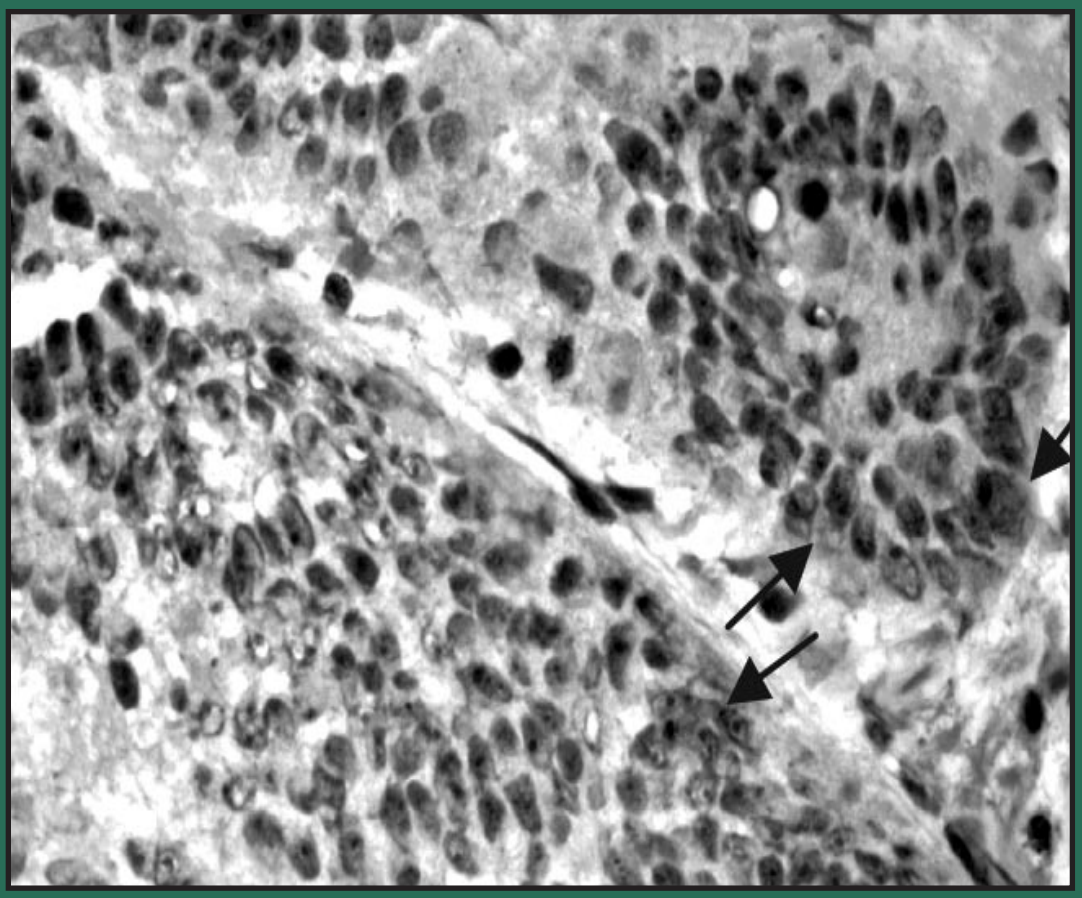

Arrows point to cells within human colon cancer samples producing a protein called CD133, which served as a marker for identifying cells that initiate colon cancer. Markers such as this one may be helpful for targeting future therapeutic approaches.

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Cancers of the Digestive System

SUMMARY OF RESEARCH GOALS

Recognizing the substantial public health impact of digestive system cancers, the Commission recommends several research goals targeted at improving the detection, prevention, and treatment of these diseases. Research is needed to develop more efficient screening tools to predict and detect digestive tract cancers and pre-malignant conditions that frequently progress to cancer. These efforts would be bolstered by identifying health disparities that influence an individual's susceptibility to digestive system cancers or their response to treatment. Understanding the underlying mechanisms common to all digestive cancers and identifying biomarkers to detect disease or predict response to treatment would accelerate the search for safe, effective therapies. In order to develop targeted strategies for cancer detection, prevention, and treatment, it is critical that researchers identify the genetic risk factors that predispose an individual to a specific form of digestive cancer, such as esophageal cancer, pancreatic cancer, gastric cancer, colorectal cancer, or certain rare gastrointestinal (GI) cancers. Together, these research goals aim to improve the health and lives of people at risk for or living with digestive cancers.

INTRODUCTION AND BACKGROUND

The digestive system, including the gut, pancreas, liver, and biliary tree, is the site of more cancers and the source of more cancer mortality than any other organ system in the body. More than 270,000 Americans develop a cancer of the GI tract each year, and half of these patients will die from the cancers (Table 2).

The burden of digestive cancers on the American population is considerable in terms of numbers of new cases, deaths, and economic costs for diagnosis and treatment. Research directed at understanding the causes of the digestive cancers will help reduce their incidence, prevent deaths, and lower healthcare costs.

Of the digestive cancers, colorectal cancer is the most prevalent, with a lifetime risk in the U.S. of 5-6 percent. Colorectal cancer is unique among cancers because it is highly amenable to screening programs that can reduce cancer mortality by early detection and, more importantly, reduce the incidence of invasive cancer by removing pre-malignant lesions. Colorectal cancer incidence and mortality have been falling over the past 2 decades for reasons that are not fully explained.

In the early 1900s, cancer of the distal stomach was the leading cause of death from cancer in the U.S. Seventy years later, gastric cancer prevalence has declined to represent the 13th leading cause of death from cancer in the U.S., but it is still ranked second worldwide. Improvements in food storage and public sanitation are considered the major reasons for the decline in these statistics, suggesting that this disease can be prevented. In 1994, the World Health Organization designated *Helicobacter pylori* as a definite carcinogen, based on the epidemiologic evidence linking the chronic gastric inflammation induced by *H. pylori* to cellular transformation in the stomach.

Esophageal cancers represent an enormous burden of morbidity and mortality worldwide. In 2002, there were an estimated 462,117 new cases and 385,892 deaths from esophageal cancer worldwide, making it the eighth and sixth leading causes of cancer and cancer mortality, respectively. Developing strategies to reduce the mortality of esophageal cancer is complicated by the fact that the two major histologic subtypes (squamous cell carcinoma and adenocarcinoma) show marked regional variation in incidence, differ substantially in etiology, and arise in different tissues. High mortality is one of the main shared characteristics of the two histologic subtypes.

Table 2. Incidence and Mortality of GI Cancers in the U.S. (2008 estimated)

Cancer Site	Overall Incidence	Male Incidence	Female Incidence	Deaths	Annual # of Deaths Divided by Incidence (%)
Esophagus	16,470	12,970	3,500	14,280	87%
Stomach	21,500	13,190	8,310	10,880	51%
Small intestine	6,110	3,200	2,910	1,110	18%
Pancreas	37,680	18,770	18,910	34,290	91%
Liver and intrahepatic duct	21,370	15,190	6,180	18,410	86%
Gallbladder and biliary ducts	9,520	4,500	5,020	3,340	35%
Colon and rectum	148,810	77,250	71,560	49,960	34%
Anus and anorectum	5,070	2,020	3,050	680	13%
Other digestive organs	4,760	1,470	3,290	2,180	46%
TOTALS	**271,290**	**148,560**	**122,730**	**135,130**	**50%**

Esophageal adenocarcinomas have been reported to be increasing in incidence in many regions of the Western world. Although esophageal cancers are less common than lung, breast, prostate, and colon cancers in the U.S., they are nevertheless the seventh leading cause of cancer death among U.S. males. Between 1972 and 2002, the incidence of esophageal adenocarcinoma in Caucasian males increased more than 600 percent, making it the most rapidly increasing cancer in the U.S., as well as in many other regions of the Western world.

Pancreatic cancer is the fourth most common cause of cancer death in the U.S., with an annual incidence of 11.4 per 100,000 men and women. Based on rates from 2002 to 2004, 1.31 percent of men and women (1 in 76) born today may be diagnosed with cancer of the pancreas at some time during their lifetime. Ninety-five percent or more of the deaths from pancreatic malignancy are due to ductal carcinomas, the most common and highly metastatic form. Less common tumor types can occur in the pancreas, but are often less lethal or even benign. The less frequent mesenchymal, hematopoietic, and endocrine tumors often share greater similarity with tumors occurring in other organs than with the pancreas-specific tumors. Pancreatic cancer is usually not diagnosed until after the disease has been manifested through clinical symptoms; as a result, only 20 percent are considered appropriate for surgical resection of the original tumor at the time of diagnosis. Even those patients whose cancer is deemed surgically resectable usually have local lymph node spread at the time of surgery, and nearly all have micro-metastatic disease that is simply undetected at presentation. The overall 5-year survival rate for pancreatic ductal cancer is less than 5 percent.

Research on digestive cancers has been generally directed toward understanding the basic biologic mechanisms of tumors. Despite major advances in this area, the research community is far from understanding how digestive cancers form, grow, and spread. An improved understanding is crucial to lowering the incidence of digestive cancers in the diverse U.S. population, identifying predictive biomarkers to prevent cancer occurrence or recurrence, and developing novel and creative approaches toward prevention or treatment strategies.

This chapter addresses digestive cancers, except liver cancer (see the chapter on *Diseases of the Liver and Biliary System*), with a focus on the four most common digestive cancers: colorectal, esophageal, gastric, and pancreatic. Rarer GI cancers (e.g., cancers affecting the small intestine, anus, gastrointestinal stromal tumors (GIST), gastrointestinal lymphomas, and carcinoids) are discussed in aggregate. The chapter outlines a set of research goals that should improve our overall understanding of basic mechanisms that are relevant to cancer etiology and prevention, as well as specific goals that are directed at individual cancer types.

RECENT RESEARCH ADVANCES

Genetic instability as an underlying mechanism of cancer

A fundamental principle underlying the formation of digestive cancers is the sequential acquisition of alterations in specific genes. These alterations lead to genetic instability that fuels the growth of cancer cells. A fraction of cancers exhibits a form of genetic instability called microsatellite instability, which is often characterized by DNA mismatch repair (MMR) enzyme deficiency. Loss of MMR functions renders tumor cells susceptible to the acquisition

of somatic mutations throughout the genome. A more common form of genetic instability is chromosomal instability, which is usually manifested by aneuploidy (a change in the number of chromosomes). For example, multiple studies have established that esophageal adenocarcinoma develops in association with chromosomal instability, which generates non-random loss of heterozygosity involving chromosomes 9p, 17p, 5q, and 18q, as well as tetraploidy (another form of altered chromosomal number) and aneuploidy. Additionally, telomere dysfunction has been shown to contribute to the onset of genetic instability in somatic cells.

Epigenetic silencing of gene expression as a mechanism in cancer formation

Chromosomal alterations or modifications have been associated with all stages of digestive tumor formation and progression. The best-characterized form of chromosomal alteration is epigenetic silencing by hypermethylation of the promoter regions of genes that have important regulatory functions in cell growth or checkpoint maintenance. Epigenetic silencing can occur during the early stages of tumor development, thus inducing the aberrant, early clonal expansion due to alterations in the various regulatory steps affected by genetic silencing. Recent studies have also suggested the presence of a unique type of cancer exhibiting the CpG island methylator phenotype (CIMP). CIMP tumors represent a clinically and etiologically distinct group of cancers that is characterized by "epigenetic instability." Lastly, a form of chromosomal modification called loss of imprinting of specific genes involved in growth regulation has been shown to predispose to cancer formation.

Cancer stem cells

Stem cells are characterized by their ability to divide asymmetrically—they can make more stem cells, a property known as self-renewal, and they can produce cells that differentiate. Recent studies support the concept that cells with properties of stem cells are integral to the development and perpetuation of human digestive cancers. Eradication of the stem cell component of a tumor may be essential to achieve stable, long-term remission or cure of cancer. Advances in the knowledge of the properties of stem cells have made the specific targeting and eradication of cancer stem cells a topic of considerable interest. The concept that GI cancers arise from hematopoietic precursor cells is a theme that was initially shown in the liver. The identification of bone marrow-derived cancer stem cells in gastric cancer is the first evidence that a luminal organ may show this property.

Cellular receptors and related signaling pathways as targets for cancer therapy

Hormones, cytokines, and growth factors control many aspects of cell proliferation, differentiation, migration, angiogenesis, apoptosis, and senescence. These chemical signals are propagated from the cell surface to intracellular processes via sequential kinase signaling, arranged in modules that exhibit redundancy and cross-talk. This signal transduction system comprising growth factors, transmembrane receptor proteins, and cytoplasmic second messengers is often exploited to optimize tumor growth and metastasis in malignancies. Thus, receptors and their signal transduction systems represent an attractive target for digestive cancer therapy, and several new drugs have been developed and shown to be effective.

Cancer genomics and proteomics

Advances in genomics, proteomics, and molecular pathology have improved the ways by which human cancers are detected, classified, staged, monitored, and treated. The

identification of genetic alterations in cancers in unprecedented detail has accelerated the understanding of the genetic basis of human cancers and provided new targets for diagnostic and therapeutic interventions.

Improvements in approaches and devices that detect and treat esophageal cancer in high-risk patients

Endoscopic imaging of squamous esophageal cancer using Lugol's solution has improved detection of this cancer in high-risk patients. Narrow band imaging and improved endoscopic magnification has enhanced the ability of the endoscope to assess areas of neoplasia without requiring topically administered contrast agents. Mucosal resection devices have been developed that permit single or multiple resections of the mucosa to allow removal of large portions of tissue for therapy and diagnosis and precise determination of the depth of invasion. Mucosal ablation devices (e.g., photodynamic therapy, thermoablation, radiofrequency ablation, cryotherapy) have been created specifically for the esophagus to ablate pre-malignant cells and, in some cases, malignant cells.

Genetic risk for gastric atrophy and cancer

Researchers have identified polymorphisms in cytokine genes that predispose individuals to gastric atrophy and cancer. This discovery underscores two important principles in gastric cancer development: that the host response (i.e., inflammation) to bacteria (presumably *H. pylori*) is essential to cancer pathogenesis; and that atrophy serves as an indicator that the mucosa is developing pre-neoplastic changes.

Mouse models that emulate human gene function in cancer

Mouse models with deleted gene function or targeted mutation similar to observed human mutations demonstrate some recapitulation of human colon cancer and include alterations of the *APC* gene, TGF-β signaling pathway, and the *PTEN* gene. New animal models of gastric cancer have uncovered a number of genetic targets that may be critical for gastric cancer formation including the cytokine receptor subunit gp130, Runx3, trefoil factor TFF1, and STAT3. New animal models of pancreatic cancer recapitulate some of the genetic and ductal abnormalities known to exist in human pancreatic cancer, including the generation of invasive ductal cancers. These highly relevant animal models may aid in the understanding of mechanisms for cancer formation and may accelerate the preclinical development and evaluation of new therapeutic compounds.

Inherited risk factors and genetic signatures for pancreatic ductal cancer

Researchers have advanced our understanding of the degree of risk acquired by members of affected families, genetic locations linked to risk (such as 4q32-34), and investigation of candidate genes that may be responsible for pancreatic ductal cancer. Special pancreatic tissue abnormalities have been found in these families, and a screening program that includes endoscopic ultrasound (EUS) has improved the detection of early and curable pancreatic lesions. In nearly 20 percent of families most affected by ductal cancer, the causative gene is now known. Approaches to treatment of ductal pancreatic cancer have taken advantage of genetic signatures of the cancer cells to test responsiveness to specific and available drugs. For example, mutations

in the *BRCA2* gene and cellular pathway are being used investigationally to assign individual patients to treatment with specific families of drugs or to explain the different responses of patients to such drugs. Also, compounds targeting cell-surface growth factor receptors are being evaluated in clinical trials based on studies showing abnormal expression of such targets in the ductal cancers.

Imaging techniques for the detection and staging of pancreatic cancer and GI luminal cancers

Advances in the quality of high-resolution CT and MRI scanners and EUS have led to a marked increase in the detection of small pancreatic cystic tumors and solid masses. EUS allows tumor features to be evaluated using complementary imaging technologies and to be directly sampled by fine-needle aspiration. Laboratory evaluation of the fluid for tumor markers (e.g., carcinoembryonic antigen), cytological evaluation of aspirated cells, and molecular analysis of suspicious cells for specific gene mutations and markers of aneuploidy represent significant advances in the early detection and diagnosis of pancreatic cancers and precancerous lesions. EUS, capsule endoscopy, double balloon enteroscopy, and improvements in the optics of endoscopes are improving detection of GI luminal cancers.

Immunologic and surgical approaches to pancreatic cancer therapy

Efforts are underway to: develop antibody therapy against specific growth factor receptors; develop and conduct clinical trials of a post-surgically administered cancer cell vaccine that generates immune responses against tumor-specific proteins; and develop new immunologic agents designed to elicit more direct immune responses against the same tumor markers. Advances in the surgical treatment of pancreatic cancer include the establishment of highly experienced pancreas cancer centers, effective reduction in the morbidity and mortality of the disease, optimal pre-surgical screening to diagnose the tumors by endoscopy and biopsy, improved planning of the surgical approach for tumors that are anatomically difficult to remove, and better means to combine surgery with radiation and chemotherapy to improve the quality and duration of life after ductal cancer surgery.

Improvements in colorectal cancer screening

Colorectal cancer is one of a small number of human cancers for which screening of the general population is cost-effective and can significantly improve outcome. Colonoscopy permits both the detection of early cancers and the removal of precursor lesions, which has the potential to reduce morbidity and mortality due to colorectal cancer. Technical advances that include CT colonography (virtual colonoscopy), fecal DNA testing for colorectal cancer, and fecal immunochemical tests provide an opportunity to improve digestive health.

Advances in genetic diagnosis of colorectal cancer

Colorectal cancer has an important familial component. Approximately one third of colorectal cancer patients have a first- or second-degree relative with colorectal cancer. Approximately 4 percent of all colorectal cancer patients have well-defined syndromic forms of colorectal cancers. Advances in understanding the genetic risk factors for colorectal cancer include improved tests for alterations in the DNA mismatch repair genes (MMR) that cause Lynch syndrome (or HNPCC); the discovery of a recessive form of familial polyposis, called *MYH*-associated polyposis; and the elucidation of "Syndrome X," which represents familial clusters of colorectal cancer that are not attributable to an inherited mutation of a known DNA MMR gene.

Chemoprevention and nutriprevention of colorectal cancer

Beginning in 1980, it was recognized that certain non-steroidal anti-inflammatory drugs (NSAIDs; beginning with sulindac) could induce the regression of adenomas in patients with familial adenomatous polyposis (FAP). Subsequently, it was shown that selective Cox-2 inhibition can significantly reduce the numbers of adenomas and carcinomas in patients who have had colorectal neoplasms in the past. However, many of these agents have unacceptable toxicities. The development of safer anti-neoplastic drugs that inhibit Cox-2 could improve treatment outcomes.

Targeted treatment for gastrointestinal stromal tumors (GISTs)

GISTs are tumors arising in the submucosa of the GI tract due to constitutively activating mutations in either the PDGFRA or KIT receptors on the interstitial cells of Cajal. Specific molecular therapies targeting the tyrosine kinase domain of PDGFRA and KIT, which were initially developed to treat certain types of leukemia, have proven to be clinically useful and superior to chemotherapy and surgery for the treatment of GISTs, although they are not curative.

GOALS FOR RESEARCH [10]

The digestive cancers represent a diverse group of disorders with respect to etiology, prevention, and treatment. The goals for research that follow include ones that are broadly applicable to digestive cancers, as well as specific goals for individual types of cancer.

Research Goal 4.1: Develop population-based strategies for screening and prevention of digestive cancers.

For some digestive cancers, such as colon cancer, technologies are available to detect pre-malignant lesions that might be used for population-based screening. Other technologies can remove these lesions, reducing the cancer risk for the patient. Clear and cost-effective utilization of the technologies will need to be evaluated. Other digestive cancer prevention strategies might target high-risk populations, such as those with family histories of cancer, GI inflammatory diseases, high-risk behaviors, or the presence of certain biomarkers.

Strategies to effectively screen and prevent digestive cancers could prove very cost-effective for society.

Objectives:

- Understand the major risk factors for digestive cancers.
- Develop risk modeling and stratification to identify high-risk populations for digestive cancers.
- Conduct large-scale trials of screening modalities to determine efficacy and cost-effectiveness and integrate effective strategies into practice.
- Improve imaging modalities to detect and/or remove pre-malignant or early malignant digestive cancers when they are more likely to be curable.

Research Goal 4.2: Ascertain the importance, detection, and natural history of pre-malignant conditions progressing to digestive cancer.

Studies to address the natural history of pre-malignant lesions that predispose to digestive

[10] *Research Goals are numbered for ease of reference only; the numbers do not indicate prioritization of scientific topics.*

cancers are crucial. Adenomatous polyps—detectable precursors to colorectal cancer—have been extensively studied. The importance of small adenomas is unknown, yet critical in evaluating the value of CT colonography. Rates and mechanisms for benign to malignant transformation of esophageal, gastric, and pancreatic lesions are likewise not known. The accumulation of genetic derangements required to develop the cancer and its ability to metastasize needs to be better understood. We also need to learn how adenoma, pancreatic intraepithelial neoplasia, or other precursor lesions develop from interaction with factors in the local environment. Indeed, environmental factors that are responsible for genetic derangements are largely unknown for any of the digestive cancers. Portions of the GI tract have the most diverse environmental-host interactions in the entire body, with food and waste metabolites, along with the high concentration of microbes, present intraluminally. Commensal bacteria, as well as viral, bacterial, parasitic, and other infections, may directly influence cancer risk by affecting the underlying genetics of digestive system cells. Inflammatory bowel diseases (IBD), which result from a disturbed host-environmental interaction in the gut, are associated with a marked increased risk for cancer development that is not completely understood. In addition, numerous syndromes can lead to the development of digestive cancers, such as FAP, Gardner's syndrome, Lynch syndrome, and diseases like gastroesophageal reflux disease and hepatitis.

Objectives:

- Characterize the genetic defects and clinical behaviors associated with syndromes that predispose to digestive cancers.
- Develop and study preclinical *in vitro* and *in vivo* models of digestive cancers to recapitulate the natural history seen in humans.
- Determine the natural history of pre-malignant lesions in the development of digestive cancers.
- Define the role of inflammation in digestive cancer development.
- Define the mechanisms that predispose patients with IBD for digestive cancers.
- Determine the role of the microflora in the initiation or propagation of digestive cancers.

Research Goal 4.3: Evaluate health disparities in digestive cancer etiology, risk, treatment management, and outcomes.

The U.S. population is extremely diverse, and some racial and ethnic groups have higher risks for developing digestive cancers. One factor may be single nucleotide polymorphisms (SNPs) of disease-modifying genes, but other genetic and epigenetic factors may influence race-related cancer risk. Some groups treated for digestive cancers do not have the same response rates to therapies or the same detection rates for pre-malignant or malignant conditions. Furthermore, end-of-life care varies among the groups for unknown reasons. Research to explore these racial and ethnic differences provides an opportunity to eliminate disparities in digestive cancer prevention, detection, and treatment.

Objectives:

- Conduct clinical studies on access, utilization, treatment, and outcomes of patients with digestive cancers who belong to diverse ethnic, racial, or high-risk groups.
- Understand the influence of genetic factors on cancer risk, prognosis, and response to therapy.
- Investigate the influence of gender on cancer risk, prognosis, and outcomes of patients with digestive tract cancers.

Research Goal 4.4: Improve outcomes in the care of digestive tract cancer patients.

Patients who develop digestive tract cancers are faced with surgery, chemotherapy, and radiation therapy, and may experience behavioral and social changes after their diagnosis. Improvements in

medical treatment may prolong life. Creative support systems and educational mechanisms may improve a patient's mental outlook and the management of their cancer. Side effects of chemotherapy and/or radiation are common. Therapies to counteract the side effects are not necessarily effective and can adversely influence palliation or potential cure. Completion of therapy is a goal to offer the best chance for those who are attempting cure or remission.

Objectives:

- Conduct studies to determine the optimal chemotherapy and/or radiation therapy—before or after surgery—for best long-term survival based on stage, biomarkers, or genetic make-up of the patient or patient's tumor.
- Determine mechanisms for tumor resistance to therapy and develop strategies to overcome resistance.
- Develop approaches to minimize the side effects of chemotherapy and/or radiation therapy.
- Investigate strategies to improve behaviors for optimized cancer treatment, including self-management or other modalities.

Research Goal 4.5: Develop biomarkers to detect neoplasia, target therapy, and evaluate therapeutic response in digestive cancers.

Biomarkers could be used to detect the possible presence of a disease and to select the higher risk population for screening. Additionally, biomarkers could track or predict the occurrence or recurrence of a digestive cancer or pre-malignant condition. Utilization of an ideal biomarker for each of the digestive cancers would greatly reduce costs to society and improve the ability to target high-risk individuals for diagnosis and intervention.

Objectives:

- Develop improved population-based assessment of risk for digestive cancers that can be detected in blood.
- Utilize preclinical *in vitro* and *in vivo* models of digestive cancers to ascertain biomarkers that predict tumor behavior and response to therapy.

Research Goal 4.6: Evaluate nutriceutical, probiotic, chemopreventive, and targeted therapies in digestive cancers.

All digestive cancers are associated with certain risk factors, and all cancers have accumulated genetic and epigenetic derangements that are favorable for the cancer and its cells to proliferate. Natural or target-developed compounds may be associated with reduced risk of developing a cancer, and such compounds might be effective in combating the disease once developed.

Objectives:

- Utilize preclinical *in vitro* and *in vivo* models of digestive cancers to ascertain potential effectiveness and mechanisms of preventive agents and small molecules.
- Conduct large-scale, randomized clinical trials utilizing agents or targeted therapies to determine effectiveness in prevention or treatment of digestive cancers.

Research Goal 4.7: Understand the molecular and cellular mechanisms common to all digestive cancers.

Many features of cancer must be understood broadly—how it develops, what subpopulations it affects, and what features distinguish the cancer. This information gives researchers opportunities to track the disease precisely and to determine if an intervention is effective for society or individually for the patient. Common themes from the understanding of one digestive cancer may be utilized to study other digestive cancers. For example, the basic finding of genomic instability is a key factor underpinning multiple cancers. Likewise, inflammation is a common condition that precedes

many digestive cancers. Tumor growth is influenced by the local microenvironment that helps sustain and propagate cancer cells.

Objectives

- Define genetic and epigenetic mechanisms that characterize digestive cancers.
- Characterize digestive cancer stem cells and factors in the local tumor microenvironment niche that support and propagate the cancer.
- Ascertain molecular signatures and the presence of commensal microflora for evaluation of linkage with population-based risk for digestive cancers.
- Determine the role of infection or host integration of microbes in risk for digestive cancers.

Research Goal 4.8: Determine the risk factors and pathogenesis of squamous carcinoma and adenocarcinoma of the esophagus and devise new methods for detection, diagnosis, treatment, and prevention of these diseases.

From 1979 to 2004, esophageal cancer, particularly adenocarcinoma, became one of the most rapidly increasing cancers in the U.S. Currently, the majority of afflicted persons die as the disease commonly progresses undetected until symptoms occur. Moreover, mortality from esophageal adenocarcinoma has not significantly decreased over the past decade. To address this issue, it will be important to understand how the normal esophageal lining changes to the pre-malignant lesion of Barrett's esophagus and, ultimately, into esophageal adenocarcinoma. Factors that influence this transformative process, such as acid exposure, tobacco use, and obesity and other local environmental influences on the one hand and stem cell genetic changes and chemopreventive interventions on the other hand, will be key to understanding and affecting disease pathogenesis.

Objectives:

- Perform comprehensive genetic analyses of esophageal squamous cell carcinoma and adenocarcinoma.
- Develop non- or minimally invasive imaging and/or molecular techniques to detect pre-malignant changes in the esophagus.
- Discover biomarkers for prediction and evaluation of therapeutic response in esophageal disease.
- Determine the factors that lead to trans-formation of normal esophagus to Barrett's epithelium and those that lead to further progression to adenocarcinoma, including the potential role of stem cells in the process.
- Evaluate the role of upper endoscopy and other technologies for screening and surveillance of Barrett's esophagus.
- Evaluate new techniques to ablate Barrett's epithelium, dysplasia, or early carcinoma to prevent death due to adenocarcinoma.

Research Goal 4.9: Understand the molecular profiles of various types of gastric cancer to improve risk stratification, prevention, and treatment.

Gastric cancer is not one disease. Cancers that develop in different regions of the stomach (e.g., antrum, corpus, fundus, cardia) are likely to have different risk factors and different biologic behavior. Being able to distinguish the different types of tumors is a critical and necessary step for making progress in this field. By understanding the basic biology of the various types of gastric cancer, innovative strategies for prevention and therapy can begin to be developed.

Objectives:

- Ascertain a complete molecular profiling of the histological types of gastric cancers from different locations within the stomach.

- Develop a molecular roadmap for gastric cancer development that mirrors the known phenotypes.
- Develop better tools to conduct transgenic animal studies to further our understanding of gastric mucosal biology.
- Refine risk stratification for screening and surveillance of gastric cancers.
- Improve imaging technologies for early detection of pancreatic cancer.
- Devise novel molecular therapeutics based on understanding of pathogenesis.
- Provide infrastructure to accelerate research by developing biosample, imaging, and data repositories.

Research Goal 4.10: Define the genetic and environmental factors contributing to pancreatic cancer and its precursor lesions and devise new methods for early detection, treatment, and prevention.

Pancreatic ductal carcinoma, or pancreatic cancer, has a 5-year survival rate of less than 5 percent. By the time patients have symptoms, less than 20 percent are deemed to be surgical candidates for attempted cure. Pancreatic cancer can develop in the setting of chronic inflammation and in familial pancreatic cancer syndromes and, in this small but important subset of patients, precursor lesions such as pancreatic intraepithelial neoplasms might be identified that confer risk for progression to cancer. Differentiating benign from malignant early lesions by imaging or biomarkers will be central to determining optimal patient candidates for surgical cure, which would minimize the use of surgery in those who may not require this intervention and direct better utilization of chemoradiation therapy.

Objectives:

- Define the genetic risk factors for pancreatic cancer in both familial cases and sporadic disease.
- Define environmental risk factors that contribute to pancreatic cancer.
- Define early ductal precursor lesions and factors that contribute to progression to cancer.
- Identify markers for early lesions and risk for progression to cancer.

Research Goal 4.11: Identify genetic and environmental risk factors for colon cancer and devise improved approaches for screening, early diagnosis, treatment, and prevention of colon cancer. (See also Goal 1.3.)

Because of its major impact on public health and the opportunities to further reduce the incidence and mortality of this disease, the focus on colorectal cancer should be expanded. Areas of colorectal cancer research that are particularly important include primary prevention (e.g., novel dietary approaches and viral vaccines), discovery of genes that produce hereditary colorectal cancer syndromes, understanding the natural history of pre-malignant colorectal lesions, and integrating genomics research with the clinical application of individualized medicine. Because colorectal cancer screening has been demonstrated to decrease incidence and mortality, efforts should be made to expand the use of screening, to understand the natural history, and to stratify patients by risk status. Small colon polyps have an enormous impact on clinical practice, even though the likelihood of malignancy is small, as most patients undergoing colon surveillance have only small polyps.

Objectives:

- Evaluate chemopreventive and other primary prevention strategies against colorectal cancer.
- Improve means to identify patients, characteristics of the colon, or pre-malignant lesions that give rise to the greatest risk for colorectal cancer.

GOALS FOR RESEARCH

- Determine strategies to expand the use of colorectal cancer screening in clinical practice.
- Determine the natural history of small colorectal adenomatous polyps, including factors and markers for malignant progression and potential role of chemoprevention.
- Determine the potential role of proximal hyperplastic polyps and serrated adenomas in progression to colorectal cancer.
- Understand and develop models for flat adenomas (i.e., non-polypoid colorectal neoplasia).
- Continue to develop new endoscopic, imaging, and other technologies for colorectal cancer screening.

Research Goal 4.12: Understand the etiology, natural history, prevention, and management of rare GI cancers. (See also Goal 8.4.)

The rarer GI tumors include cancers affecting the small intestine and anus, GISTs, gastrointestinal lymphomas, and carcinoids. Individually, these cancers occur less often than the organ-based cancers, but many of these occur with higher frequency in certain populations. For example, immunocompromised patients have a higher prevalence of lymphomas; those with celiac disease have a higher prevalence of small intestinal lymphomas; and anal cancers are linked to infection with human papilloma virus. Collectively, this group of tumors affects approximately 15,000 Americans annually. Because of their relatively rare occurrence, research into these conditions lags behind that for organ-based digestive cancers.

Objectives:

- Improve imaging technologies and therapeutic options to detect and remove small intestinal cancers.
- Determine predictive factors or biomarkers that more accurately predict patient outcome, such as with MALT lymphoma and *H. pylori* eradication; anal carcinoma and immunosuppression or human papilloma virus infection; or the development and behavior of intra-abdominal desmoids in FAP.

MAJOR CHALLENGES AND STEPS TO ACHIEVE THE RESEARCH GOALS

Collaborative research and centralized resources: Research on digestive system cancers would be accelerated by promoting mechanisms for collaborative research. For example, centers could be established to collect and maintain clinical information and epidemiologic data linked to a repository of biologic specimens and other data, such as gene expression profiles, SNPs, and other patient characteristics. Such multi-institutional repositories of samples and data from well-characterized patients would enable collaborative research on disparities among ethnic, racial, or high-risk groups that often cannot be performed effectively in individual clinical sites with limited patient populations. The development of high-throughput genomic and proteomic facilities to complement the current Cancer Genome Anatomy Project to profile digestive tract cancers and their subtypes would also strengthen the entire field and promote progress. Finally, the creation of high-throughput drug discovery programs based on targeted approaches to cancer biology would present an opportunity for collaboration with industry in the area of drug development and evaluation.

Technology development: The development of advanced non- or minimally invasive imaging or molecular techniques for detection of pre-

malignant changes in digestive tract cancers has the potential to improve cancer diagnosis in the early stages of the disease and dramatically reduce the burden of these diseases on individuals and the healthcare system.

Animal models: New transgenic animal models do not faithfully replicate sporadic digestive cancer occurring in the adult human. Therefore, improved, rigorously validated animal models are needed.