi traveled to the Confederated Tribes of the Goshute Reservation in remote Ibapah, Utah. This tribe and many others, she said, are ready to learn about genomics, precision medicine, and genetically targeted therapies. “This small, rural, underserved tribal nation is poised to accept and participate in studies that will benefit their tribal members if given the chance, resources, and support to do so,” she said.



Pettit Nassi, Huntsman Cancer Institute.

## A Bridge Within the Hispanic Community

People of Hispanic origin form the largest ethnic or racial minority—48 million people—in the United States. Forty-five percent of New Mexico’s population is Hispanic.

Monica Toquinto grew up in New Mexico and wanted to give back to her Mexican-American community. She became an outreach worker with the University of New Mexico Cancer Center (UNM). The importance of her work hit home recently, when her mother was diagnosed with cancer.

“Everybody has the right to the right information about cancer,” Toquinto said. “And we all deserve the best treatment.” She knew many Hispanic people who lacked basic information about cancer. “I didn’t know anything about cancer. I thought it was the end, but it’s not,” she said. At the cancer center’s outreach training, she learned that when people are diagnosed early, they have a better chance of surviving cancer. She learned that people need to take an active role in maintaining their health, and not wait 2 to 5 years to see a doctor. Now she shares that message, in English and Spanish, with communities throughout New Mexico, sometimes driving 4 hours to reach rural communities of 500 that have no access to services. She works as a patient navigator for people who don’t know where to start. “Our job is to let them know the first step and the last step,” she explained. “We get them to the right place right away.”



Monica Toquinto (center) with Michelle Suina (left) and Maria Otera, University of New Mexico Cancer Center.

UNM’s outreach programs go where the people are. For example, through a partnership with the Mexican Consulate, called *Ventanilla de Salud* (Window of Health), UNM holds “Cancer 101” education sessions in the consulate’s waiting room. While more than 100 people wait for their documents or information, they attend sessions on cancer, risk reduction, and screening. Through the consulate, outreach workers see 15,000 people each year and handle 300 to 400 referrals. For each referral, the outreach staff members follow up to make sure the person connects with the health care system. Word of mouth leads to many more referrals throughout the year.

cancer control in Native American and Alaska Native populations, to establish a successful partnership with the Menominee Tribe. The study also includes qualitative analyses of participant interviews to inform future improvements in treatment.

At CNP-Appalachia, researchers went to a new setting, food pantries, with tested and validated educational materials about breast cancer screening from the American Cancer Society's Tell-A-Friend program. In 18 rural food pantries throughout Indiana County, Pennsylvania, the researchers used the program's three-contact approach of information dissemination, one-on-one education, and phone calls. Researchers distributed promotional flyers in food bags, volunteers visited each pantry to educate and answer questions, and health workers called every woman who expressed interest to provide information on scheduling a mammogram. Of the 379 women contacted, 302 were eligible on the basis of age; of those, 52 percent were in need of a screening mammogram. Eighty-seven percent of those women subsequently received mammograms; three of those women were diagnosed with breast cancer and entered treatment. The project led to a 28 percent increase in breast cancer screening among underserved residents of Indiana County during the intervention year, demonstrating the effectiveness of this community-based approach in boosting screening rates.

### Church-Facilitated Initiative to Promote Health in Appalachia

The Appalachia Community Cancer Network, an NCI-supported CNP, is partnering with churches across the Appalachian region of Kentucky, Ohio, Pennsylvania, Virginia, and West Virginia to implement the Faith-based Initiative to Promote Health in Appalachia project. This initiative will utilize the strengths of the faith-based community to promote health and raise awareness about cancer prevention and early detection. The project, which was launched in September 2011 and will continue through August 2015, involves 20 churches across the five states. Participants at 10 of the churches (chosen at random) were invited to participate in a program that addresses physical activity and healthy food choices, while participants in the other 10 churches received education on cancer screening. In addition to measuring the effects of these interventions, the researchers will try to determine whether using churches to deliver these programs results in durable effects among the participants. Toward the end of the study period, the churches will switch programs, so the 10 that received the physical activity and healthy food choices program will also receive the screening program, and vice-versa. All participating churches will have the opportunity to participate in both programs.

*The project led to a 28 percent increase in breast cancer screening among underserved residents of Indiana County during the intervention year.*

## Overall Cancer Incidence and Death Rates

	All Sites	
Racial/Ethnic Group	Incidence	Death
All	465.2	178.7
African American/Black	489.5	216.4
Hispanic/Latino	353.7	146.3
American Indian/Alaska Native	328.9	156.2
White	471.7	177.6

Statistics are for 2005–2009, age-adjusted to the 2000 U.S. standard million population, and represent the number of new cases of invasive cancer and deaths per year per 100,000 men and women.

### Native Americans:

- American Indians and Alaska Natives continue to have the poorest 5-year survival rates, among all racial and ethnic groups, for all cancers combined.
- Cancer is the second leading cause of death among Native Americans over age 45.

### Hispanics:

- For all cancers combined, and for the most common cancers (prostate, female breast, colorectal, and lung), age-adjusted incidence and death rates are lower among Hispanics than among non-Hispanic whites.
- Cancers for which rates are higher in Hispanics than in other racial or ethnic groups include those of the stomach, cervix, liver, and gallbladder, and acute lymphocytic leukemia.
- Although Hispanics have lower incidence and death rates than non-Hispanic whites for the most common cancers, they are more likely to be diagnosed with a more advanced stage of disease.
- Statistics reported for Hispanics overall may mask wide variations in the cancer burden for specific populations according to country of origin.

### African Americans:

- African American/black men have the highest incidence rate for prostate cancer in the United States and are more than twice as likely as white men to die of the disease.
- In the United States, white women have the highest incidence rate for breast cancer, although African American/black women are most likely to die from the disease.
- African American/black men and women have the highest incidence and death rates for both colorectal and lung cancers.

# The Frederick National Laboratory for Cancer Research

The Frederick National Laboratory for Cancer Research (FNLCR) was established in 1971 under the National Cancer Act to provide rapid response capabilities and one-of-a-kind resources for the biomedical research community. Its scientists develop technologies and perform studies to support NCI's mission, as well as the work of other NIH institutes. Like Los Alamos, Brookhaven, Sandia Labs, and others, it is a Federally Funded Research and Development Center (FFRDC), using this special contract with SAIC-Frederick, Inc., to cut red tape and bring public and private partners to the table swiftly to undertake difficult medical research. Changes in how NCI and the biomedical community conduct and support research, however, and the kind of research that characterizes contemporary science, have created an opportunity to re-envision the role of a national laboratory devoted to cancer research. For this purpose, NCI recently established an advisory committee to help identify new projects and emerging needs that might benefit from the processes and resources available at Frederick. The committee, chaired by Zach W. Hall, Ph.D., former executive vice chancellor for research at the University of California, San Francisco, requested at its first meeting that NCI develop a strategic plan for FNLCR designed to achieve the full potential of the capabilities made possible through its designation as an FFRDC.



In the 1980s, early in the HIV/AIDS epidemic, medical progress reached a critical technological impasse: HIV had been identified as the virus that causes AIDS, but what stymied medical investigators was how to grow the virus quickly and in sufficiently large quantities for pharmaceutical companies to develop a diagnostic test to determine whether a patient—or a potential blood donor—carried HIV.

As it happened, NCI scientists were well versed in tumor virus culture from work they'd already done on similar retroviruses that cause cancer. So the nation turned to NCI to solve this problem, and NCI turned to its Frederick National Laboratory for Cancer Research for solutions. FNLCR shifted gears in its virus production facility from churning out virus on their current project to churning out HIV. NCI partnered with five private companies, with which it shared the HIV viruses, and in less than a year this public-private effort had produced a validated FDA-approved blood test for HIV. Access to the blood test changed the trajectory of the epidemic because the blood supply could finally be protected from products containing HIV, and people were once again willing to receive donated blood. The blood test has also been used to identify people in the general population who are infected with HIV.

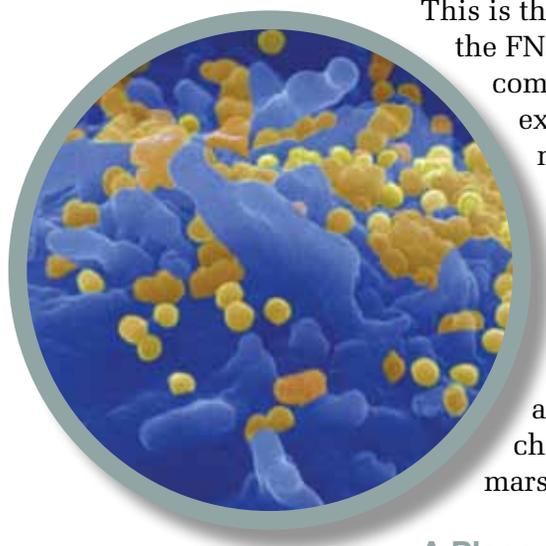
This is the kind of fast-response, one-of-a-kind research for which the FNLCR was created. “Our work benefits the greater scientific community,” said David Heimbrook, Ph.D., who became chief executive officer of SAIC-Frederick, Inc., the contractor that manages FNLCR, in 2011 (see Q&A on p. 59). “We provide solutions to move their science forward.”

FNLCR remains ready to respond to such emerging priorities, acting as a test bed for new technologies and novel research concepts in genomics, proteomics, imaging, high-performance biomedical computing, nanotechnology, and others. Leaders at NCI and SAIC-Frederick are exploring new opportunities or challenges that could be addressed through FNLCR's ability to marshal people and expertise.

## A Place and a Way of Doing Business

Located on the Fort Detrick campus in Frederick, Maryland, (about 18 miles northwest of the main NIH campus), FNLCR is a government-owned facility that is currently operated largely through a contract with SAIC-Frederick, Inc. Approximately 1,900 SAIC scientists and technicians at the facility perform a range of highly specialized research functions, several of which are described below, that give NCI the capacity and flexibility to respond quickly as new priorities emerge.

The FNLCR campus also houses approximately 800 NCI staff members, including 80 principal investigators from NCI's Center for Cancer Research whose work focuses on genomics and proteomics, structural biology, signaling, gene regulation, and other areas.



Craig Reynolds, Ph.D. (left), associate director of the Frederick National Laboratory for Cancer Research, and David Heimbrook, Ph.D., chief executive officer of SAIC-Frederick.

Above: Budding HIV particles. Colored scanning electron micrograph (SEM) of HIV particles (yellow) budding from the membrane of the host cell (blue).

After NCI, the largest user of FNLCR's services is the National Institute of Allergy and Infectious Diseases, which relies on FNLCR to support its efforts to develop and test vaccines for HIV, influenza, and other infectious diseases.

FNLCR is more than a collection of research facilities up the road from Bethesda. The "glue" that makes FNLCR a national laboratory instead of just another research campus lies in the contracting mechanism enabled by the laboratory's status as a Federally Funded Research and Development Center (FFRDC).

FFRDCs are independent nonprofit entities sponsored and funded by the U.S. government to meet specific long-term research and development needs that cannot be met by any other single organization. FFRDCs typically assist government agencies with scientific research and analysis, systems development, and systems acquisition. They bring together the expertise and outlook of government, industry, and academia to solve complex technical problems. FFRDCs are typically operated by a university, nonprofit parent organization, or an industrial firm in accordance with statutory and regulatory rules, and these organizations act as the government agency's strategic partner.

First established during World War II, FFRDCs operate in the industries of defense, energy, aviation, space, health and human services, and tax administration. There are currently 39 FFRDCs funded by the government. Examples are the Argonne National Laboratory, Brookhaven National Laboratory, Lawrence Berkeley National Laboratory, Los Alamos National Laboratory, and Sandia National Laboratories. FNLCR is the only FFRDC operated by the Department of Health and Human Services, and the only one dedicated exclusively to biomedical research.

Unlike a typical contract that has a defined statement of work, an FFRDC has a broad charter that provides flexibility without the need to issue change orders as projects are added, terminated, or revised. Where speed and timeliness are required, or a special skill set needs to be pulled together quickly to address a scientific challenge, the FFRDC can turn on a dime to provide the tools and environment scientists need to move forward. Among the areas where the FFRDC mechanism has proved helpful are developing prototype drugs for testing; supporting regulatory approval for new drugs, vaccines, and other therapies; setting standards for nanotechnology applications; generating large amounts of clinical-grade vaccines; and developing genetically engineered mouse models for research use.

Here, we focus on a handful of programs currently operated under FFRDC authority for NCI and the research community: the Nanotechnology Characterization Laboratory, the Biopharmaceutical Development Program, core facilities on the campus, the Natural Products Branch, the Vaccine Pilot Plant, the Core Genotyping Facility, and the Advanced Technology Research Facility.

## Nanotechnology Characterization Laboratory

The relatively new science of nanotechnology enables scientists to study and manipulate molecules to detect cancer-related molecules in the body and devise new anticancer therapies. With excitement over the potential opportunities of nanotechnology came many questions. The nanoparticles can carry drugs or imaging agents through the body directly to tumor cells while hiding them from the immune system and keeping them away from healthy tissue. But how would these particles—so small that 8,000 of them side by side would equal the thickness of a human hair—act in the body? What were the safety issues? No one had the answers, or even knew how to get them. As scientists at universities, small businesses, and biotech companies began sending proposals to FDA for the testing of nanotech drug delivery systems in humans, the field hit a wall. FDA told the developers they would have to figure out how to do safety testing.

To break the logjam and move the field forward, FNLCR was tasked with determining how to get these unique compounds—which combine a physical particle and a drug—into clinical trials. The FNLCR launched the Nanotechnology Characterization Lab (NCL) as part of NCI's Alliance for Nanotechnology in Cancer in a formal collaboration with the FDA and the National Institute of Standards and Technology (NIST) to perform preclinical efficacy and toxicity testing of nanoparticles. The NCL characterizes the particle's physical attributes and biological properties, as well as certain biological effects that can be measured in animal models. More than 250 nanomaterials have been characterized from more than 75 collaborators (90 percent non-governmental). Five nanomaterials are now in clinical trials, according to Piotr Grodzinski, Ph.D., director of NCI's Office of Cancer Nanotechnology Research.

Nanotechnology also offers opportunities to resurrect cancer drugs that have failed during development because of toxicity. Nanoparticles can be used to encapsulate or carry very toxic drugs and deliver them directly to the tumor, breaking down and releasing the drugs only once they are out of the general bloodstream, so the drugs affect only the cancer cells. For example, NCL tested CytImmune Sciences' Aurimune, gold nanoparticles with tumor necrosis factor (TNF) bound to their surface. TNF is a potent chemotherapeutic agent that was tested in clinical trials in the 1990s, but its development was stopped because of adverse side effects. In a recent phase 1 clinical trial of Aurimune, however, researchers were able to safely direct up to three times what had previously been a lethal dose of TNF directly to tumors, avoiding most of the negative side effects that plagued direct administration of the drug.

## Biopharmaceutical Development Program

The Biopharmaceutical Development Program makes novel antibodies and other proteins that require early development or aren't ready for industry to take on. The program's biopharmaceutical production and testing facilities are compliant with current FDA guidelines for good manufacturing practices. For example, FNLCR is manufacturing a monoclonal antibody to treat advanced forms of neuroblastoma, a cancer of nerve tissues that primarily affects children. The monoclonal antibody, called ch14.18, was first tested in NCI-supported early-phase trials. A later phase 3 multicenter study led by the Children's Oncology Group showed that immunotherapy with ch14.18, in combination with three other agents, significantly improved patient survival. (Two-year event-free survival was 66.5 percent in the experimental treatment group versus 46.5 percent in the standard therapy group without ch14.18.) FNLCR is manufacturing ch14.18 to meet an immediate need for the antibody while the production process is transferred to a commercial pharmaceutical manufacturer (United Therapeutics Corp.).

## Core Facilities

The core facilities at FNLCR can do many things that an individual investigator's lab generally cannot. For example, NCI bought every commercially available drug, as well as about 30 drugs that were not commercially available, and ran them through a panel of 60 different human tumor cell lines, representing leukemia, melanoma, and cancers

A technician at the Frederick National Laboratory for Cancer Research prepares test plates containing samples of the NCI-60, one of the most commonly used sets of cell cultures in cancer research, for reading.



of the lung, colon, brain, ovary, breast, prostate, and kidney (the NCI-60). They made the data available to help researchers choose the most promising drugs to test against different types of cancer. Anyone who wants to do an experiment with drug X can see what concentration to use and where to begin. FNLCR went a step further and reformulated many of the drugs so their quality is controlled, and is giving away test samples of the drugs so researchers can study them in cell lines.

### Natural Products



Of approximately 170 antitumor drugs approved worldwide since the 1930s, more than 65 percent are derived from natural products, ranging from deep-sea sponges to the flowers and insects of our planet's jungles and rainforests. More than 50,000 plant samples and 10,000 marine invertebrates and marine algae have been collected with partners worldwide and are stored at FNLCR. Because many of these compounds are difficult to work with, NCI sent large numbers of extracts to the NCI-designated cancer center at the Sanford-Burnham Medical Research Institute in La Jolla, California, where researchers made them soluble and dispersed them into plates to be used for screening drugs. Now extracts from the repository—considered a national resource—are being made in 1,584-well plates, and will be available in the future for distribution to qualified organizations.

### Vaccine Pilot Plant

FNLCR helps develop vaccines for some of the world's most devastating infectious diseases, including AIDS, influenza, and possible bioterrorism agents. After September 11, 2001, the White House and the Department of Health and Human Services asked NIH to enhance its capacity to make vaccines for emerging infectious diseases, including Ebola, HIV, and SARS, as well as for biodefense. FNLCR quickly set up the capacity to make pilot-scale vaccines for testing before moving into large-scale commercial production. Working with the Vaccine Research Center of the National Institute of Allergy and Infectious Diseases, the facility has developed several next-generation vaccines, including vaccines for SARS, Ebola, and West Nile Virus. "Many vaccines coming out of NIAID come through the Vaccine Pilot Plant at FNLCR," said Craig Reynolds, Ph.D., associate director of FNLCR.

### The Core Genotyping Facility

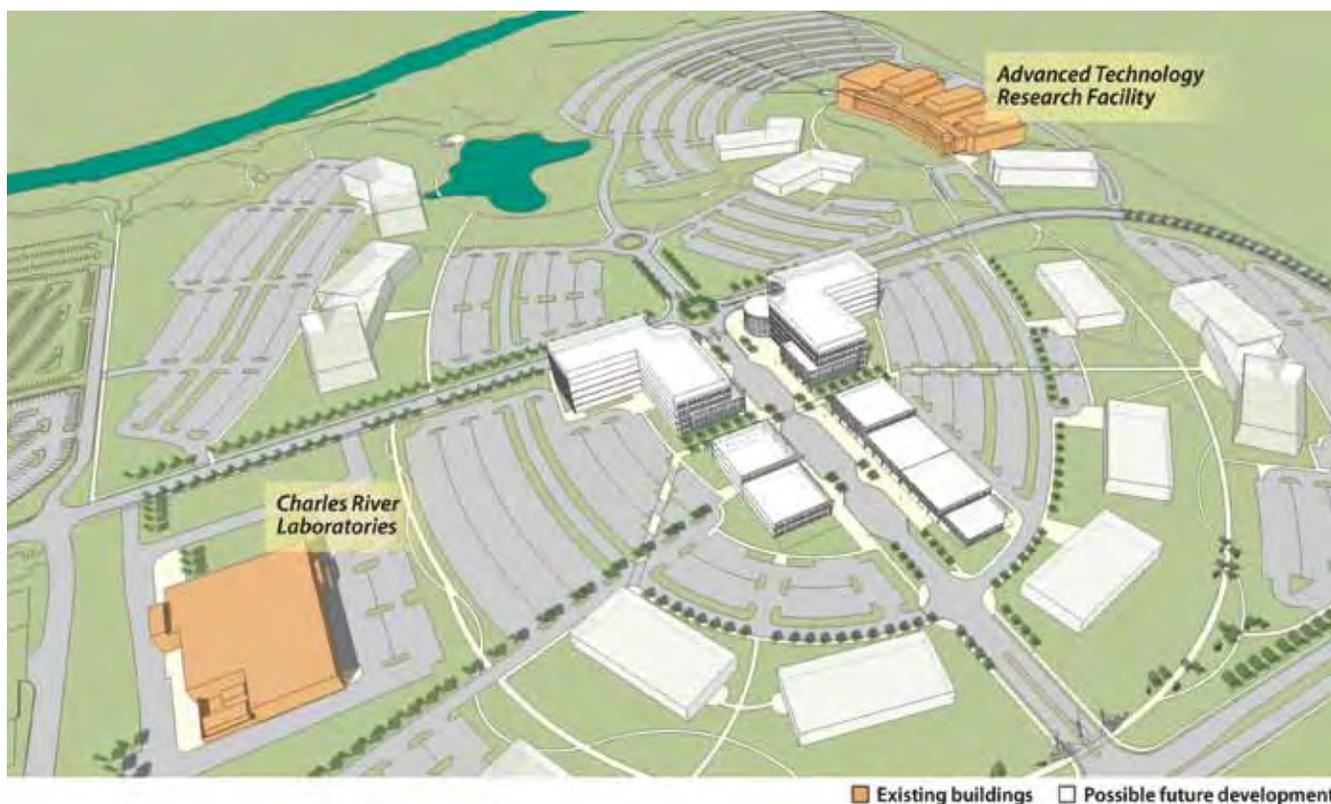
The Core Genotyping Facility at FNLCR provides researchers with tools to explore the role of genetic variation in cancer risk and outcome. It is one of several ways that FNLCR supports NCI's molecular and genetic epidemiology studies. Through genome-wide association studies (GWAS), researchers scan the entire genome looking for small variations (known as single nucleotide polymorphisms, or SNPs) that occur more frequently in

people with a particular disease than in people without the disease. From these associations emerge hypotheses about how the underlying disease is caused, and therefore how it might be treated.

Under FNLCR, the Core Genotyping Facility has genotyped nearly 70,000 subjects, including participants in large, NCI-supported epidemiologic studies such as the Prostate, Lung, Colorectal and Ovarian cancer screening trial, according to Stephen Chanock, M.D., director of the Core Genotyping Facility and chief of the NCI Laboratory of Translational Genomics, both within the NCI Division of Cancer Epidemiology and Genetics (DCEG). DCEG investigates the etiology of cancer by examining known risk factors, such as smoking habits or body mass index, together with genetic variations to assess cancer risk. The division's GWAS studies investigate the contribution of germline DNA, the constitutional DNA that people inherit from their parents, to the risk of developing various types of cancer.

“We needed to ramp up to genotyping and other assay capacity for large-scale population-based studies,” said Peggy Tucker, M.D., director of the Human Genetics Program in DCEG. “To do so, we needed a capable and flexible group of scientists who could essentially industrialize the boutique assays that were done in academic labs and do them reproducibly, efficiently, and with cost savings. FNLCR has given us this important capability.”

Riverside Research Park, Frederick, MD., showing the existing buildings and proposed development.





Advanced Technology Research Facility in Riverside Research Park, Frederick, MD.

DCEG researchers have engaged in large-scale collaborations with extramural investigators to conduct GWAS research on a range of cancers that include lung, prostate, renal cell, and urinary bladder cancers, as well as other common and uncommon cancers. “To date, we have completed about 12 GWAS studies, with a number still in the pipeline,” Tucker said. “All of the genotype data are made available to investigators. We receive about 500 requests each year for this information.”

### Advanced Technology Research Facility

The Advanced Technology Research Facility (ATRF) is a new 330,000-square-foot facility that opened in the summer of 2012. Located 5 miles from the FNLCR campus, the leased facility will consolidate many of FNLCR’s high-tech resources, including biologics manufacturing, nanotechnology, sequencing, genomics, and informatics. About 60 percent of the space will be occupied by SAIC-Frederick programs and about 11 percent by NCI’s intramural research programs and other federal programs. The remaining space will be made available to outside entities—such as industry, academic, and nonprofit groups—to pursue partnerships that leverage the ATRF’s resources and expertise to rapidly translate the latest genetic and molecular discoveries about cancer into new treatments.

“By consolidating our work in a state-of-the-art facility, and by setting aside space for outside partners to work with us side-by-side, we hope to see stronger interactions and cross-fertilization of ideas,” said David Heimbrook, Ph.D., chief executive officer of SAIC-Frederick. (See sidebar on page 59.)

The ATRF, which sits on 33 acres, is part of the 177-acre Riverside Research Park. The ATRF is the anchor tenant for the park, and NCI has temporary right of refusal for other companies that want to build within the 33 acres. The park’s developer hopes to add a state-supported technology incubator and higher education center. A Charles River Laboratories animal facility is located adjacent to the site.

## The Future of FNLCR

The current suite of research and other activities at FNLCR is broad and hits many of the critical areas of science that NCI invests in. Programs like ATRF, however, signal that the new focus of FNLCR is on what lies in the future: What will be the emerging issues or challenges for the national lab in the next decade and beyond? The newly established advisory committee for the FNLCR will have both a short-term role in helping to develop a strategic plan to guide FNLCR and a continuing role to identify new projects and new collaborations that could use the FFRDC approach to gain efficiencies and expand capacities for biomedical research, said Reynolds.

In particular, the committee is interested in finding the best role for FNLCR in a rapidly changing research environment. Unlike many of the other FFRDCs across the federal government, FNLCR doesn't have a unique core facility like a reactor or light beam source to pin its mission to. But the tremendous challenges inherent in cancer genomics, for example—storing the tsunami of data coming in from sequencing thousands of tumors, annotating the information, and making it available to researchers at many institutions in accessible common formats—offer one potential area of exploration for an expanded opportunity at FNLCR.



## David Heimbrook

The new chief executive officer of SAIC-Frederick brings a depth of knowledge of drug development and project oversight in the pharmaceutical industry. David Heimbrook, Ph.D., was the global head of discovery for the Oncology Discovery and Translation Area of Hoffman-LaRoche, Inc. He was responsible for developing and implementing Roche's oncology research strategy, including personalized health care and partnering relationships, and supporting development of compounds through clinical proof-of-concept to pivotal registration studies. Heimbrook previously held positions with Merck Research Laboratories and Smith Kline & French Laboratories.

### **What surprised you when you arrived at FNLCR in May 2011?**

I was inspired by the dedication of the scientists at the bench level and the sense of collaboration and shared mission among the NCI scientists and the SAIC-Frederick scientists. I found that to be invigorating.

### **What are your goals for FNLCR?**

Like all of my colleagues here, I'd like to expand our impact on translating research, development, and diagnostic discoveries into meaningful benefits for patients afflicted with cancer and AIDS. One way we can help achieve this is to streamline some of the processes and remove barriers to communication and collaboration, both internally and externally. For example, it is apparent that many potential external partners don't understand the opportunity for collaboration with FNLCR. The FFRDC structure provides some distinctive approaches, and we have to exploit those.

### **How is genomics research helping drug development?**

We now understand that diagnosing and treating cancer based on its location in the body and its physical appearance are inadequate. Molecular examination of the patient's tumor can provide insights on what caused it and what maintains it, and therefore how to treat it. We're linking treatment with particular drugs to genetic mutations that exist within a patient's tumor. This can provide better safety and efficacy for the patient, because if the patient doesn't have the matching profile, we don't treat with the drug—the patient is not exposed to the risk or the cost of a drug that won't help them, and other treatment options can be considered. We're seeing more examples of "precision medicine" coming to fruition. It's not a concept anymore; it's happening.

I'm not saying that all cancers will submit to this type of approach. We're a long way from having that detailed level of understanding of most cancers, and we don't have drug candidates for many different potential targets. Genomics is only part of the story. There is regulation of cell growth and survival at many levels. Even when we can genetically match a patient and a drug, responses often aren't durable. The cancer picks up other mutations as it goes. This was evident in a new melanoma drug that I was fortunate enough to work on at Roche. But the pace of discovery is accelerating. Programs like The Cancer Genome Atlas will provide much more insight into the genetic variability in many different types of cancer, and we have to distill this information into actionable targets. The global cancer research and development community is generating an armamentarium of small molecules and biologics targeting specific proteins. And in some instances, FDA is allowing physicians to combine unapproved drugs in trials to try to achieve more durable responses. All of these efforts should accelerate the pace of translating biological knowledge into meaningful therapies for patients.

### **You were a cancer researcher in industry for 25 years. What changes have you seen?**

It's an exciting time in cancer research and drug discovery. Really transformational, and it's been a long time coming. Twenty-five years ago, there wasn't much evidence that all of the investment in cancer cell biology would translate into new drugs, but now that's happening. Industry has also changed. There is recognition that internal research and development alone are insufficient to drive the bottom line, even in the companies that do it best. So, there is now much more focus on partnering and collaboration, and investment overseas. This increases the diversity of ideas while keeping costs down. The enthusiasm for partnerships is a big opportunity for academics, biotechs, and NCI. This is one reason why the new Advanced Technology Research Facility at FNLCR is so important: Its shared partnering space is specifically designed for collaboration. We hope that it will help catalyze the next wave of research—therapeutic and diagnostic discoveries that will benefit cancer patients. That's why we're here.

# Small Business Innovation Research, Small Business Technology Transfer (SBIR, STTR)

Catalyzing the translation of cancer research into technologies and products for the benefit of patients involves the collaboration and engagement of both public and private sectors. Small businesses are an important part of the cancer research enterprise. Small businesses are not only vital to the U.S. economy, providing jobs for over half of the nation's private workforce, but they are also key drivers in cancer research. Congress created, and recently expanded, the Small Business Innovation Research (SBIR) and Small Business Technology Transfer (STTR) Programs to strengthen the role of small businesses in fostering research and development (R&D) and to facilitate the commercialization of technologies across a range of industry sectors.



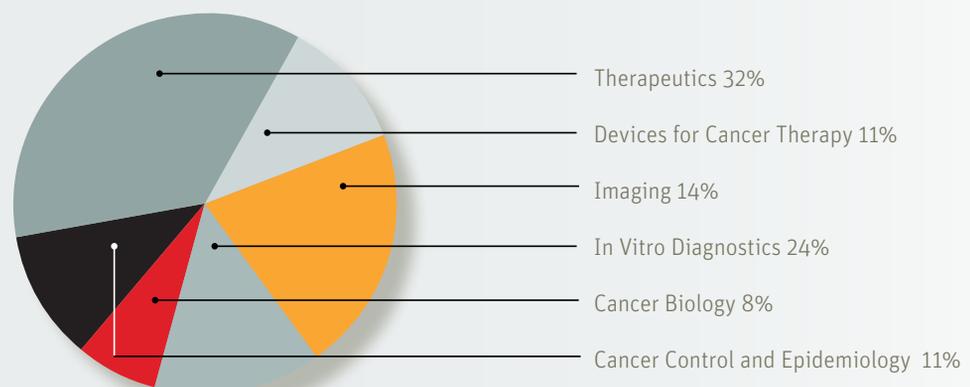
At the NCI, small businesses and research institutions foster R&D in a variety of cancer-related areas, including anticancer agents, diagnostics, health information technologies, medical devices, and imaging technologies. This work is conducted by small biotech companies with strong scientific and business expertise, but without the access to capital needed to fund the translation and ultimate commercialization of the technology. To address this problem and accelerate technological innovation in cancer, NCI takes an active role in supporting small companies and research institutions through grants, contracts, partnership development, and small business support. The ultimate goals of the NCI SBIR & STTR Programs are to support NCI's mission to reduce cancer incidence, morbidity, and mortality; extend survival; and increase the quality of life of cancer patients.

For fiscal year 2013, federal agencies with extramural R&D budgets of more than \$100 million are required to set aside 3.05 percent of their R&D budgets for SBIR/STTR contracts or grants to small businesses. The SBIR & STTR Reauthorization Act of 2011 will gradually increase the set-aside amounts to 3.65 percent by 2017, and expand eligibility to include small businesses majority-owned by venture capital operating companies, hedge funds, or private equity funds in 2013.

### The NCI Portfolio

In FY2012, NCI provided more than \$115 million in seed funding to support nearly 400 early-stage projects focused on cancer technology development. Over 40 percent of these projects are developing targeted therapeutic agents or devices for cancer therapy; and 38 percent are developing diagnostic and imaging technologies to support early detection, treatment planning and stratification, monitoring, and secondary prevention. About 19 percent of the portfolio is devoted to cancer biology to advance cancer research tools and to cancer control and epidemiology to advance primary prevention. (See Figure 1.)

Figure 1. The NCI SBIR Portfolio



In addition to providing funding through SBIR & STTR, NCI created an SBIR Development Center to provide strategic and partnership development support to SBIR & STTR award recipients, mentor awardees throughout the SBIR grant/contract on their technology goals and commercialization strategy, and assist them in finding follow-on investments. As part of efforts to help small businesses translate cancer research concepts to the commercialization stage, the NCI SBIR Development Center created the NCI SBIR Investor Forum to bring together 200 investors, strategic partners, and SBIR awardees. Participating SBIR companies in a recent forum secured additional funding and strategic partnerships worth up to \$230 million, an amount that is twice the value of the entire NCI SBIR & STTR Programs budget. The SBIR Development Center is focused on attracting top small business applicants; driving innovation in emerging, high-impact technology areas; and providing the support needed to help stimulate novel approaches to cancer control and care to help patients in need.

## Targeting cancer cells and sparing healthy tissue

NCI's SBIR portfolio aims to stimulate small business involvement in several areas: development of small molecule drugs and biologics, cancer diagnostics, cancer imaging, and electronic health and education tools.

One of NCI's SBIR grant recipients, Acoustic MedSystems, Inc. (AMS) in Champaign, Ill., is developing a minimally invasive technology to destroy a tumor, while minimizing harm to healthy tissue nearby. These devices deliver high-intensity ultrasound energy to targeted areas. The technology is being tested for treating tumors in a wide range of soft tissues, including the kidneys, liver, cervix, prostate, brain, and breast, as well as metastatic spine tumors, multiple myeloma, and uterine fibroids. Devices are planned for lung and bladder cancers as well.

For cancers in the kidneys and liver, the approach involves a needle that is guided by real-time imaging. High-intensity ultrasound is delivered through the

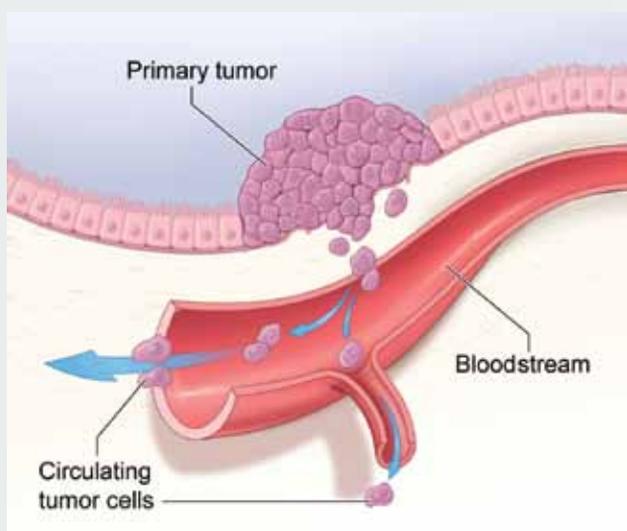
needle into the tumor. In animal studies, the device kills the tumor without harming nearby tissue. A similar approach is used for targeting metastatic spine tumors using a different device configuration. For cervical or colorectal cancers, the ultrasound is delivered through a transvaginal or transrectal applicator probe. According to founder and CEO Clif Burdette, Ph.D., "The SBIR & STTR programs have been pivotal to the development of nearly every product by our company. Without the initial support of the SBIR program, most of the medical products that our group has commercialized would not have been developed."

AMS has leveraged its \$6.8 million in NIH SBIR (\$6.1 million contributed by NCI) funding to attract \$11 million in private financing and more than \$19 million in non-federal revenue from products and services since 2000.

## Speeding development of technologies to detect and analyze circulating tumor cells

The California-based company Advanced Cell Diagnostics (ACD) is using SBIR funding to translate its RNAscope™ technology to detect and profile at the molecular level circulating tumor cells (CTCs) (see related story p. 42). In contrast to current CTC detection technology that is protein-based, RNAscope™, an automated system launched in 2008, is a technology capable of detecting messenger RNA molecules in individual cells with very high sensitivity and specificity. Multiple RNA targets can be detected and measured simultaneously. ACD is now working to adapt the tool as a way of scanning the gene expression phenotype of CTCs from cancer patients. Already, tests of RNAscope™ have shown that it can detect differences in messenger RNA profiles between normal tissues and tumor tissue specimens from patients with breast, cervical, and head and neck cancers. The next generation version of this technology, CTCscope™, is an automated assay designed to specifically look simultaneously at as many as 11 distinct messenger RNAs in order to better understand and predict CTC biology, and make correlations. Unlike current CTC detection technology,

### Circulating Tumor Cells



When a patient has cancer, a small number of cells may shed from the primary tumor and enter the bloodstream, leading to metastasis. Technologies that detect tumor cells circulating in the blood may offer a new avenue for diagnosing cancer and guiding treatment.

CTCscope™ does not require a step to concentrate CTCs, avoiding the potential loss of important CTCs in the sample. In addition, CTCscope™ detects live CTCs, the rare tumor cells that have the potential to form new tumors and are targets for therapy.

In San Diego, Epic Sciences, one of the first awardees of an SBIR contract focused on CTC analysis, is also developing technologies to improve CTC detection. Unlike the CTC scope, the Epic HD-CTC (High Definition-Circulating Tumor Cell) test does not require a step to concentrate or isolate CTCs, avoiding the potential loss of CTCs in the sample. The test has been able to find significant numbers of CTCs in patients with advanced prostate, breast, lung, and pancreatic cancer. Initial studies indicate that the Epic CTC test has been especially effective in detecting CTCs in metastatic lung cancer patients, a group in which it has been historically difficult to find significant numbers of CTCs. On top of its detection platform, Epic is developing assays to study the expression of key cancer genes in CTCs and detect any new mutations that appear during cancer progression. This information could be used to tailor the therapy to every patient. In a recent study, senior investigator Peter Kuhn, Ph.D. at Scripps Research Institute and co-founder of Epic Sciences, demonstrated that HD-CTC is capable of detecting CTCs even in patients with early-stage cancer, suggesting that the test may one day be used to diagnose cancer.

Epic is collaborating with a number of academic partners, including researchers at Yale, the University of Texas M.D. Anderson Cancer Center, the Translational Genomics Research Institute (TGen), and Moffitt Cancer Center, as well as major companies, including Genentech, Pfizer, and Celgene to develop HD-CTC commercially for diagnostic products in personalized cancer care. In partnership with a major pharmaceutical company, Epic recently launched its first international clinical trial of the technology. Through these academic and pharma collaborations, Epic has tested their technology in more than 1,000 patient samples from clinical trials.

Company	Location (Founding Year)	Technology Description	Why?
<b>Omniox, Inc.</b> <a href="http://www.omnioxinc.com">www.omnioxinc.com</a>	San Francisco, CA (2006)	Oxygen delivery technology (called H-NOX) that sensitizes tumors to radiation and chemotherapy.	Strong preclinical data showing that the lead candidate, in combination with radiation, leads to significant tumor growth delay and enhanced survival in mouse models. Major improvement over prior clinical efforts to re-oxygenate tumors. Approved for Phase IB clinical trials in glioblastoma.
<b>Etubics Corporation</b> <a href="http://www.etubics.com">www.etubics.com</a>	Seattle, WA (2006)	Immunization platform technology to generate therapeutic and preventive vaccines.	Completed Phase I and II clinical trials for an immunotherapeutic to treat colorectal cancer patients, and preparing to move to Phase III clinical trial. Additional immunotherapies are moving toward clinical trials for treatment of breast cancer. The Etubics platform solves issues involved with current adenovirus-based immunotherapy, including improved safety.
<b>Eutropics Pharmaceuticals</b> <a href="http://www.eutropics.com">www.eutropics.com</a>	Boston, MA (2005)	Development of a drug to trigger cell death specifically in cancer cells, along with a companion diagnostic tool to identify which patients will respond to this drug. Targeting multiple myeloma, small cell lung cancer, and ovarian cancer.	Development of companion diagnostic tools along with therapeutics informs treatment decisions, guiding the use of the therapeutic to treat the right patients. The diagnostic assay in development may also be useful for other therapeutic drugs currently on the market that depend on cell death pathways.
<b>Presage Biosciences</b> <a href="http://www.presagebio.com">www.presagebio.com</a>	Seattle, WA (2008)	Device that can inject multiple drugs into a tumor at once.	This technology allows the direct comparison of drug effects with each other, as well as the testing of drug combinations, to determine the most effective treatment for an individual. Presage is working with major oncology pharmaceutical company Millennium Pharmaceuticals to enable the identification of effective novel drug combinations to treat solid tumors.

Company	Location (Founding Year)	Technology Description	Why?
<b>Firefly BioWorks, Inc.</b> www.fireflybio.com	Cambridge, MA (2009)	Biomarker detection platform useful for diagnostic tests and discovery research, starting with detecting microRNA to diagnose cancer and other diseases.	First product, kit for detecting microRNA in life sciences research, has been launched commercially. The Firefly platform enables detection of clinically relevant biomolecules with an unprecedented combination of performance, flexibility, throughput, and cost. This technology lends itself to simple bedside or handheld devices for early disease detection or point-of-care diagnostics.
<b>Metabolomx</b> www.metabolomx.com	Mountain View, CA (2008)	Breath test for lung cancer that is non-invasive, rapid, and inexpensive.	Currently in clinical trials, this technology can detect lung cancer and other cancers in about 5 minutes, for less than \$100, and non-invasively by “smelling” the chemical profile present in the bloodstream and picked up in exhaled breath.
<b>Thermedical</b> www.thermedical.com	Somerville, MA (2008)	SERF™ Ablation therapy uses heat to rapidly and completely remove large solid tumors.	SERF™ Ablation therapy for liver cancer is under review by the FDA. This technology can treat tissue 100 times the volume of tissue that conventional radiofrequency energy can heat, expanding treatment options to patients with larger tumors.
<b>Gamma Medica</b> www.GammaMedica.com	Northridge, CA (2001)	Gamma Medica’s FDA-approved LumaGEM® Molecular Breast Imaging (MBI) device can image cancer regardless of breast density, making it possible to detect cancer where mammography often misses it.	Gamma Medica has developed a commercially successful system for breast cancer secondary diagnosis, and is expanding the system’s use for breast cancer screening, biopsy and surgery guidance, and treatment monitoring. The cost of the system is less than 1/3 of MRI, and this technology can be applied to prostate, brain, and other small organ cancer imaging.
<b>eMedonline</b> www.eMedonline.com	Crystal Lake, IL (1990)	Medication management system that uses smartphones and behavioral informatics to facilitate medication compliance.	eMedonline integrates the patient, caregiver, and provider to monitor the status of a patient and provide timely feedback. Through randomized control clinical trials, it has demonstrated sustainable compliance levels of 98 percent along with clinically significant improvements. More than 38,000 doses have been successfully administered among a variety of patient populations.

## NCI Center for Global Health

Cancer doesn't stop at national borders. Yet, there are differences in how any given cancer may manifest itself in different countries and different peoples, and science increasingly must confront cancer rates that vary from nation to nation, causes that are affected by living conditions, and screening and treatment options that are culturally appropriate in one region but not another. One fact, however, has become clear: We will not gain the upper hand on cancer unless we address it as a global public health problem.



In 2008, nearly 7.6 million people died from cancer worldwide. By 2030, the number of cancer deaths may be as high as 13.2 million, with more than two out of three deaths occurring in low-income and middle-income countries. More than 35 percent of these deaths may be preventable by controlling tobacco use, diet, and alcohol use, and by immunizing against infections that can lead to cancer—especially HPV, which is responsible for nearly all cases of cervical cancer and large percentages of anal, vulvar, and oropharyngeal cancers. Screening for breast, cervical, and colorectal cancer—when combined with effective treatments—can also prevent deaths from those diseases.

In 2011, NCI established the Center for Global Health to coordinate and prioritize NCI’s research efforts that can have a direct impact on global cancer, primarily in low-income and middle-income countries. Ted Trimble, M.D., M.P.H., is director of the new center.

The Center for Global Health will strengthen collaborations with other NIH entities, including the National Institute of Allergy and Infectious Diseases, which has large research programs overseas on infection-related cancers. NCI will work with the National Heart, Lung, and Blood Institute and the National Institute of Diabetes and Digestive and Kidney Diseases on issues related to overcoming obesity, an important cancer risk factor. In March 2012, the center convened a 2-day planning meeting with stakeholders from NCI and other federal agencies, as well as from academia and industry, to set priorities for global cancer research.

“We have an opportunity to help people ward off diseases,” Trimble said, with benefits that will be felt abroad and within the United States. “We have the highest obesity rates in the world and our tobacco use rates remain stubbornly high. We can learn from other countries.”

Combating cancer on a global level is also a priority for NCI’s director, Harold Varmus, M.D. The topic is getting extra attention, thanks to the United Nations’ new focus on non-communicable diseases in the developing world, which began with a high-level forum held in September 2011.

“I think everyone recognizes that it’s time to put cancer on the marquee for global health,” Varmus said.

### Global Issues, Local Solutions

University of Chicago researcher Olufunmilayo “Funmi” Olopade, M.D., is one of a growing cadre of cancer researchers whose work takes place in the global cancer arena but whose ties are to NCI-funded programs in the United States (see sidebar on p. 71). Her genetics and genomic studies of women in Africa have helped explain why African American women are more often diagnosed with breast cancer at younger ages than white women in the United States.

Ted Trimble, M.D., directs  
NCI’s Center for Global Health.

Similarly, some NCI-designated cancer centers have been working to establish cancer control programs in developing countries in Africa and Latin America. Each of those cancer centers has made a long-term commitment to build sustainable programs that meet the needs of the local populations, several of which are described here.

### Fred Hutchinson Cancer Research Center in Uganda

The Uganda Cancer Institute (UCI) in Kampala is the sole cancer treatment facility in a country of 32 million people. It was founded in 1967 through collaboration between the Ugandan Ministry of Health and NCI.

The most common cancer in Ugandan children, Burkitt lymphoma, was first described in Kampala in 1957 by Irish surgeon Dr. Denis Burkitt, and studies by the UCI and NCI characterized the remarkable response of this tumor to combination chemotherapy. The UCI, in its early years, also conducted seminal research on Kaposi sarcoma and hepatocellular carcinoma, but the collaboration with NCI was halted in 1972



Fred Hutchinson researcher Corey Casper, M.D., M.P.H. (right).

amid political turmoil in Uganda. International collaborators returned to the UCI in the 1990s, and in 2004 the Fred Hutchinson Cancer Research Center began its close partnership with the UCI. In October 2011, the UCI/Hutchinson Center Cancer Alliance broke ground for the first collaborative, comprehensive cancer training and outpatient treatment facility in sub-Saharan Africa.

Fred Hutchinson researcher Corey Casper, M.D., M.P.H., and colleagues are asking: What strategies can we find to deal with the enormous problem of cancer in low-income and middle-income countries? Three important cancers in Uganda are Burkitt lymphoma, which is caused by the Epstein-Barr virus, and two HIV-related cancers: Kaposi sarcoma and non-Hodgkin lymphoma. In Uganda, the problem is especially complex because more than 1.2 million Ugandans are living with HIV/AIDS.

This problem led researchers to ask whether chemotherapy regimens for patients with non-Hodgkin lymphoma should be modified when the patient also has HIV. Their study revealed that among patients with NHL and HIV, four less toxic oral drugs offered the same outcomes as intravenous chemotherapy.

“We believe we can adapt regimens we use in the United States to be used in Uganda and make them equally effective,” Casper said.

Now the UCI/Hutchinson Center Cancer Alliance has set an ambitious goal: to improve survival rates for patients with Kaposi sarcoma from the current 10 percent to 90 percent in 3 years. To succeed, they will have to overcome four obstacles: low knowledge of cancer among providers and the public, weak infrastructure and training, drug shortages, and a lack of supportive care. Right now, 90 percent of all cancer patients at the UCI are diagnosed with stage 3 or stage 4 cancer. To diagnose patients earlier requires improving the public’s knowledge of signs and symptoms of cancer. With Kaposi sarcoma, this is made easier because it usually presents as cancer of the skin. Providers and patients who are at highest risk for Kaposi sarcoma, those with HIV, can be trained to do skin exams and detect cancers at stage 1 or stage 2. A better infrastructure requires more space and supplies and more well-trained health care providers. In 2004, there was a single cancer specialist in Uganda. Today, there are seven cancer specialists who have been trained through the NIH Fogarty International Center and NCI. By the end of 2012 there will be 11. The Ugandan Minister of Health has made a commitment to obtain chemotherapy drugs and make them available to patients. The final key is supportive care, Casper said. To survive cancer, patients have to survive treatment, which means preventing infection and making people comfortable during care. “If we do all four, we’ll have a meaningful impact,” Casper said. “In 3 years,” Casper continued, “we want to be able to show we’ve built capacity and that in the international setting, we can make meaningful progress in treating cancer and flip mortality rates—and that there are scientific advances to help people in the United States that justify the work we do overseas.”

### University of North Carolina Lineberger Comprehensive Cancer Center in Malawi

The University of North Carolina (UNC) began its work in Malawi in the early 1990s. UNC has 17,000 square feet of laboratory space at Kamuzu Central Hospital in Lilongwe, with 250 Malawian employees. The original focus was HIV-related clinical trials in this impoverished country of 14 million people in southeastern Africa. The core of the activity is still research on HIV, but they are using the existing research capacity to expand into cancer research.

In 2006, UNC surgeon Carol Shores, M.D., Ph.D., traveled to Malawi to help obtain biopsies from children with Burkitt lymphoma. Through an NCI-supported grant, Shores and colleagues completed a proof-of-principle study, published in *Clinical Cancer Research* in April 2010, suggesting that a common chemotherapy, cyclophosphamide, can shift Epstein-Barr virus to a stage of its life cycle that is more susceptible to antiviral therapy. The group has completed a phase 1 study of the antiviral valacyclovir with cyclophosphamide in Burkitt patients. Their findings provide the rationale

for a trial testing synergistic tumor cell killing using cyclophosphamide with an antiviral drug. They also illustrate the importance of having cancer researchers on the ground in third-world countries, developing and testing new approaches to treatment.

Training is another key component of the UNC/Malawi partnership. Today there are 25 surgeons in Malawi. UNC Surgery and Otolaryngology, in collaboration with Kamuzu Central Hospital, has established a surgery residency program, setting the stage to double the number of surgeons in the country in 15 years. The Malawian surgery residents are involved in research alongside U.S. trainees at Kamuzu. In August 2011, the program obtained full certification from the College of Surgeons of East, Central, and Southern Africa, so that training at Kamuzu is recognized throughout Africa and the European Union.

“Train Malawian surgeons to provide much-needed clinical care and these surgeons will become principal investigators in Malawi-based research projects, nurturing a sustainable, vibrant health care system,” said Shores.

### The Indiana University Melvin and Bren Simon Cancer Center in Western Kenya

Kenya spends \$8.30 per person on health care each year. A system of such limited resources needs an approach that is heavy on “MacGyver moments,” said IU Simon Cancer Center director Patrick Loehrer, M.D., referring to the hero of a 1980s TV series about an always-inventive secret agent. They need to use their resources—including older, off-patent drugs and limited diagnostic capabilities—as efficiently as possible for the biggest benefit. Cervical cancer screening is a prime example.

In 2001 a consortium of North American academic medical centers and the Moi University School of Medicine in Eldoret, Kenya, established the AMPATH program to combat HIV/AIDS in western Kenya. AMPATH—Academic Model Providing Access to Healthcare—is supported by the United States Agency for International Development and delivers care to 70,000 patients. Through the existing infrastructure, AMPATH-Oncology provides clinics in pediatric, adult, and gynecologic oncology plus cervical screening and palliative care. The program is run by Kenyans providing clinical care that is reinforced by research and education.



**With help from Lineberger’s Division of Bioinformatics, UNC established the Kosciusko Community Hospital Cancer Database in September 2010. This Web-based system contains details on more than 1,800 cancer cases, including demographic data and information on site and histology of the cancer. The system will include treatment and outcome data in the future.**

## Olufunmilayo “Funmi” Olopade

As director of the Center for Clinical Cancer Genetics at the University of Chicago Medical Center, Olufunmilayo “Funmi” Olopade, M.D., has been studying breast cancer in U.S. and in Nigerian women, learning how to better treat both.

When she began seeing patients in Chicago, the Nigerian-born Olopade saw differences among women with breast cancer. Her African American patients were more likely than white patients to be diagnosed at younger ages, and their cancers were more aggressive. She set out to learn why and eventually expanded her research to study breast cancer across the African diaspora.

Her group found that breast cancers in African women exhibit a different pattern of gene expression than is seen in white women. Tumors in African women are more likely to be estrogen-receptor negative and originate from different cells within the breast. The tumors are also less likely to respond to many standard therapies.

“We treat patients with cancer in this country who come from diverse backgrounds,” said Olopade.

“Until we have a deeper knowledge and understanding of how cancer incidence and etiology vary geographically and how they affect the immigrant populations in this country, we’re never going to be able to reduce cancer health disparities.”

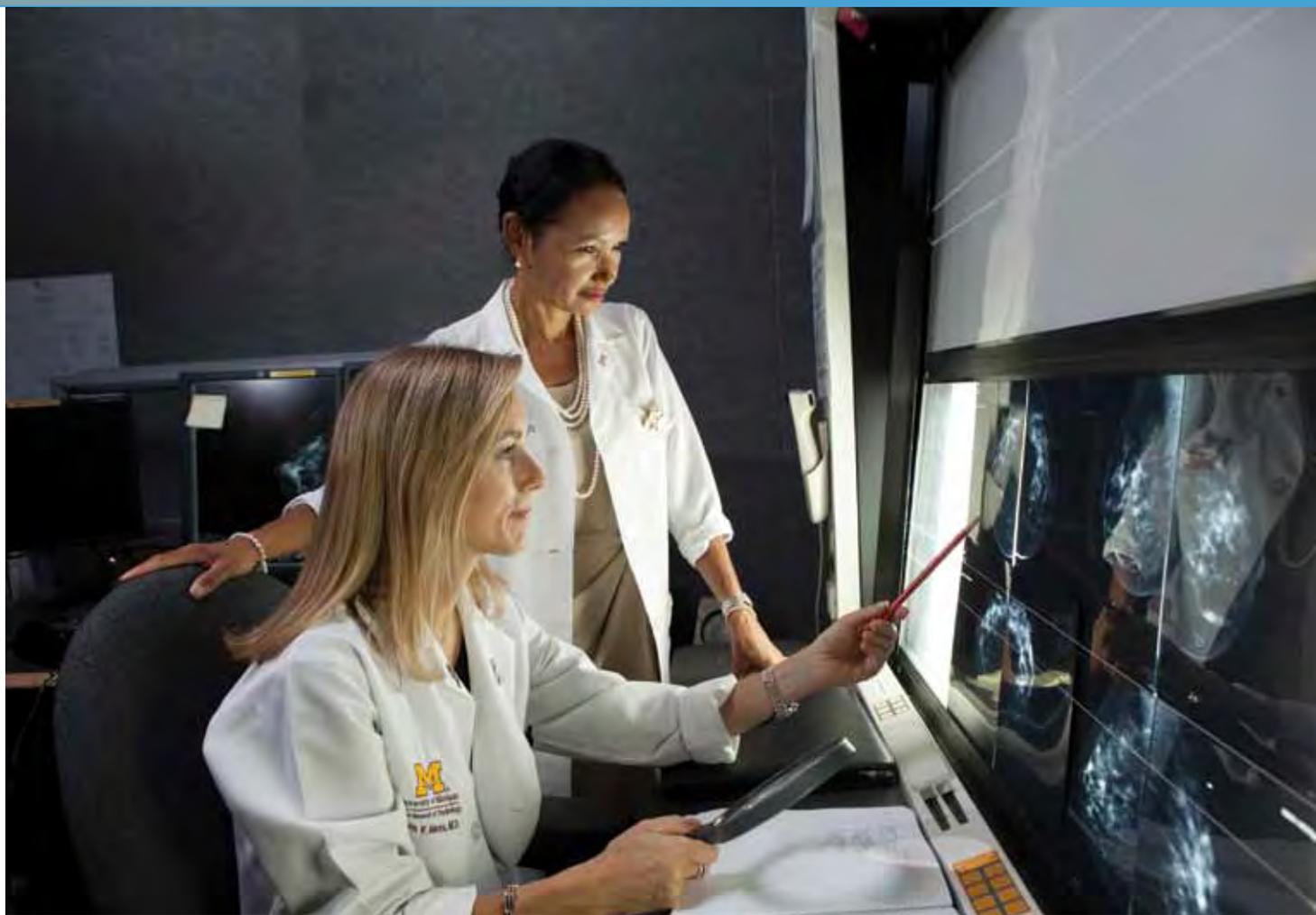
In 2011, President Obama appointed Olopade to the National Cancer Advisory Board. “It’s really very exciting that NCI is taking global leadership in cancer research and investing in the new Center for Global Health. We should do research where the interesting problems are,” she said. Olopade is also an executive council member of the African Organization for Research and Training in Cancer, which aims to further research related to cancers prevalent in Africa, support the management of training programs in oncology for health care workers, address the obstacles to creating cancer control and prevention programs, and raise public awareness of cancer in Africa.

“It’s important to continue to advocate for more resources in cancer,” said Olopade. “If we continue with the trajectory we’re on, cancer will be the leading cause of death by 2030, even in Africa.” And many of those cancer deaths are preventable.



# NCI-Designated Cancer Centers

Outside the Washington Beltway, when the public thinks about NCI or about cancer research more generally, chances are they're thinking about research and care at one of the nation's 67 NCI-designated cancer centers. Represented in every region of the United States, these cancer centers—established as a full-fledged program in the 1971 National Cancer Act—are NCI's “boots on the ground” in conducting leading-edge basic research, driving informatics and genomic applications in cancer diagnosis and treatment, recruiting patients for clinical trials, and developing and testing new standards of practice in cancer screening, diagnosis, treatment, and care.



Alexis Nees, M.D., (foreground) and Lisa Newman, M.D., M.P.H.,  
University of Michigan Comprehensive Cancer Center.

NCI's 67 designated cancer centers, located in 34 states plus the District of Columbia, form the national backbone of the institute's programs for studying and controlling cancer. The centers are the primary source of new discoveries into cancer's causes, prevention, diagnosis, and treatment. They deliver up-to-date care to patients and their families, inform health care professionals and the general public, and offer the potential to reach many diverse, and often underserved and understudied, patient populations. Every state with a density of more than 150 people per square mile contains at least one NCI-designated cancer center.

Receiving that designation is no small achievement. The qualification process is stringent, involving an intense and thorough review. Cancer centers receive a core support grant from NCI, in addition to the substantial funding for cancer research the centers obtain from other competitive grants and contracts with NCI and other sources, both public and private.

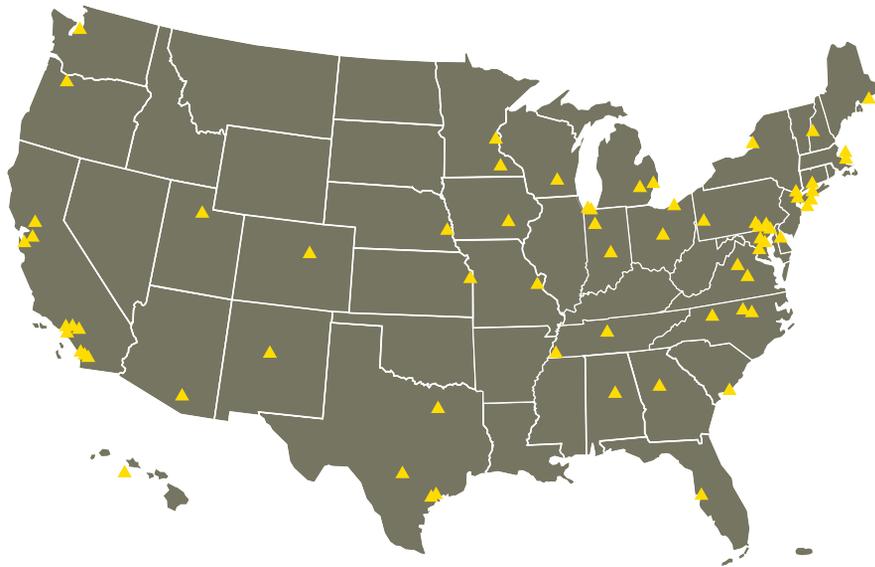
NCI offers two designations: Cancer Center and Comprehensive Cancer Center. A Cancer Center has a scientific agenda focused on one of three major areas—laboratory, clinical, or population science—or some combination of the three. The Comprehensive Cancer Centers have depth and breadth of research activity in all three areas and also must demonstrate a commitment to public education and dissemination of advances into the communities they serve, as well as continual education of professions responsible for cancer care. Forty-one of the NCI-designated cancer centers are Comprehensive Cancer Centers and 26 are Cancer Centers. Of the 26, seven centers conduct only basic research and offer no clinical programs.

*Every state with a density of more than 150 people per square mile contains at least one NCI-designated cancer center.*

The centers are continually updating and reshaping themselves to take advantage of new scientific opportunities, with particular emphasis today on the genetic and genomic underpinnings of cancer, clinical trials of new therapies, and the bioinformatic tools and technologies that make fruitful the huge volumes of data emanating from laboratories. They work along a continuum, from basic research to translational studies that bridge the lab and the clinic, as well as with long-term observation studies and outreach.

NCI-designated cancer centers are unique because of their interdisciplinary nature, says Linda Weiss, Ph.D., director of NCI's Office of Cancer Centers. "The collaborative environment created at each cancer center—and across cancer centers—fosters creativity that helps move science forward."

Collaboration between centers is proving particularly valuable in the area of cancer genomics. Researchers at the University of New Mexico Cancer



NCI's 67 designated cancer centers, located in 34 states plus the District of Columbia, form the national backbone of NCI's programs for studying and controlling cancer.

Center, for example, observed a significant increase in acute lymphoblastic leukemia (ALL) among their pediatric Hispanic population. Knowing that ALL patients of Hispanic or of American Indian genetic ancestry have historically experienced some of the disease's worst outcomes, the New Mexico scientists turned to comprehensive genomic and gene sequencing methods in the hope they could identify new mutations that might be causing the high-risk disease and therapeutic resistance they were seeing in their patients. Working with the Children's Oncology Group, a cooperative research organization sponsored by NCI and St. Jude Children's Research Hospital in Memphis, Tenn., the team employed several NCI-supported tools and initiatives, including TARGET, TCGA, and Strategic Partnering to Evaluate Cancer Signatures (SPECS). The team of investigators discovered a unique mutation in a gene called *CRLF2* (cytokine receptor-like factor 2), which is strongly associated with Hispanic ethnicity and American Indian ancestry, as well as mutations in a gene called *JAK*. They are now studying novel therapeutics to target these mutations and, with the Children's Oncology Group, have opened new clinical trials testing targeted therapies for these mutations.

This spirit of collaboration is especially strong in the many NCI-designated cancer centers that are embedded with America's largest research universities. For them, collaboration begins with inter-departmental linkages.

The Massachusetts Institute of Technology (MIT) has had a cancer center focused on basic research that has been designated by NCI since 1974. In 2007, it became the Koch Institute for Integrative Cancer Research at MIT, with a novel plan to combine the faculty of the center with an equal number of MIT engineers. Today, the work of that faculty includes efforts to develop systems to deliver drugs to cancer cells more effectively, designing new agents to perturb the cancer cell, and modifying cells to improve

the body's response to therapy. MIT's Robert Langer, Sc.D., has created nanoparticles that are "smart bombs" embedded with high concentrations of cancer drugs—on the order of 10,000 to 100,000 drug molecules per nanoparticle. The outside of the particle is decorated with materials that allow it to travel unnoticed through the body. Then, tags on the surface of the nanoparticle bind to the surface of the cancer cells. A phase 1 safety trial conducted by Bind Biosciences, a company launched by MIT and Harvard scientists, began in January 2011.

MIT researchers are also trying to figure out how to use small RNAs, which are key regulators of gene expression and genome function, to inhibit gene function and stop a tumor. "I'm extremely optimistic that we will get small RNA therapies to work for cancer," said Koch Institute director and National Cancer Advisory Board member Tyler Jacks, Ph.D.

"It's not a brand new idea, but the challenges have been in their delivery. It's an engineering problem and we're working on that."

By combining nanomaterials with small interfering RNAs (siRNAs), short strands of RNA that can selectively intercept and destroy messenger RNA before it delivers its instructions, MIT's Sangeeta Bhatia, M.D., Ph.D., tackled this problem with William Hahn, M.D., Ph.D., at Boston's Dana-Farber Cancer Institute. Hahn determined which genes are relevant to an ovarian cancer cell's survival and Bhatia devised a nanoparticle that, in mice with human ovarian cancer, successfully delivered siRNAs to silence one of those genes. It shrank the tumors and prolonged the lives of the mice.



Tyler Jacks, Ph.D., Director, David H. Koch Institute for Integrative Cancer Research at MIT and chair of the NCI's National Cancer Advisory Board.

The Koch Institute also has invested heavily in making the immune system a stronger ally to defend the body against cancer.

Researchers such as Darrell Irvine, Ph.D., who has a materials science background, are using nanomaterials as a kind of "feedbag" attached to the immune system's T cells. The nanomaterials help the T cells stay alive longer and resist the agents that tumors secrete to fight the immune system. In the laboratory, the researchers have demonstrated that these modified T cells are much more effective than regular T cells, and they are moving quickly toward clinical application.

## Clinical Trials

NCI-designated cancer centers have a proud history of leadership in clinical trials that have led to important advances in treatment and prevention.

In 2011 alone:

- A study led by scientists from Memorial Sloan-Kettering Cancer Center in New York found that the combination of bevacizumab, a widely used anticancer drug, with standard chemoradiation is safe and could prolong survival in patients with advanced nasopharyngeal carcinoma.
- A study led by researchers at the Chao Family Comprehensive Cancer Center at the University of California, Irvine, showed that combining

two anti-estrogen drugs, anastrozole and fulvestrant, extended the median survival time of women with hormone receptor-positive metastatic breast cancer by more than 6 months, compared with those who underwent standard treatment with anastrozole alone.

- Researchers at the University of California, San Francisco, Helen Diller Family Comprehensive Cancer Center and colleagues reported that the HPV vaccine can safely and effectively prevent anal cancer.

Many cancer centers develop partnerships with other organizations in their regions that are involved in clinical care, research, and community outreach.

For example, like other cancer centers, the Huntsman Cancer Institute (HCI) at the University of Utah relies on partnerships to offer clinical trial opportunities throughout a geographically large yet sparsely populated state. HCI teams with Intermountain Healthcare, the state’s largest insurance carrier/hospital system, to expand its reach. “Together, Huntsman Cancer Institute and Intermountain see 85 percent of the state’s cancer patients,” said Wallace Akerley, M.D., HCI’s senior director of community oncology research, who has high hopes for the relatively young partnership. “Working with a large multi-hospital network allows HCI to bring our investigator-initiated clinical trials to a much larger group of patients and gives us room to expand clinical research participation across our entire state. This will allow us to answer key questions much faster.”

The Holden Comprehensive Cancer Center at the University of Iowa is evaluating whether a ketogenic diet—a relatively high-fat, low-carbohydrate diet that limits blood glucose levels—can increase sensitivity to cancer therapy. The cancer center was awarded an NCI grant in 2011 for a clinical study of whether a ketogenic diet can increase the effectiveness

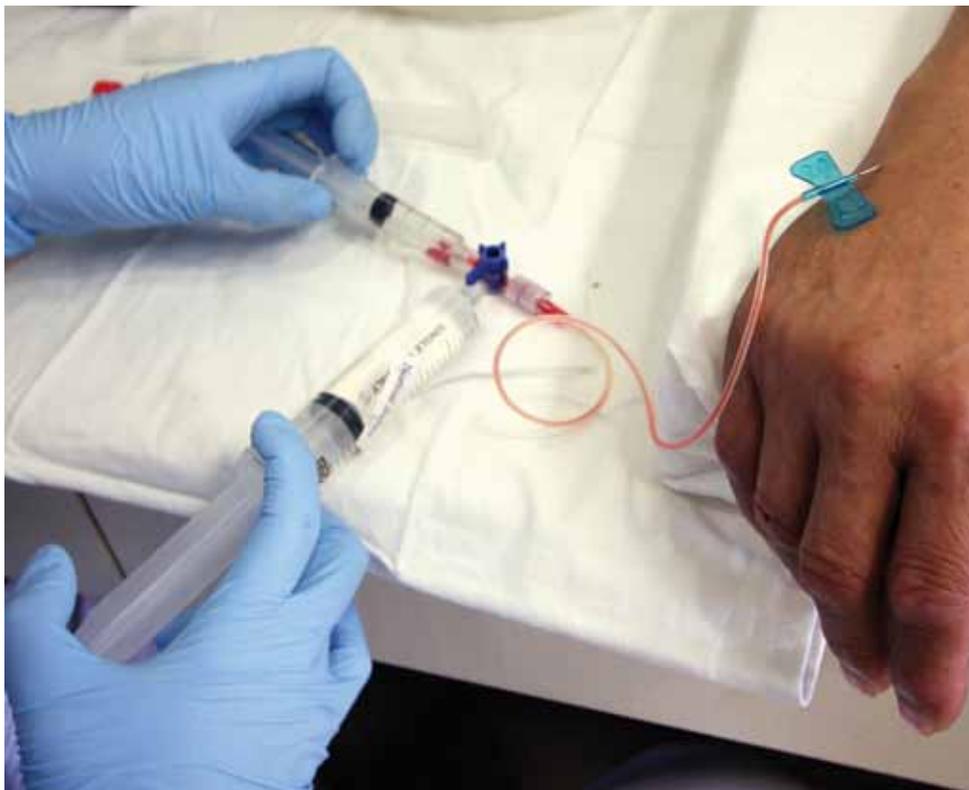


Case Western researchers are studying effects of exercise on outcomes in older cancer patients.

of radiation and chemotherapy for patients with lung and pancreatic cancers. “We have real expertise in a number of research areas, including free radical cancer biology, cancer immunology, and novel clinical trials in pancreatic cancer,” said George Weiner, M.D., the center’s director.

Case Western Reserve Cancer Center in Cleveland has a program focused on older people with cancer called the Aging and Energy Balance Program, which has a clinical trials component. Its four priority areas are: treatment efficacy and tolerance, effects of comorbidities, psychosocial aspects of cancer in the elderly, and biology of aging and cancer. The program is well positioned to study how treatments are tolerated among people age 70 and older, identify approaches to quality of life issues, and understand the impact of comorbidities (see related story p. 39). The program’s co-director, Julia Rose, Ph.D., and colleagues are using randomized clinical trials to explore coping and communications in advanced cancer patients, with an effort to look at age group differences. Historically, older adults with cancer are reluctant to get involved with psychosocial programs. Her group designed an intervention to see if older adults would engage in an intervention if they could control the level of contact. When given the opportunity to do so on their own terms, older adults were engaged in the intervention as much as middle aged adults. Both age groups saw benefits in reduced depression, increased satisfaction with their oncologists’ explanations, and decision-making about care. Families also had more contact with the team and saw positive outcomes.

Case Western scientists are studying how well older patients tolerate cancer treatment.



**Bioinformatics.** One of the important roles the cancer centers play is in creating and implementing a national cancer bioinformatics enterprise. Bioinformatics provides researchers with the tools, information technologies, and analytical methodologies needed to manage the large volumes of data generated by today's genomic studies, large observational studies, and networked clinical trials—and to harvest insights from the information that is collected. Even in a time when high-volume storage of digital data is plentiful and less costly than just a few years ago, the amount of information from genomic studies is astronomical, pushing beyond gigabytes and terabytes to petabytes. The collection and storage of that data remain a stiff challenge that pales in comparison to the computing capacity necessary for its analysis. Finding common protocols for data collection and analysis is also key to information sharing among all of NCI's components and grantees, and many others. Consequently, from genomics to clinical trials, bioinformatics capacity becomes a critical asset. Moffitt Cancer Center recognized that managing the large multi-site Total Cancer Care effort requires a dedicated workforce. So, it launched M2Gen, a company wholly owned by Moffitt that employs 152 people to implement Total Cancer Care. The Huntsman Intermountain Health Care Program pulls together data from multiple sources, including Utah's unique population database linked to data from the Department of Motor Vehicles, the Division of Vital Statistics in the Health Department, and IHC's own databases. Its end goal is to link all outcomes on a statewide basis. With the Utah population database, IHC can develop risk profiles going back three generations. Geocoding is also possible, so the team knows where patients live and can crosslink with Utah environmental records, including radon exposure, radiation exposure, and selenium levels in the soil.

To make data gathered from patients in clinical trials available for use in standard care, NCI recently created a computer tool to support interoperability between clinical research and electronic health record systems. Using templates developed by the health care industry's standards-making body, the freely available software will facilitate data exchange between systems with diverse applications and information models, a task that is normally time- and resource-intensive. The first application of the new software will be within a breast cancer trial known as I SPY2, led by Laura Esserman, M.D., at the University of California, San Francisco, Helen Diller Family Comprehensive Cancer Center.

## Translational Research

A major part of every NCI-designated cancer center's portfolio is work to move laboratory findings to the clinic as quickly as possible. At Case Western, researchers used a special mouse model to explore the impact of exercise on outcomes in older cancer patients. They engineered a transgenic mouse model that overexpresses an enzyme called phosphoenolpyruvate carboxykinase (PEPCK) in muscle. The mice with the extra enzyme exercises more than normal mice. They also eat more, weighs less, and have a longer lifespan and more reproductive months than normal mice. The researchers also noticed that the mice were not getting spontaneous cancers, as mice often do. So they crossed a PEPCK mouse with a mutated mouse, the Apc-min mouse, which develops hereditary intestinal tumors.

Todd Soplinski, M2Gen Laboratory at the Moffitt Cancer Center, prepares a slide of a patient's tumor for analysis.



The progeny of the crossed mice also exercised more than normal mice and their colon tumors occurred later and grew more slowly than in the usual Apc-min mice.

With additional study, the researchers saw a relationship between lowered insulin and certain cytokines known to stimulate cancer. To move these findings into geriatric patients, the Case Western group has launched a feasibility study in African American women who just finished treatment for breast cancer. The women are put on an exercise program, including aerobic and resistance exercise, for 20 weeks, with progressive increases in aerobic activity. “We want to determine the amount of exercise required to get cytokine levels down,” said Nathan Berger, M.D., co-director of Case Western’s Aging and Energy Balance Program. “We will also look at how exercise affects quality of life, time to recurrence, and progression-free survival.”

## Research Over the Long Term

Long-term NCI support of cancer centers allows many of them to undertake the kinds of research that spans years, if not decades. In 2003, the Moffitt Cancer Center in Tampa, Florida, began developing Total Cancer Care (TCC), a massive observational study including cancer patients from 18 health care sites in 10 states (see box, p. 78). Patients volunteer to contribute their tumor tissue and clinical and quality-of-life data throughout their lives. To date, more than 80,000 patients are enrolled and 300 to 400 new patients are being added weekly. The aim of TCC is to improve the standard of cancer care by combining information technology, science, and clinical treatment to meet the needs of individual patients. A large part of TCC is identification of genetic biomarkers that will help doctors predict who is at high risk for cancer and to offer better detection and predictors of response to therapy, on an individualized basis.

Patients at each site are enrolled in a single protocol and are asked three questions: May we follow you throughout your lifetime? If you have a tumor that is biopsied or removed, may we study the tissue using molecular technology, including genetic and genomic profiling? If we find something of benefit, may we re-contact you? Participants in TCC complete a comprehensive history and quality-of-life questionnaire online, including information on risk factors—alcohol and tobacco use, physical activity, and family history—as well as other medical problems and comorbidities. Already, TCC is yielding research results. Moffitt researchers have published data on biomarkers and gene expression patterns in lung cancer and colorectal cancer that may help doctors nationwide predict which patients will respond best to certain treatments.



Richard Gilbertson, M.D., Ph.D., Director, Comprehensive Cancer Center (left), and Paul Gibson, Ph.D., of the Molecular Clinical Trials Core, St. Jude Children's Research Hospital.

Clinicians who enroll patients have a portal to TCC, so they can ask their own questions of the research team: How many patients look like the one I just enrolled? What therapies did they receive? What were the outcomes? Researchers can compare cases to learn what treatment worked best for what kind of patient, and to tailor cohort identification for research projects based on the molecular data and other information collected. Patients have access to the portal, as well.

“We’re not just taking data from them,” said William S. Dalton, Ph.D., M.D., president/CEO and director of the center. “It’s extremely important that this is a grassroots effort with community involvement. The program’s users have a say in how this is developed.” For part-time residents, which represent a large segment of Florida’s population, the patient portal allows them to access their records from anywhere. TCC is working to develop algorithms so that ultimately patients will be able to ask questions and find information relevant to their specific experience.

St. Jude Children’s Research Hospital, an NCI-designated cancer center, launched its long-term population study, called St. Jude Life, to learn about long-term effects of treatments given to children with cancer and learn how to improve cure rates while leaving survivors with fewer side effects. Every St. Jude survivor who agrees to participate travels to Memphis periodically for a comprehensive battery of blood, neurocognitive, and performance assessments. Close to 75 percent of those patients contacted have agreed to participate.



Beth Eastwood, left, and Sabrina Haralson, University of Michigan Comprehensive Cancer Center.

## Outreach to Rural, Minority, and Underserved Populations

“In the last decade, cancer centers have been playing a much larger role within their communities,” explained Max Wicha, M.D., a cancer researcher and founding director of the University of Michigan Comprehensive Cancer Center. “We develop clinical trials prevention studies with partners. Many states have launched consortia to reduce the burden of cancer, and in most cases, the cancer centers are leading the effort. We have the Michigan Cancer Consortium, a statewide effort involving all cancer-related institutions, and the Department of Public Health.”

Iowa’s Holden Comprehensive Cancer Center is a leader in statewide cancer control efforts, in collaboration with the Iowa Department of Health and the Centers for Disease Control and Prevention. Cancer Center Director George Weiner, M.D., is president of the Iowa Cancer Consortium, a partnership between the cancer center, local hospitals, the American Cancer Society, and the Department of Public Health to raise awareness about cancer. A current focus of the group is radon, a naturally occurring, invisible, and odorless radioactive gas. Radon exposure is the leading cause of non-smoking related lung cancer, according to Environmental Protection Agency estimates. Every county in Iowa has high radon levels. Cancer center staff members are doing health communication research and public policy evaluations to find the best way to increase the number of homes and schools that are tested for radon.

The University of New Mexico Cancer Center builds partnerships with its multiethnic communities and the state’s scientific and engineering communities. As a result, it offers a unique blend of outreach to all citizens of New Mexico. New Mexico has the highest rate of uninsured citizens in the country, 26 percent. The state also has the largest percentage of Hispanics in the United States and is home to 19 pueblos, two Apache nations, and three bands of the Navajo nation; these populations experience very different patterns of cancer incidence and mortality. Before the university decided to start a cancer center, “our population did not have access to state-of-the-art care,” said Cheryl Willman, M.D., the center’s director and CEO. “We argued that all New Mexicans deserve state-of-the-art care and deserve to benefit from the fruits of great cancer research.” The cancer center received its NCI designation in 2005. For its outreach activities, the UNM Cancer Center is building extensive community networks with the state’s Hispanic and American Indian populations on cancer screening, clinical trials education, and patient navigation (see related story on p. 44).

Many cancer centers reach the research community and patients through their websites. St. Jude functions as a national resource, for example, by sharing the results of laboratory studies, clinical trials, and long-term survivorship studies through scientific publications and its website, Cure4kids.org.

## Glossary of Terms

**Angiogenesis:** Blood vessel formation. Tumor angiogenesis is the growth of new blood vessels that provide tumors with oxygen and nutrients they need to survive and grow. This process is caused by chemicals that are released by the tumor and by host cells in the tumor's microenvironment.

**Apoptosis:** A type of cell death in which a series of molecular steps in a cell lead to its death. This is one method the body uses to get rid of unneeded or abnormal cells. The process of apoptosis may be blocked in cancer cells. Also called programmed cell death.

**B cell:** A B cell is a type of white blood cell (also called a B lymphocyte) that produces antibodies. B cells are part of the immune system and develop from stem cells in the bone marrow.

**DNA methylase:** An enzyme (a protein that speeds up chemical reactions in the body) that attaches methyl groups to DNA. (A methyl group is a chemical group containing one carbon and three hydrogen atoms.) Also called DNA methyltransferase.

**Driver mutation:** Mutations in cancer genomes that push cells toward cancer.

**Epigenetics:** The study of how age and exposure to environmental factors, such as diet, exercise, drugs, and chemicals, may cause changes in the way genes are switched on and off without changing the actual DNA sequence. These changes can affect a person's risk of disease and may be passed from parents to their children.

**Exome:** The part of the genome formed by exons (the protein coding portion of genes).

**Gene expression profile:** Information about all messenger RNAs that are made in various cell types. A gene expression profile may be used to find and diagnose a disease or condition and to see how well the body responds to treatment. Gene expression profiles may be used in precision medicine.

**Genome:** The complete genetic material of an organism.

**Kinase:** A type of enzyme that causes other molecules in the cell to become either active or inactive. Kinases work by adding chemicals called phosphates to other molecules, such as sugars or proteins. Kinases are a part of many cell processes. Some cancer treatments target certain kinases that are linked to cancer.

**Mutation:** Any change in the DNA sequence of a cell. Mutations may be caused by mistakes during cell division, or they may be caused by exposure to DNA-damaging agents in the environment. Mutations can be harmful, beneficial, or have no effect. If they occur in cells that make eggs or sperm, they can be inherited; if mutations occur in other types of cells, they are not inherited. Certain mutations may lead to cancer or other diseases.

**Passenger mutation:** Mutations in cancer genomes that do not contribute to the growth of the cancer but have occurred during the growth of the cancer.

**Proteasome:** A large protein complex that helps destroy other cellular proteins when they are no longer needed. Proteasome inhibitors are being studied in the treatment of cancer.

**Protein:** A molecule made up of amino acids. Proteins are needed for the body to function properly. They are the basis of body structures, such as skin and hair, and of other substances such as enzymes and antibodies.

**Protein expression:** Refers to the production of proteins by cells. The study of protein expression in cancer cells may give information about a specific type of cancer, the best treatment to use, and how well a treatment works.

**Receptor:** A molecule inside or on the surface of a cell that binds to a specific substance and causes a specific effect in the cell.

**Signaling pathway:** Describes a group of molecules in a cell that work together to control one or more cell functions, such as cell division or cell death. After the first molecule in a pathway receives a signal, it activates another molecule. This process is repeated until the last molecule is activated and the cell function is carried out. Abnormal activation of signaling pathways can lead to cancer, and drugs are being developed to block these pathways. This strategy may help block cancer cell growth and kill cancer cells.

**T cell:** A T cell is a type of blood cell. T cells belong to a group of white blood cells called lymphocytes. They are part of the immune system and develop from stem cells in the bone marrow. T cells help protect the body from infection and may help fight cancer.

# The 2013 Budget Request

This budget request consists of two components: the increase required to maintain our present level of operations (current services) and the increase required to initiate new initiatives and expand existing ones.

It should be noted that we have carefully reviewed our current expenditures and have found important efficiencies and savings. The current services increase is the amount that will be required to sustain NCI programs, restore some of the funding cuts that have been implemented over the past several fiscal years, and provide for minimal growth. Noncompeting Research Project Grants (RPGs) would be funded at committed levels, the number of competing RPGs would slightly increase, and most other mechanisms would receive sufficient increases to cover cost of living adjustments based on the Biomedical Research and Development Price Index (BRDPI). This budget level also includes increased funds to support critically needed capital repairs and improvements at the Frederick National Laboratory for Cancer Research.

The second component's request for additional funds reflects the Institute's assessment of where more funding will make the greatest difference in reducing cancer incidence and mortality. Together with growing the research grants portfolio, these new or expanded initiatives – cancer genomics, transformation of the clinical trials system, and more effective translation of research results to clinical utility – offer the greatest current hope of advances against cancer.

## National Cancer Institute

### At a Glance (dollars in thousands)

Fiscal Year 2012 Estimate	5,072,183
Current Services Increase	177,227
<b>Subtotal</b>	<b>5,249,410</b>
<b>Fiscal Year 2013 Additional Resources</b>	
Support Individual Investigators	173,000
Genomics	145,600
Clinical Trials	125,000
Translational Sciences	115,000
Provocative Questions	25,000
Subtotal	583,600
<b>Total NCI</b>	<b>\$5,833,010</b>





NATIONAL<sup>®</sup>  
CANCER  
INSTITUTE

---

NIH Publication No. 13-7957  
Printed November 2012

