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Report of the Stomach/Esophageal Cancers Progress Review Group

Stomach/Esophageal Cancers Progress Review Group Priority Recommendations

Population Studies	Establish collaborations for conducting interdisciplinary, population-based, endoscopic, multi-institutional studies to identify populations at greatest risk for gastric cancer, esophageal adenocarcinoma, and esophageal squamous cancer, and to determine the prevalence and natural history of premalignant lesions.
Prevention	Develop prevention strategies based on the mechanisms of host/environment interactions that lead to metaplasia and neoplasia of the stomach and esophagus. Evaluate their effectiveness in at-risk populations.
Patient/Provider Education	Educate patients and their families, health care professionals, and the public regarding risk factors, risk reduction, and treatment options and outcomes for gastroesophageal cancers and their precursor states.
Therapy	Develop and test novel therapeutics, and optimize existing treatments for gastroesophageal cancers and their precursors, based on the identification and understanding of molecular pathways involved in oncogenesis, tumor response and resistance.
Therapeutic Targets	Define host and molecular/biologic tumor characteristics that will help customize treatment and best predict recurrence and/or survival.
Markers and Molecular Profiling	Profile the molecular, cellular, and epidemiological features of gastroesophageal tumors and their precursor lesions to identify diagnostic, prognostic, predictive, preventive, and therapeutic targets.
Outcomes	Develop and refine disease-specific, patient-oriented methods to assess quality of life, quality of care, and cost effectiveness of treatment in patients with gastroesophageal cancers and their precursors through all stages of disease and treatment, and include these instruments in clinical trials and observational studies.
Host/Environmental Interactions	Identify, develop, and validate genetic, biochemical, and biological markers that will help uncover host-environment interactions in esophageal and gastric carcinogenesis.
Technologies for Screening/Surveillance	Develop noninvasive and minimally invasive technologies (e.g. serum markers and imaging techniques) for screening and surveillance of premalignant and malignant gastroesophageal lesions.
Preclinical Models	Establish models to understand the biology of gastroesophageal cancers and their precursor lesions, and to stimulate prevention, diagnostic and treatment strategies.

**REPORT OF THE
STOMACH/ESOPHAGEAL CANCERS
PROGRESS REVIEW GROUP**

National Cancer Institute

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December 2002

From the Leadership

It is a great pleasure to submit this Report of the Stomach/Esophageal Cancers Progress Review Group (S/E PRG) to the Director and Advisory Committee to the Director of the National Cancer Institute (NCI). The S/E PRG accepted the charge of former NCI Director Dr. Richard Klausner to develop a national plan for stomach and esophageal cancer research over the next 5 years. The charge was advanced with the support of the current NCI Director, Dr. Andrew von Eschenbach. This report represents the collaborative efforts of the scientists, clinicians, industry representatives, and patient advocates who participated in the S/E PRG Roundtable Meeting. The priorities outlined in this report are a blueprint for progress toward preventing, diagnosing, and treating stomach and esophageal cancers. We look forward to discussing these priorities and the plan for their implementation with the leadership of the NCI.



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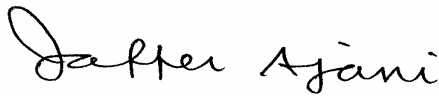
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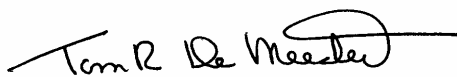
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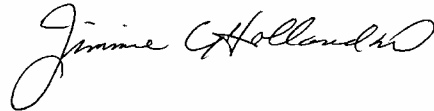
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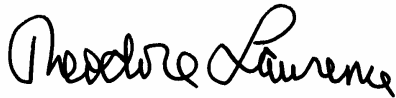
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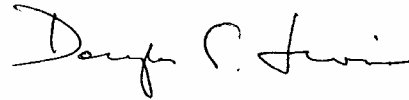
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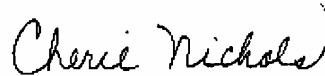
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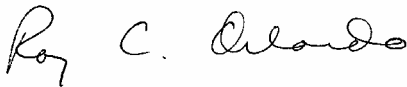
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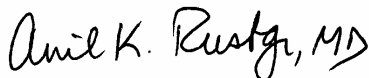
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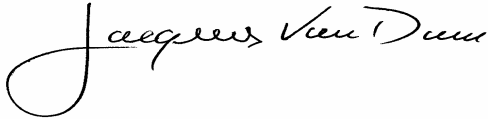
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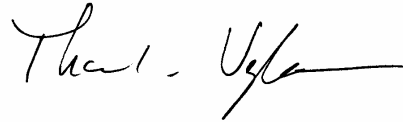
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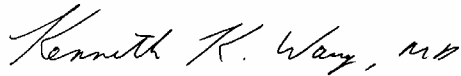
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**Priorities of the Stomach/Esophageal Cancers
Progress Review Group**

Overview

Gastroesophageal cancers are an enormous cause of morbidity and mortality worldwide. In the year 2000, it was estimated that more than 1,288,000 new cases of gastroesophageal cancers were identified, and more than 984,000 people died from them, making this combination of cancers the most common form of incident cancer and the second most common cause of cancer death in the world.¹

In the United States, gastroesophageal cancers are relatively uncommon; however, esophageal cancer appears to be on the rise. This suggests that there are many more individuals at risk for the disease, although their risk status may be unrecognized. Three issues particularly relevant to gastroesophageal cancers and their impact on the U.S. population include: 1) the significant morbidities associated with the diseases and their treatments, 2) their almost uniformly poor prognoses, and 3) their burden among minorities.

Several aspects of gastroesophageal cancers provide opportunities for rapid scientific and clinical advancements. The stomach and esophagus are relatively easy and safe to access, which can provide ample specimens for research. Additionally, the technologic advances in molecular profiling, imaging, and molecular targeting of preventive/therapeutic agents provide a foundation for further developments to reduce the burden of these cancers and perhaps others. At a minimum, advancing these important research opportunities will improve the identification, care, and management of persons at risk for and living with gastroesophageal cancers.

There are several challenges to advancing these research opportunities. At a molecular level, the development of tumor models and a further understanding of the molecular

basis for these cancers and the host/environment interactions underlying them are needed. Practical challenges include gaining access to adequate numbers of at-risk persons or cancer patients, recruiting physicians with the expertise to manage the many at-risk patients, and dealing with a disparate collection of cancers (i.e., gastric adenocarcinoma, esophageal squamous cell carcinoma, and esophageal adenocarcinoma).

To capitalize on the current state of the science and to overcome these challenges, collaboration across borders is needed. Only through collaborative efforts can enough patient data be collected to enhance the understanding of the biology, etiology, pathology, and treatment of the diseases. To gain access to large numbers of at-risk patients for these cancers, there is a critical need to involve gastroenterologists and other specialists who perform esophagogastroduodenoscopy in NCI-sponsored research efforts. Pathologists, molecular biologists, epidemiologists, and clinical trial researchers can then use these data to identify important new markers and targets.

There is a great opportunity-to-investment ratio related to research in these cancers. For instance, risk markers may be applied in screening, diagnosis, and prognostication; interventional response markers may identify new approaches to modulate risk. Therapeutic targets can inform agent identification and development. Additionally, many aspects of the molecular etiology of gastroesophageal carcinogenesis may be shared with other cancers that are less accessible or amenable to serial investigations; therefore, research findings may have broader implications.

To develop these opportunities, the Stomach/Esophageal Cancers Progress

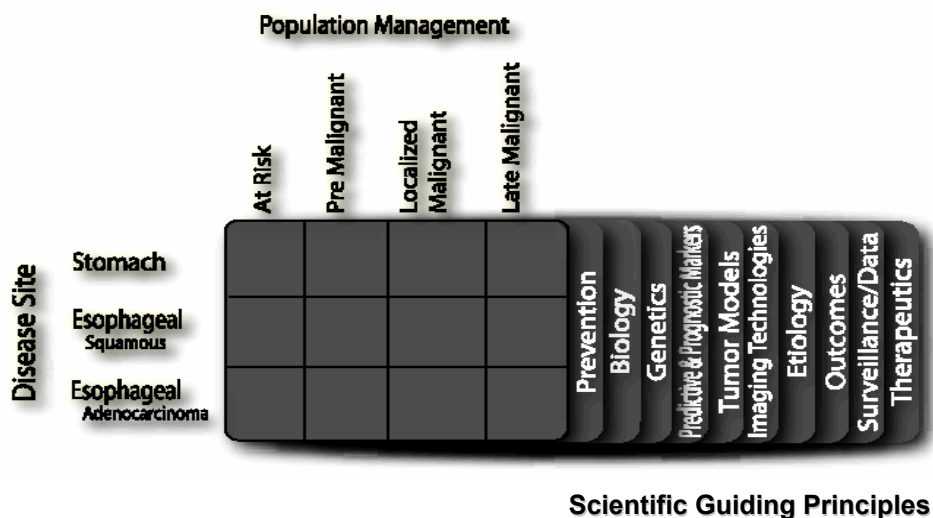
Review Group identified and prioritized research recommendations that will advance the understanding of these cancers over the next 5 years.

Stomach and Esophageal Progress Review Group Process

Premise for Planning. The Stomach/Esophageal Cancers Progress Review Group (S/E PRG) held a planning meeting January 24 and 25, 2002, to organize the Roundtable Meeting that would classify progress, identify gaps, and highlight research opportunities across the continuum of stomach and esophageal cancers research. A primary challenge was identifying an approach that would include the various stomach and esophageal cancers. It was agreed to focus on gastric adenocarcinoma, esophageal adenocarcinoma, and esophageal squamous cell

carcinoma. A secondary challenge was to make certain that the full spectrum of the disease and the foundational scientific principles that underlie scientific advances in disease management were addressed. A three-dimensional, overlapping approach was developed to ensure that ideas had multiple audiences. The attendees would consider the cancers through the lenses of Scientific Guiding Principles, Population Management, and Disease Sites. Figure 1 represents the conceptual foundation that organized the roundtable subgroup discussion format. This organization ensured that each topic would be discussed in adequate detail, with attention to the full spectrum of important issues. To guarantee expert facilitation of each discussion topic, S/E PRG members were assigned to serve as co-chairs, and roundtable participants were identified for each of the breakout subgroups.

Figure 1. PRG Organization



Roundtable Meeting. The S/E PRG Roundtable Meeting, which included approximately 112 participants, convened May 5–7, 2002, at Westfield’s Conference Center in Chantilly, Virginia. Participants attended one session each on Scientific Guiding Principles, Population Management, and Disease Sites. Each

session created three priorities and rationales addressing specific gastroesophageal cancers. Afternoon sessions incorporated the morning sessions’ priorities and rationales into their discussions to ensure that comprehensive views were represented in each session. Each subgroup’s report and priorities can be found in Appendix B. The

Population Management and Disease Sites subgroups developed 21 priorities; each priority had its own rationale, partnership platforms, and resources needed to capitalize on existing opportunities and to overcome current challenges. On the final day, the S/E PRG Leadership clustered the 21 priorities to elucidate similar recommendations. These 21 priorities were presented to the roundtable participants at the final

consensus session. The roundtable participants reached consensus on 10 high-priority research recommendations (Table 1) and a single partnership platform aimed at improving prevention, diagnosis, and treatment of stomach and esophageal cancers. Recommendations and corresponding rationales are detailed in the Recommendations section that follows.

Stomach/Esophageal Cancers Progress Review Group Priority Recommendations

Table 1.

Population Studies	Establish collaborations for conducting interdisciplinary, population-based, endoscopic, multi-institutional studies to identify populations at greatest risk for gastric cancer, esophageal adenocarcinoma, and esophageal squamous cancer, and to determine the prevalence and natural history of premalignant lesions.
Prevention	Develop prevention strategies based on the mechanisms of host/environment interactions that lead to metaplasia and neoplasia of the stomach and esophagus. Evaluate their effectiveness in at-risk populations.
Patient/Provider Education	Educate patients and their families, health care professionals, and the public regarding risk factors, risk reduction, and treatment options and outcomes for gastroesophageal cancers and their precursor states.
Therapy	Develop and test novel therapeutics, and optimize existing treatments for gastroesophageal cancers and their precursors, based on the identification and understanding of molecular pathways involved in oncogenesis, tumor response and resistance.
Therapeutic Targets	Define host and molecular/biologic tumor characteristics that will help customize treatment and best predict recurrence and/or survival.
Markers and Molecular Profiling	Profile the molecular, cellular, and epidemiological features of gastroesophageal tumors and their precursor lesions to identify diagnostic, prognostic, predictive, preventive, and therapeutic targets.
Outcomes	Develop and refine disease-specific, patient-oriented methods to assess quality of life, quality of care, and cost effectiveness of treatment in patients with gastroesophageal cancers and their precursors through all stages of disease and treatment, and include these instruments in clinical trials and observational studies.
Host/Environmental Interactions	Identify, develop, and validate genetic, biochemical, and biological markers that will help uncover host-environment interactions in esophageal and gastric carcinogenesis.
Technologies for Screening/Surveillance	Develop noninvasive and minimally invasive technologies (e.g., serum markers and imaging techniques) for screening and surveillance of premalignant and malignant gastroesophageal lesions.
Preclinical Models	Establish models to understand the biology of gastroesophageal cancers and their precursor lesions, and to stimulate prevention, diagnostic, and treatment strategies.

The top research priority is the creation of a multi-institutional, multidisciplinary partnership of researchers focused on rapid translational biomedical advances in these cancers (detailed in the last section of the main report). This solution best addresses the S/E PRG recommendations within the context of the current state of the science and the incidence in the United States. The infrastructure is similar to cancer cooperative groups and other clinically oriented research consortia; however, two critical features distinguish this initiative from others. First, innovative and progressive management strategies will facilitate effective and efficient components that will foster group-wide priorities. These will include multi-institutional, inter-disciplinary collaborations and shared resources to enhance knowledge and reduce the burden of stomach and esophageal cancers. Second, involvement of gastro-enterologists and other funding partners will provide access to patients at risk for gastroesophageal cancers (a group not commonly cared for by specialists within traditional cancer cooperative groups) and diversify funding sources. Gastroesophageal tissues representative of the full spectrum of pathogenesis will be secured. The shared resources and the multidisciplinary experts will facilitate a true translational focus.

This kind of comprehensive partnership, which will help to overcome the scattering of patients across the country and the limited resources of any one institution, is crucial to the NCI's ability to make advances in combating stomach and esophageal cancers and addressing the S/E PRG recommendations. This model is explained in detail in the Infrastructure section that follows.

Introduction

Scope of the Problem

Each year, gastroesophageal cancers account for an estimated 34,700 new cancer cases and 25,000 deaths in the United States.²

Gastroesophageal cancers are heterogeneous with regard to their molecular and cellular genesis, specific risk factors, and histopathologic character. For this report, the term “gastroesophageal cancers” encompasses three distinct cancers: esophageal squamous cell carcinoma, esophageal (or Barrett's-related) adenocarcinoma, and gastric adenocarcinoma. Although they are distinct entities that originate in the same general anatomic region of the digestive system, these three cancers share some characteristics. Most importantly, they tend to remain clinically silent until late in the disease process; thus, they are often associated with later diagnoses, poorer prognoses, significant morbidities, and high mortality rates.

Stomach Cancer. Worldwide, the incidence of stomach cancer is declining, pointing to a critical environmental component in its etiology. Although the specific reason for this decline is unknown, the increased consumption of fruits and vegetables and the decreased intake of salty foods, both at least partially resulting from improved methods in food preservation and storage, are often credited. Despite this encouraging trend, stomach cancer is the fourth most common new cancer diagnosis and the second leading cause of cancer mortality in the world, accounting for an estimated 876,341 new cancer cases and 646,567 deaths worldwide in 2000.¹ The highest incidence of stomach cancer occurs in Japan and Eastern Asia; by contrast, its incidence is relatively low in Western Europe.

Stomach cancer was the most common cancer in the United States during much of the early 20th century; however, its incidence has declined significantly since the 1950s. U.S. incidence rates for stomach cancer are higher for Asian/Pacific Islanders, blacks, and Hispanics than for whites or American Indians/Alaska Natives. Men are 1.5 to 2 times as likely to develop stomach cancer as women are.

Table 2. SEER Incidence Age-Adjusted Rates, 11 Registries, 1992–1999³

Race/Ethnicity	ESOPHAGUS			STOMACH		
	All	Males	Females	All	Males	Females
All	4.5	7.5	2.1	9.3	13.5	6.3
White	4.2	7.1	1.9	7.9	11.7	5.2
Black	8.0	12.9	4.4	13.9	19.6	9.9
American Indian/ Alaska Native	1.5	2.8	0.5	7.6	9.8	5.9
Asian or Pacific Islander	3.0	5.6	1.0	18.5	24.9	13.6
Hispanic	2.9	5.4	1.0	12.5	17.1	9.2

Age-adjusted rates, 2000. Rates are expressed as cases per 100,000.

Esophageal Cancer. Esophageal cancer has been relatively uncommon in the United States, but recent trends are of concern. Incidence rates for adenocarcinomas involving the gastric cardia and lower esophagus (Barrett’s esophageal adenocarcinoma) have increased markedly since the mid-1970s. Among white males, the rate of esophageal adenocarcinoma has increased more than 350 percent between 1974 and 1994, making this one of the most rapidly rising cancers in the U.S. population and suggesting that environmental factors play important roles in its etiology. In the United States, Blacks have the highest rate of esophageal cancer, primarily squamous cell, almost double the incidence of all other groups. Incidence is higher among men than among women: men are 3 to 5 times as likely to develop esophageal cancer as women are.

Esophageal cancer is the eighth most common new cancer diagnosis and the sixth leading cause of cancer death in the world, accounting for an estimated 412,327 new cancer cases and 337,501 deaths in 2000.¹

Epidemiologists have identified some unexplained and remarkable differences in its distribution across the world. For example, esophageal cancer is more common in developing countries than in the United States. In addition, histopathologic types vary between these regions, with squamous cell carcinoma dominating in developing countries and adenocarcinomas becoming an increasing problem in the United States.

Mortality. Stomach and esophageal cancers, while relatively uncommon in the United States, are highly lethal. The estimated overall 5-year survival rate is 22 percent for stomach cancer and 14 percent for esophageal cancer. In fact, mortality rates for these cancers approach their incidence rates, suggesting that current treatment options for these patients are limited and often ineffective. Notably, minorities tend to have disproportionately high mortality rates from these cancers. For stomach cancer, the rates are more than twice as high in blacks and Asian/Pacific Islanders, compared with whites.

Table 3. SEER Mortality Age-Adjusted Rates, Total U.S., 1990–1999³

Race/Ethnicity	ESOPHAGUS			STOMACH		
	All	Males	Females	All	Males	Females
All	4.3	7.5	1.8	5.4	7.7	3.7
White	3.9	6.9	1.6	4.8	6.9	3.3
Black	8.1	14.3	3.8	10.3	15.2	7.1
American Indian/ Alaska Native	2.4	4.0	1.0	5.3	7.1	3.9
Asian or Pacific Islander	2.4	4.1	.96	10.4	13.6	8.0
Hispanic	2.4	4.4	.91	7.2	9.7	5.3

Age-adjusted rates, 2000. Rates are expressed as cases per 100,000.

Three factors are associated with the poor survival rates associated with gastroesophageal cancers. First, symptoms are rare in the early stages of cancer development, often only occurring with advanced cancer; even then, they can be nonspecific. Second, although screening and diagnostic techniques exist for these cancers, the risks, benefits, and feasibility of screening have not been adequately tested and consequently are not routinely recommended by physicians. Finally, patients often fail to seek appropriate medical attention due to lack of knowledge of important risk factors and symptoms and/or reluctance to undergo invasive and relatively costly endoscopic procedures. Therefore, many patients present at late stages.

Morbidity. Patients diagnosed with stomach and esophageal cancers often have significant morbidities (e.g., difficulty swallowing, painful swallowing, weight loss) as a result of their cancer or the treatments intended to help them. Necessary treatments often involve the removal of portions of the esophagus and/or stomach or the placement of a stent to maintain the patency of the GI tract. After surgery, some esophageal cancer patients may need to receive nutrients directly into a vein or through a feeding tube. If only a part of the

stomach is removed, a patient should still be able to eat fairly normally. However, if the entire stomach is removed, a new eating pattern must be adopted, including frequent, small meals low in sugar and high in fat and protein. For many patients, chemotherapy and radiation also are necessary, so additional side effects are common.

The incidence, morbidity, and mortality of stomach and esophageal cancers make them an important health concern, particularly within minority sectors of the population. The rapid rise of adenocarcinomas of the distal esophagus and proximal stomach among whites, as well as the high rates of esophageal cancer in blacks, suggests that these cancers are an important health issue today. With the increasing rates of Asian/Pacific Islander and Hispanic immigration, these cancers will be an important medical and public health issue in the future as well.

State of the Science

Opportunities for Scientific Advancement

Gastroesophageal cancers are significant causes of morbidity and mortality in the United States; most individuals with these

cancers are not identified until the cancer is advanced and symptomatic. In these cases, even the best therapies are associated with significant morbidities and poor outcomes. Only a small fraction of patients is found to harbor preinvasive neoplastic lesions (e.g., Barrett's dysplasia) while undergoing an endoscopic evaluation for nonspecific symptoms. Typically, such patients would have periodic endoscopic surveillance, and a small number of them would develop early stage cancer. Identified in this way, a patient would undergo an esophagectomy with the potential for significant post-operative morbidities, and in most instances, would have an excellent prognosis for long-term survival.

There are tremendous opportunities to improve the management and care of people who have gastroesophageal cancers, as well as those at risk. Three factors specific to gastroesophageal cancers make scientific and clinical progress imminently attainable. First, the marked distributional heterogeneity of gastroesophageal cancers within the population suggests the presence of effective risk and preventive factors. Second, relatively easy and safe access to the stomach and esophagus is available through established technologies for serial endoscopic assessments with mucosal biopsies. Finally, technologic advances in genomics, proteomics, invasive and noninvasive imaging, as well as in the molecular targeting of preventive/therapeutic agents, can be applied for rapid advances in a highly translational environment in which patients harboring preinvasive neoplasia undergo serial surveillance of their gastroesophageal mucosa as a matter of standard care.

Several common conditions—for example, gastroesophageal reflux disease (GERD) and *Helicobacter pylori* infection—place affected individuals at increased risk for one or more of these cancers. Recent cohort

studies suggest that symptoms of GERD occur weekly in approximately 20 percent of Americans, implying that the number of persons at risk for these cancers may be substantial. Of course, both of these diseases are much more common in other parts of the world, so attention to the problem within immigrants to the United States from Asian or Central/South American countries is important. Indeed, the marked heterogeneity in the worldwide distribution of these cancers, as well as their rapidly changing incidence patterns within the United States, suggest that there are important environmental risk or preventive factors acting at the molecular level, which, once identified, may be employed to reduce the burden of these diseases.

Disease Pathogenesis. A detailed understanding of a disease's pathogenesis and natural history is necessary to advance the care of affected individuals. Gastroesophageal cancers are believed to develop over decades with few or no presenting symptoms during most years. Fortunately, the availability of esophagogastroduodenoscopy (EGD) allows gastroenterologists to directly visualize the lining of these organs and easily obtain biopsies for molecular, cellular, and histopathologic assessments over time. Thus, gastroenterologists can use EGD to gain access to tissues at risk for these cancers, thus allowing improvements in the understanding of the disease process.

Technologies. Recent technologic advances are providing opportunities to reduce the burden of gastroesophageal cancers. As evidenced from the study of other organs, knowledge of the molecular basis may lead to further understanding and identification of targets. Research may elucidate the identification of reliable indicators of cancer risk and patient response to interventions, as well as targets for preventive or therapeutic interventions. For example, with the advent

of genomic and proteomic technologies, it is now possible to examine the genesis of gastroesophageal neoplasia from the earliest molecular alterations through precursor lesions (cellular and tissue abnormalities) to invasive and metastatic cancers. Charting the molecular changes underlying the natural history of gastroesophageal cancers during every step of this process may allow the identification of environmental risk factors, genetic risk factors, and/or biomarkers that can be used for non-invasive screening and diagnostic tests.

Bioinformatics. The advent of novel analytic approaches has facilitated deriving meaning from novel genomics and proteomics data. These approaches include, but are not limited to, hierarchical agglomerative clustering, significance analysis of microarrays, GeneFinder comparisons, artificial neural networks, and principal components analysis. Widespread use of such strategies will identify global patterns of gene and protein expression potentially useful *a priori* as early detection, diagnostic, prognostic, or risk assessment tools. Moreover, these techniques will identify individual genes or groups of genes worthy of further study and useful in hypothesis generation, such as in the implication of novel molecular pathways, environmental and socioeconomic factors, dietary influences, genetic makeup, and the host response in the genesis or progression of these important cancers.

Molecular Profiling. Understanding the molecular basis of these cancers also affords the opportunity for more careful study of host-environment interactions. For example, epidemiological evidence indicates a relationship between infection by the bacterium *H. pylori* and the development of gastric ulcers and adenocarcinoma. Genomic and proteomic technologies will facilitate the identification of genetic differences that may predispose one person to a gastric ulcer

and another to gastric adenocarcinoma. Likewise, the molecular basis for the relationship between other agents, such as bile or nitrosamines, and gastroesophageal cancers also may become evident. Investigators will be able to develop prevention strategies based on the mechanism of protective host/environment interactions.

Genes. Genomics-based methodologies may facilitate drug discovery and the translation of drugs from “bench to bedside”; they also may provide a means to monitor patient responses or resistance to new interventions applied with preventive or therapeutic intent. In addition, the examination of molecular genetic and host factors during clinical trials involving an intervention will provide another level of understanding of patient response and resistance.

Models. Scientific advances require the use of appropriate *in vitro* and *in vivo* models, few of which exist for stomach and esophageal carcinogenesis. The development of improved tumor models—including cell lines, xenografts, and animal models—therefore represents an opportunity for scientific advancement. Once standardized and validated, tumor models specific to gastroesophageal cancers will aid investigators in the identification of molecular and cellular changes that mark disease progression and improve understanding of host/environment interactions. These models will provide a means for investigators to develop new molecularly targeted approaches to prevention and therapies.

Patient Care and Outcomes. In addition to molecular and technologic efforts, the scientific community has the opportunity to make significant advances in patient care and morbidity reduction. Clinical researchers can develop disease-specific, patient-oriented methods to assess the

quality of life, quality of care, and cost effectiveness of preventive and therapeutic approaches. In addition, education and outreach measures addressing risk factors and screening that target the public and community physicians are likely to reduce morbidity and mortality from these diseases.

Integration/Translation. Preliminary data from interdisciplinary translational research in stomach and esophageal cancer are promising. When interdisciplinary teams involve combinations of molecular biologists, gastroenterologists, pathologists, epidemiologists, medical/surgical oncologists, and other members, knowledge grows quickly and exponentially. For example, a recent study of familial gastric cancer identified a tightly linked mutation in E-cadherin that may provide insights into the pathogenesis of the syndrome. In addition, two studies of patients with Barrett's metaplasia recently noted a significant correlation between cytometric aneuploidy and the future development of dysplasia or cancer.

Challenges To Be Addressed

Low Incidence. The relative rarity of these cancers in the United States presents a significant research challenge. Individual centers do not treat enough patients to conduct adequately powered clinical studies intended to evaluate the natural history of these diseases, develop new methods for screening and surveillance, or test new preventive and therapeutic interventions. As a result, few adequately powered studies addressing these issues have been completed, and most current care is based on observational data and expert opinion. To transcend this challenge, NCI must evaluate the current research infrastructure and develop a means to coordinate research and management of these relatively rare cancers in order to secure the critical mass of cases needed for scientific advancement.

Incomplete Network Systems. There is a clear need for a coordinated, multi-institutional partnership that involves a wide range of research professionals, some of whom—particularly gastroenterologists—are not adequately represented in existing NCI consortia. In addition to providing a means for rigorous study of current and new treatments, a network will provide investigators with access to patients at different stages of carcinogenesis, and to the critical tissue samples needed for studies of the biology and etiology of these cancers.

Lack of Awareness. Another challenge is the underestimation and limited awareness of these cancers by the public and some physicians. Unlike many other cancer cohorts, people with gastroesophageal cancers have not had a specific advocacy group or an important public figure to draw attention to the disease and advocate for resources. Public education in gastroesophageal cancers might encourage at-risk persons to seek earlier screening and diagnosis, thereby potentially reducing morbidity and mortality.

To capitalize on the scientific opportunities and to overcome the challenges, the S/E PRG was convened by NCI and charged to provide recommendations to reduce the burden of these cancers.

Recommendations

The S/E PRG recognizes that these high-mortality cancers present a unique set of challenges and opportunities. Gastroesophageal cancers represent diverse malignancies that have rapidly changing incidences, and their ethnic and gender disparities are not well understood. These cancers also have long premalignant phases that are uniquely accessible for endoscopic visualization and biopsy; this, combined with the rapidly advancing field of cancer genetics, offers unparalleled opportunities

for mechanism-based approaches to screening, surveillance, prevention, early detection, and treatment.

It is difficult for any one center in the United States to generate enough cases to make an impact on gastroesophageal cancer morbidity and mortality. However, U.S. cases could, if combined, provide data for appropriately powered clinical and epidemiological studies. Through collaboration of clinical, population, laboratory, and computational scientists, private industry, and the NCI, the burden of these malignancies on society can be reduced.

Therefore, the S/E PRG offers the following 10 prioritized research recommendations and a high-priority infrastructure resource:

Population Studies: *Establish collaborations for conducting interdisciplinary, population-based, endoscopic, multi-institutional studies to identify populations at greatest risk for gastric cancer, esophageal adenocarcinoma, and esophageal squamous cancer, and to determine the prevalence and natural history of preneoplastic lesions.*

Rationale

Patients with gastroesophageal cancers usually present at late stages and have poor prognoses. To reverse this trend, patients at highest risk must be identified earlier. Recent epidemiologic studies suggest protective and risk factors for each of the gastroesophageal cancers. Non-steroidal anti-inflammatory drugs (NSAIDs) appear to be protective against esophageal squamous cell carcinoma, esophageal adenocarcinoma, and gastric adenocarcinoma. A diet high in fruits and vegetables may protect against all gastroesophageal cancers. *H. pylori* is a risk factor for gastric adenocarcinoma but is protective against

esophageal adenocarcinoma, and gastroesophageal reflux and obesity are risk factors for esophageal adenocarcinoma. Although these associations are clear, critical gaps exist in our knowledge of the underlying mechanisms. Multidisciplinary, tissue-based studies across the spectrum of progression are needed to identify the linkages between molecular, cellular, and clinical pathogenesis. This knowledge then can be applied to better define the risk status of individuals and groups.

Although gastroesophageal cancers are relatively uncommon in the United States, their predisposing conditions are relatively common: Barrett's esophagus may be seen in as many as 10 percent of asymptomatic adults, and *H. pylori* infection rates may be as high as 40 percent. Despite the frequency of these conditions, the true population prevalence and natural history of preinvasive neoplastic lesions in the stomach and esophagus are poorly established because studies have come mainly from single institutions. Endoscopy can safely and systematically visualize and biopsy stomach and esophageal pre-malignant conditions prospectively, providing an unprecedented opportunity to define the prevalence and natural history of these conditions, establish risk stratification, and characterize the genetic and biological mechanisms of carcinogenic progression. Data from these multi-institutional, multidisciplinary studies must be aggregated to define statistically significant at-risk populations, risk and protective factors, and the natural history of gastroesophageal neoplasia.

Prevention: *Develop prevention strategies based on the mechanisms of host/environment interaction that lead to metaplasia and neoplasia of the stomach and esophagus. Evaluate their effectiveness in at-risk populations.*

Rationale

Neoplastic progression in the stomach and esophagus is a multi-decade process characterized by genomic instability and the evolution of neoplastic clones, providing time and targets for intervention long before the development of cancer. Premalignant conditions can be prospectively monitored by endoscopic biopsy surveillance, providing an unparalleled opportunity to understand the evolution and impact of risk and protective factors in humans.

Preliminary studies implicate gastric acid, bile, *H. pylori*, diet, tobacco, NSAIDs, obesity, and other exposures as risk and/or protective factors for these cancers, but little knowledge exists as to the molecular and cellular mechanisms involved. Knowledge of the mechanisms that predispose people to gastroesophageal cancers, especially at the genomic, transcription (expression) and proteomic levels, could identify novel interventions to prevent these cancers.

Additionally, insight could be gained that may be useful in preventing or controlling the evolution of intervention-resistant clones. Finally, after promising interventions have been identified, they must be tested in adequately powered, well-controlled clinical prevention trials that allow prospective, tissue-based molecular and cellular characterizations of response.

Patient/Provider Education: *Educate patients and their families, health care professionals, and the public regarding risk factors, risk reduction, and treatment options and outcomes for gastroesophageal cancers and their precursor states.*

Rationale

Gastroesophageal cancers represent a diverse group of malignancies, and each subtype has a different risk profile. Some subtypes show recent rapid changes in incidence as well as striking variations by

ethnicity, gender, and socioeconomic status. For example, esophageal adenocarcinoma, which was rare two decades ago, now accounts for 60 percent of all esophageal cancers. As many as 25 percent of gastric cancer patients receive no surgical treatment, even though they present at a treatable stage. These issues suggest that a critical lack of knowledge about risk factors, risk reduction, treatment options and outcomes among health care providers, patients, and the public. There is a lack of public awareness of the scope, magnitude, and premalignant stages of gastro-esophageal cancers. Specifically, there has been a lack of focus on educating high-risk groups, including people with Barrett's esophagus, GERD, and *H. pylori* infection. In addition, the possible roles of alcohol, tobacco, and diet in the etiology of these cancers have not been emphasized. Furthermore, public education on risk factors, common presenting symptoms, and interventions has been inadequate to motivate the public to seek early diagnosis. Presumably, more at-risk patients would self-identify and seek treatment earlier if risk profiles were more widely understood by the public, advocacy groups, and health care professionals. In addition, morbidity and mortality could decrease with well-developed tools, such as videos available in physicians' offices and user-friendly Web sites, to assist the educational process.

From primary prevention to survivorship and end-of-life issues, communication empowers people to make informed cancer-related decisions and to engage in behaviors that will improve their health. To build on our progress in refining health communication theories and interventions, we must close major gaps in our understanding of how people access and use health information, as well as the discrepancies between what is known and what is practiced.

The quality of cancer communication can be enhanced by gaining a better understanding of the information needs of patients, families, and other decision makers involved in the choice of stomach and esophageal cancer interventions. These findings can lead to accurate and balanced information about areas such as cancer prevention, diagnosis, treatment, and care. In addition to these findings, current dissemination systems for quality, evidence-based cancer education materials and the use of multi-media technologies must be evaluated and improved. This information eventually will be applied to help people understand important health risks and to assist them in making informed choices despite exposure to contradictory or inaccurate health messages.

Therapy: *Develop and test novel therapeutics, and optimize existing treatments for gastroesophageal cancers and their precursors, based on the identification and understanding of molecular pathways involved in oncogenesis, tumor response and resistance.*

Rationale

Gastroesophageal malignancies continue to be highly lethal, despite therapeutic advances over the past 30 years. Although treatment has become more complex—often involving combinations of surgery, chemotherapy, and radiation—physicians still do not know which patients benefit most from which approaches. The overall similarity of outcomes belies the biologic and genetic heterogeneity of these malignancies and the potential for differential sensitivities to existing and novel therapeutics. Identifying and understanding molecular pathways involved in oncogenesis and tumor sensitivity, as well as the evolution of therapeutic resistance, are facilitated by repeated endoscopic

assessments with biopsies. Indeed, as oncologic drug development orients itself toward more molecularly targeted, “cytostatic” agents, serial assessment of tissue-based response markers becomes critical, particularly in early-phase clinical trials intended to prioritize agents before entry into more costly phase III trials. Knowledge from molecular inquiries during therapy also may be useful to improve the accuracy and reliability of predictions regarding response, survival, and long-term outcomes.

Therapeutic Targets: *Define host and molecular/biologic tumor characteristics that will help customize treatment and best predict recurrence and/or survival.*

Rationale

Therapies for gastroesophageal cancers are largely empirical. Despite surgery and adjuvant therapy, the majority of patients with gastroesophageal cancers run a substantial risk for both local and distant recurrences. There is an urgent need to identify molecular markers and pathways that confer sensitivity and resistance to existing and novel therapies. Advances in genomic, transcription (expression) and proteomic technologies, combined with endoscopic access for biopsy of the stomach and esophagus, make it possible to safely evaluate neoplastic tissue before and after therapy in a unique and unparalleled fashion. Insights gained from pre- and post-treatment tissue evaluation by a committed multidisciplinary team would guide development of customized therapy by identifying markers of sensitivity or resistance to existing and novel therapies. Using these markers, clinical researchers could better determine which patients were most suitable for which therapies, as well as develop therapies targeted specifically to gastroesophageal cancers.

Markers and Molecular Profiling: *Profile the molecular, cellular, and epidemiologic features of gastroesophageal tumors and their precursor lesions to identify diagnostic, prognostic, predictive, preventive, and therapeutic targets.*

Rationale

Rapid technologic advances in genomics, expression arrays, proteomics, and bioinformatics, combined with the unique access of gastroesophageal cancers and their precursors to endoscopic biopsy, offer innovative and exciting opportunities to understand, prevent, and treat these malignancies. Endoscopic biopsies can be processed within seconds of being obtained, providing optimal material for genomic expression and proteomic analyses. In addition, premalignant gastroesophageal tissues are not typically removed according to current standards of care, so molecular findings may be evaluated with regard to prospective outcomes. These comprehensive methodologies can give insight into the molecular genesis and signatures of gastroesophageal cancers and their precursors. This knowledge provides unprecedented opportunities to develop molecular diagnostics for risk stratification and to predict therapeutic response.

Such comprehensive methodologies also can identify molecular targets to prevent or treat cancer, as well as molecular endpoints to evaluate the success of interventions. New molecular markers and targets can aid in developing novel, customized treatment strategies that are more effective and less toxic than existing regimens.

Outcomes: *Develop and refine disease-specific, patient-oriented methods to assess quality of life, quality of care, and cost effectiveness of treatment in patients with gastroesophageal cancers and their precursors through all stages of disease and*

treatment, and include these instruments in clinical trials and observational studies.

Rationale

Solid data exist that describe patterns of recurrences and survival in patients treated for gastroesophageal cancers, but information is limited on patients' long-term functional outcome and quality of life. Patients with gastroesophageal cancers have unique functional problems relating to both disease and treatment morbidity. Specific quality-of-life scales exist for stomach and esophageal cancers, but without longitudinal studies across large populations, generalizations cannot be made. Challenges to the study of patient-centered outcomes include the small number of cases and high mortality rates. In addition, patient-centered issues vary across the premalignant to late malignant disease spectrum. Thus, additional organ-specific instruments need to be created and utilized in large-scale clinical trials. Findings will inform assessments of quality-of-life and quality-of-care issues, cost of care, patient preferences, and quality of symptom management.

Host/Environment Interactions: *Identify, develop, and validate genetic, biochemical, and biological markers that will help uncover host/environment interactions in esophageal and gastric carcinogenesis.*

Rationale

Gastroesophageal cancers encompass a diverse group of malignancies, each with identified protective and risk factors. Some environmental exposures appear to be risk (e.g., tobacco) or protective (e.g., a diet high in fruits and vegetables, NSAIDs) factors for most gastroesophageal cancers, whereas others appear to be specific for certain sites or histologic subtypes. For example, gastroesophageal reflux and obesity correlate with esophageal adenocarcinoma,

and *H. pylori* infection may even be a risk factor for gastric adenocarcinoma but a protective factor against esophageal adenocarcinoma. The mechanisms by which these factors modulate cancer progression are not well understood. The stomach and esophagus are accessible to endoscopic biopsy and prospective evaluation and thus are uniquely suited to research on environmental exposures and host-response relationships, which can be assessed comprehensively using genomic expression and proteomic technologies. Additionally, a new generation of molecular markers to identify at-risk patients for premalignant and malignant lesions will assist in both developing new prevention strategies and stratifying patients for surveillance.

Technologies for Screening/Surveillance:

Develop noninvasive and minimally invasive technologies (e.g., serum markers and imaging techniques) for screening and surveillance of premalignant and malignant gastroesophageal lesions.

Rationale

Gastroesophageal carcinogenesis occurs over decades, and the long premalignant phases for these cancers provide great opportunities for screening, surveillance, early detection, and prevention. Unlike people with many other premalignant conditions, high-risk populations are identifiable, but many people do not seek evaluation because of the invasive procedures involved. Serologic markers to identify persons at increased risk would permit cost-effective screening of the population. Novel imaging technologies for screening (e.g., ultrathin endoscopes, colorimetric devices, capsule endoscopy) and surveillance (e.g., laser-induced fluorescence spectroscopy, reflectance spectroscopy, light-scattering spectroscopy, trimodal spectroscopy, Raman spectroscopy, optical coherence tomography, confocal microendoscopy) show promise, but multi-

center clinical trials and comparisons among technologies are lacking. Such novel noninvasive and minimally invasive techniques could facilitate screening and surveillance by making the procedures more cost effective, acceptable, and available.

Preclinical Models: *Establish models to understand the biology of gastroesophageal cancers and their precursor lesions and to stimulate novel prevention, diagnostic, and treatment strategies.*

Rationale

Few clinically relevant tumor models of stomach and esophageal cancers exist. Preclinical studies need well-characterized epithelial cell cultures, cell lines, xenografts, and animal models that accurately represent physiologically and genetically defined stages in human gastroesophageal carcinogenesis, including gastroesophageal reflux, intestinal metaplasia, *H. pylori*-mediated progression, and gastroesophageal clonal evolution. Such preclinical tumor models could provide crucial mechanistic evidence for translation of advances in laboratory research and host-environmental interactions into clinical prevention and therapeutic trials. Preclinical tumor models also provide an efficient use of resources to investigate the efficacy and safety of therapeutic agents prior to human trials. Finally, gastroesophageal tumor models would be valuable assets for genomic expression and proteomic exploration to identify new targets for intervention.

These recommendations constitute a scientific framework to translate bench, bedside, and population advances into improved care for patients with and at risk for gastroesophageal cancers. The S/E PRG offers a high-priority infrastructure resource, the Stomach/Esophageal Neoplasia Translational Research Network (SENTRNet) to overcome challenges to

efficient translation of these research recommendations, as described below.

Infrastructure: Resources and Partnerships

The primary challenge in achieving the S/E PRG's recommendations is that no single institution or organizational structure currently possesses the resources necessary to address the opportunities and challenges specific to gastroesophageal cancers outlined above. The rarity of these cancers means that no one center sees enough patients to conduct necessary clinical trials. Additionally, a single center may not have access to the tools, such as bioinformatics, that may be critical to the success of trials. Likewise, the dearth of patients at any single center prevents the development of quality-of-life interventions and assessment of prevention strategies. Thus, it is imperative that NCI supports the multidisciplinary, multi-institutional efforts of gastroesophageal cancer research.

Accomplishing the priorities set forth by the S/E PRG will require resources specifically designed to capitalize on translational research opportunities and meet the challenges uniquely presented by gastroesophageal cancers. The progression of the disease, the late stage at diagnosis, the rarity of each of these cancers, and the coordination of translationally oriented biomedical investigators capable of thorough evaluation of these diseases are best addressed through the creation of a Stomach/Esophageal Neoplasia Translational Research Network (SENTRNet).

The Stomach/Esophageal Neoplasia Translational Research Network

Overview

SENTRNet (Figure 2) will be charged with prioritizing translational research

opportunities with regard to their efficient and effective contributions to key foundational elements of trial design. These include 1) better risk characterization for cohort identification/stratification; 2) agents/interventions with greater efficacy and/or safety; and 3) markers/endpoints with greater accuracy and reliability. Once priorities are agreed upon, SENTRNet will conduct laboratory, clinical, and population-based studies to achieve the goals. Population feedback will be used to refine interventions and improve patient care.

The components of the model will include experts from various disciplines and institutions, a tissue repository, epidemiological data, surveillance, and the technologies necessary to develop basic science discoveries that will translate into high-quality prevention and treatment practices. SENTRNet will share scientific leadership with a coordinating center that will utilize a business model approach and foster linkages with academia, industry (both pharmaceutical and device-oriented), consumers, and federal agencies. A mutual dependence prototype for funding and collaborations will be employed to provide incentives for productivity and rewards for effective partnerships and resource sharing.

The conceptual foundation, infrastructure, management strategies, and research priorities are further described below.

SENTRNet's Conceptual Foundation

SENTRNet will have multi-agency, multiinstitutional, and multidisciplinary collaborations with shared leadership. The innovative infrastructure and unique management style are likely to enhance collaborations as well as to facilitate achievement of the S/E PRG recommendations.

In developing the idea for SENTRNet, existing institutions, consortia, and networks

devoted to clinical research (such as Cancer Cooperative Groups, Cancer Centers, the Cancer Genetics Network [CGN], the Early Detection Research Network [EDRN], the Specialized Programs of Research Excellence [SPORES], the Nonalcoholic Steatohepatitis consortium, and others) were considered and reviewed. Although each of these entities has strengths, none was ideally suited to meet the unique translational research challenges and opportunities available in stomach and esophageal cancers. Success is dependent upon the participation of gastroenterologists, as well as translationally focused interactions between diverse scientists working at the laboratory, clinical, and population levels. In addition, the proposed management system for SENTRNet is unique. For all of these reasons, we felt that the research agenda regarding stomach and esophageal cancers would be best advanced by the creation of SENTRNet.

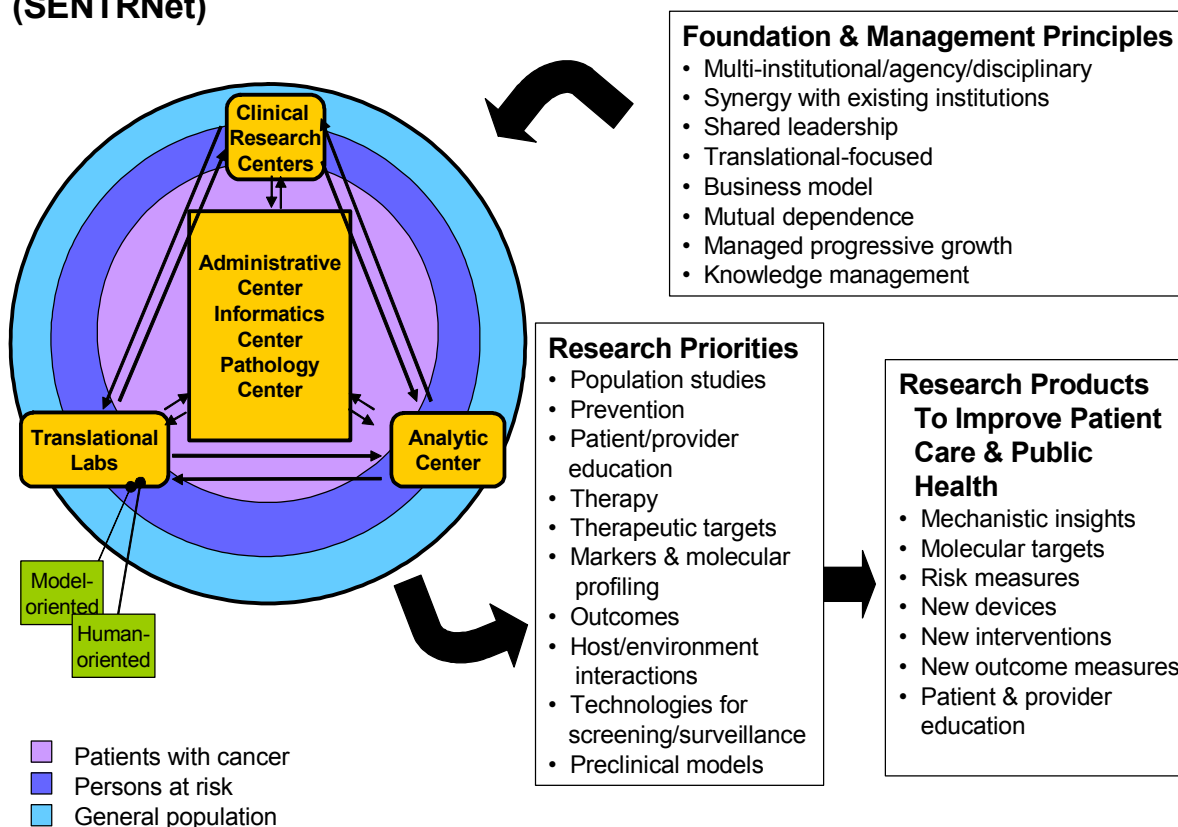
Multi-Agency Partnerships and Linkages.

A wide range of federal research agencies should be invited to partner scientifically and financially with NCI in this initiative as a means of drawing on needed expertise and

resources, and providing coordination and information dissemination across relevant research and practice enterprises. NCI is not in a position to bring the full scope of the S/E PRG recommendations to fruition alone. Other potential support agencies include the National Institute of Allergy and Infectious Diseases (NIAID), the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), the National Institute of Nursing Research (NINR), the National Institute on Aging (NIA), the Department of Veterans Affairs (VA), the Department of Defense (DOD), the Centers for Disease Control and Prevention (CDC), the Centers for Medicare and Medicaid Services (CMS), and the Agency for Healthcare Research and Quality (AHRQ). The John E. Fogarty International Center can be utilized to develop a better understanding of the international implications of these cancers and seek international research partners wherever possible. In addition, SENTRNet will seek biotechnology, pharmaceutical, and medical device industry partners as well as solicit the advice of the Food and Drug Administration (FDA) to steer new devices and therapies through the clinical trials process more effectively and efficiently.

Figure 2. Schematic Diagram of the Structure and Function of SENTRNet.

Stomach/Esophageal Neoplasia Translational Research Network (SENTRNet)



SENTRNet will seek scientific collaborations with other established NCI programs, cooperative groups, and consortia. For example, the SENTRNet Virtual Tissue Resource might partner with already established programs, such as the EDRN, Cooperative Human Tissue Network, Tissue Array Research Program, Tissue Expeditor, Tissue Locator, and others.

Finally, SENTRNet also will seek to include community physicians, consumer advocacy groups, relevant professional associations (e.g., the American Gastroenterology Association, American College of Gastroenterology, American Society for Gastrointestinal Endoscopy, American College of Surgeons, Oncology Nursing Society, American Society of Clinical

Oncology, and others) and private cancer research foundations (e.g., the American Cancer Society, Cancer Research Foundation of America) to promote adequate representation of all interested parties. In addition, these affiliations will ensure that as many health care professionals and patients as possible will have access to the new information and advances this partnership will provide.

Multidisciplinary and Multi-institutional. Representatives from many disciplines and institutions will be necessary to implement this comprehensive gastroesophageal cancers research plan, which will focus on the discovery and application of effective educational, prevention, and treatment strategies to improve patient care and the public's health. Disciplines and

representatives will include basic scientists, especially geneticists and cell biologists, biostatisticians, epidemiologists, pathologists, gastroenterologists, informatics specialists, nurses, psychologists, prevention strategists, surgeons, radiation oncologists, medical oncologists, and consumers. These cross-disciplinary, multi-institutional collaborations will be essential to facilitate timely discoveries that can improve prevention, early detection, treatment, and comprehensive cancer care. The outcome of this collaboration could potentially reduce the burden of disease and increase the quality of life for those with or at risk for gastroesophageal cancers.

Shared Scientific Leadership. A steering committee coordinated through the administrative center will provide scientific direction to SENTRNet to assure its efficient and productive translational focus. The SENTRNet steering committee will consist of one representative from each member institution and/or discipline, chosen to reflect the diversity of research professionals and advocates.

Research Products. Clinical care is improved by the generation of high-quality reproducible data from unambiguously defined risks and benefits of tested devices, drugs, and behaviors. Once these data are generated, they may be assimilated into evidence-based recommendations and clinical/public health practices. SENTRNet's first priority is the generation of products that will expedite clinical trials to improve the clinical care of patients with, or at risk of, gastroesophageal cancers, thereby improving the public's health. Specific research products will exploit new mechanistic insights gained in the course of this research that will iteratively improve recognition of molecular targets and development of new interventions. It is expected that this research will suggest new risk and outcome measures that can be used

to evaluate devices and interventions more efficiently and effectively. Finally, improved patient and provider education will apply these advances in a more equitable and productive manner.

Key Elements of SENTRNet's Infrastructure/Components

Administrative Center. The administrative center, under the scientific leadership of the steering committee, will attend to all administrative details and coordinating functions. These functions will include the development and adoption of standard common data elements, protocols, and informed consents; development and monitoring of budgetary expenditures and product timelines; development and promulgation of incentives; facilitation of communication within and across the network; promotion of industry relations; and dissemination of information beyond SENTRNet. A business administrator will lead the center, which will follow a business model of management (described later). Scientific priorities will be generated by the SENTRNet Steering Committee and implemented by the other components.

Informatics Center. Knowledge management is key to the usefulness of the data generated. The network will assess the market pulls and demands to determine what data is needed and to assess how, when, and why this information is best translated into improved practice. Internally, the data will be used to identify needs, track progress, motivate future directions, and improve delivery capacity. In addition, bioinformatics tools will be developed for promoting, accessing, and adopting evidence-based interventions.

Pathology Center. The histopathologic designation of premalignant conditions of the stomach and esophagus is hampered by tremendous inter- and intra-individual

heterogeneity. Unfortunately, current standards of care depend upon pathologic interpretations (e.g., low- versus high-grade dysplasia). For this reason, a pathology center devoted to histopathologic standardization is essential. Tissues subjected to molecular and cellular inquiries will first be characterized with regard to histopathology so that accurate and reliable interpretations of molecular and cellular data can be offered.

Clinical Research Centers. These centers, positioned throughout the United States, will serve as the essential links to persons at risk for and living with gastroesophageal cancers, as well as their families. A team of clinicians (e.g., gastroenterologists, GI surgeons, medical oncologists, psychologists, nurses or clinical research associates, data or protocol managers) will staff the centers. These sites will develop clinical protocols; recruit, enroll, and manage the cohorts involved; assure the development of institutional tissue repositories; and monitor the epidemiologic data collection to identify risk and protective factors for gastroesophageal cancers and define the stages at which they act during carcinogenesis.

Analytic Center. The analytic center will assume responsibility for the development of management tools, such as electronic databases and on-line study forms. Additionally, they will interact with the clinical research centers to develop clinical and population studies/protocols, emphasizing standardization of methods and tools. In addition, the analytic center will serve as SENTRNet's biostatistical unit, closely linked to bioinformatics, providing support in the development of studies and analyzing data as they emerge.

Translational Laboratories. A primary focus of SENTRNet is to move science into practice, and this can best be achieved

through human-oriented and model-oriented translational laboratories.

Human-oriented Translational Labs. These laboratories will focus on high-priority research involving human specimens, including both resected and pinch biopsy specimens. These units will develop standard protocols for the handling and transportation of human materials from the moment they are obtained until they are received by the laboratories or virtual tissue repositories. Specimens delivered to these laboratories will be subjected to a variety of technologic inquiries, including expression arrays, genetic and epigenetic assays, assessments of cellular apoptosis and proliferation, and proteomics. There are two goals: first, to identify key aspects of human neoplastic progression for development as markers of risk, response, and therapeutic targets; second, to evaluate these markers as surrogate endpoints in epidemiological studies of risk and protective factors as well as in clinical treatment-response investigations. The human-oriented translational labs will interact closely with established NCI programs, such as the EDRN, to identify synergies and avoid overlap.

Model-oriented Translational Labs. These labs will improve gastroesophageal stem cell models; identify stem cell-specific promoters for use in animal models; and develop, appropriate, and maintain cell lines. In addition, they will develop and maintain optimal animal models of these diverse diseases, use available models to evaluate preventive and therapeutic agents, and standardize criteria in mouse histopathology related to premalignant and malignant lesions. Previously established effective and ineffective agents in humans will be back-validated by the models to definitively define them as reasonable positive or negative predictors of human efficacy. Additionally, molecular and cellular

investigations will be carried out in these models to identify risk markers, therapeutic targets, and response markers that may be rapidly translated into similar aspects with humans. The model-oriented translational labs will interact closely with established NCI programs, such as the Mouse Models of Human Cancers, to identify synergies and avoid overlap.

Virtual Tissue Repository. A number of the S/E PRG's priorities rely on the collection of tissues and/or blood of serially acquired samples that can be linked to patient demographic and medical information. The data can be used to exploit genomics, proteomics, and translation of basic science findings into everyday patient care. Therefore, SENTRNet will employ a virtual tissue bank with centralized reading as opposed to a centralized storage facility.

The bank will be an electronic virtual tissue repository where specimens are handled in a standardized fashion and cataloged in a centralized location, but specimens will be housed at the individual institutions under uniform storage conditions. Researchers participating in SENTRNet will have incentives to share these tissue resources. Tissue samples will be prioritized for use centrally for collaborative studies of highest impact. This component will establish linkages with other established tissue resources. The multi-institutional collection and access to tissues will facilitate new discovery and rapid translation into daily clinical care of these rare cancers.

The management of SENTRNet is as important as its multidisciplinary, multi-institutional structure in assuring its translational function. SENTRNet will utilize unique management strategies that build upon the current research consortia and cooperative groups, and SENTRNet will adopt advances from other disciplines to resolve many issues specific to

gastroesophageal cancers and contemporary models of translational research. Research conducted will be along the continuum from basic to practice to population.

Unique Management Strategy Concepts

SENTRNet's concept is different from current cooperative efforts in a number of ways. SENTRNet's unique management strategy will help achieve the recommendations of the S/E PRG and overcome the challenges of current models. SENTRNet will be managed with a business model approach and a spirit of mutual dependence. A strategy for progressive growth and the utilization of technology will be integrated throughout the components.

Business Model Approach Strategy. Since 1955, NCI has established a number of multi-institutional collaborative cancer groups to conduct coordinated therapeutic trials. However, gaining institutional cooperation was challenging, even when governing boards had been established. In addition, although cooperative groups require detailed attention to complex budgets, complicated issues in personnel management, and multifarious structures of tasks and authority, the groups' scientists, clinicians, and government project officers typically were not trained in business management strategies. A well-managed matrix organization simplifies and organizes the uses of information processing, highly specialized resources, staff, and equipment.

The predicted future of limited budgets and high performance demands sets the stage for shared resources and better management of participating individuals, organizations, and assets. Cooperation can enhance the cost to benefit ratio; thus, partners will be required to cooperate with SENTRNet's concept of the matrix organizational governing structure for shared resources and better

business management. Those electing to participate in SENTRNet will receive training in general managerial skills, data management, systems evaluation, resource allocation and utilization, strategic planning, assessment, and monitoring. Those trained will evidence an overall awareness of the interrelationship and interdependency of various financial, economic, and administrative considerations within a business environment. This training will be required of participating investigators.

Mutual Dependence Strategy. SENTRNet will address operational challenges by encouraging a spirit of mutual dependence between partners. In the spirit of mutual dependence, collaborations and partnerships will be stressed, but each of the components will be funded and peer-reviewed separately. The concept of mutual dependence capitalizes on the strengths and needs of SENTRNet's partners and creates incentives for collaboration. For example, by creating an interface through which laboratory specialists gain access to patients and human tissues, clinical researchers have direct access to laboratory expertise. Mutual dependence, as opposed to individual accomplishments, rewards those who share resources, encourages productivity, promotes resourcefulness, strengthens collaborations, and provides latitude for creative endeavors, especially for translational progress.

Those who participate in SENTRNet's matrix organizational structure must demonstrate effective business management of their site, sharing of resources, collaborative discoveries (according to foundational review criteria that will be developed and employed), and translational productivity. Decisions related to continued support will be based on these accomplishments and not mere membership. Performance matters and is more important than participation. Using this philosophy as

a framework, SENTRNet might reward productive collaborative research with additional funding and easier access to needed resources.

Mutual dependence strategy applied to the virtual tissue resource will prevent any single institution or individual from wielding undue influence over the use of tissue. By applying the mutual dependence strategy, the Steering Committee or its designee (i.e., the Repository Subcommittee) will be able to prioritize utilization of the tissue and types of studies, while the investigators develop and maintain the tissue resource. The group will place the highest priority on collaborative studies of the greatest potential impact; however, an individual also may utilize the tissue for scientific discoveries based on his/her own initiative.

Managed Progressive Growth Strategy. The intended scope of SENTRNet's operation is quite large; however, the group will start on a smaller scale and move to a larger effort to ensure that all participants are trained and ready to participate in the group's organizational structure and knowledge management systems. Training will be continuous as management, technology, and scientific advances progress. Standardized protocols and procedures will be established across partnering sites to protect data quality; to produce quality analyses; and to facilitate the development, translation, application, and dissemination of scientific advances into quality care. Standardized protocols will aid in ensuring aggregation of data and maintaining a focus on SENTRNet's collaborative intent during the managed growth process.

Knowledge Management and Technology Advances Strategy. The goals of knowledge management are twofold: it provides a means to share information and it

establishes user-friendly resources to obtain essential information to enhance individual and collective productivity. Knowledge management entails the storing of electronic files that have been created, edited, and tailored to a particular need. Information technology infrastructures facilitate the distribution of knowledge specific to the organizational needs for which it was developed. The electronic management of information facilitates knowledge-based categorization of new and archived data.

SENTRNet will develop and capitalize on the daily use of a tailored knowledge management system that will enhance communication capabilities of partners; facilitate information sharing; provide a mechanism for information transfer; and foster standardized data collection within the partnership. In addition, the SENTRNet system will develop and establish technology capable of linking databases from various sources in an effort to speed research and to aid in accomplishing the S/E PRG's priorities.

Therefore, an integrated organizational matrix infrastructure, combined with sound management, will support multi-institutional and multidisciplinary research. SENTRNet will facilitate progress toward achieving all 10 of the S/E PRG recommendations.

How SENTRNet Will Facilitate Progress Toward Achieving the PRG Recommendations

Population Studies. The unique accessibility of stomach and esophageal premalignant conditions to endoscopic biopsy is a driving force for translational research on neoplasms of these organs. Current knowledge concerning the natural history of stomach/esophageal premalignant conditions, risk and protective factors that modulate progression to cancer, and biomarkers for risk stratification have

typically been accumulated at single centers or in large studies evaluating only patients who have progressed to cancer. Although these studies have made significant advances, existing approaches contain critical gaps in the accumulation of knowledge necessary to translate the research advances into improved patient care and public health.

SENTRNet provides a vehicle to translate research results more rapidly than existing mechanisms. The patient/research participant is the foundation of SENTRNet's research approach, and all clinical, epidemiological, and laboratory data are directly linked to a specific endoscopy for a specific patient. These results can be more rapidly generalized than those of single centers because of the multi-institutional nature of SENTRNet. For instance:

- The clinical research centers will include gastroenterologists, who are presently not well represented in the NCI research and prevention community. These specialists are critical because they can provide access to tissue from their patients at risk for and with stomach and esophageal cancers. This access is essential to delineate the natural history of neoplastic lesions, validate biomarkers for risk stratification, and understand the effects of environmental risk and protective factors on the premalignant epithelium.
- SENTRNet's epidemiology section within the analytic center will develop standardized procedures and questionnaires that can be applied uniformly to patients in the clinical research centers at the time of endoscopy.
- Tissue obtained by endoscopic biopsy can be evaluated by the Translational Laboratory to validate markers for

clinical risk stratification and provide surrogate endpoints to determine the mechanisms by which risk and protective factors modulate progression to cancer.

- These data can be related to the pathology center, minimizing the confusion caused by significant intra- and interobserver variations in dysplasia diagnosis and grading in single-center studies.
- Database components of SENTRNet can be linked with existing databases, such as SEER, the gastrointestinal databases of existing cooperative cancer groups, the National Coalition of Cancer Survivorship, and the NIDDK database. The aggregated information may fill gaps in the information that any one database can provide. The technology developed for linking these databases also can be used for the network's communication and bioinformatics efforts.

Thus, SENTRNet can provide a clinical, epidemiologic, laboratory, pathology, and analytic research infrastructure. Those working within the infrastructure will be better able to estimate the prevalence of significant risk factors, to determine efficiently the natural history of premalignant disease states, and to determine the mechanisms by which risk and protective factors modulate progression as a prelude to prevention studies. In addition, they will validate markers that identify patients at high risk for progression to cancer, and establish or merge databases for hypothesis generation and disease modeling. SENTRNet's contributions to population studies will facilitate the accomplishment of other S/E PRG priorities, including prevention, patient/provider education, markers and molecular profiling, outcomes, and host/environmental interactions.

Prevention. SENTRNet's research platform provides a vehicle for rapidly translating hypotheses on risk and preventive factors generated from preclinical and epidemiologic studies (such as those that will be done within the model-oriented translational labs and the analytic center) into efficient prevention trials in the clinical research centers. The development of those trials will be facilitated by other components of SENTRNet in several ways. Advances in the understanding of the prevalence and natural history of neoplasia (derived from epidemiologic research within SENTRNet) can provide solid data for power/sample size calculations of clinical trials, thereby improving their efficiency. For example:

- Validated risk markers can improve risk estimates, thereby allowing intervention trials targeted more specifically toward persons most likely to benefit from them.
- Tissue-based surrogate endpoints can be derived from an understanding of the mechanisms by which the risk and protective factors modulate carcinogenesis.
- Translational Laboratories that have gained experience in population studies can provide high-throughput data for tissue-based inclusion/exclusion criteria and surrogate endpoints in prevention trials.
- The pathology center can provide standardized interpretations to minimize the confounding influence of observer variation in dysplasia diagnosis.
- The analytic center can provide data analysis.

As new information is gained, prevention strategies can be refined to improve cost effectiveness. Thus, data obtained by SENTRNet population studies (such as information on the mechanisms by which NSAIDs and a diet high in fruits and

vegetables are protective against gastroesophageal cancers) can fuel randomized clinical trials to develop effective prevention strategies for these cancers. Similarly, SENTRNet population studies that lead to a better understanding of the mechanisms by which risk factors (such as gastroesophageal reflux, obesity, and *H. pylori*) promote esophageal and gastric adenocarcinomas can be translated efficiently into prevention trials.

SENTRNet's research platform provides a vehicle for prevention studies to synergize with other S/E PRG priorities, including patient provider education, therapy and therapeutic targets, markers and molecular profiling, outcomes, host/environmental interactions, and preclinical models.

Patient/Provider Education. Previously, critical knowledge concerning at-risk symptoms, risk stratification, clinical trials, and outcomes has been scattered among a number of centers across the United States, with inadequate compilation and standardization of data and knowledge in a central resource.

SENTRNet, through its centralized review, compilation, and updating of relevant information on at-risk subsets, risk stratification, clinical trials, and patient-oriented measures, can provide a unique resource for research into the informational needs of patients with and at risk for cancer. Once those needs are better defined, SENTRNet can serve as a platform for the dissemination to the public of knowledge concerning gastroesophageal cancers. More specifically, SENTRNet can partner with NCI's Physician Data Query, AHRQ, and the Centers for Disease Control and Prevention—in collaboration with representative professional organizations, advocacy groups, and private cancer foundations—to develop a central, standard resource of disease-specific knowledge and

insights. That resource then can serve as a common information platform available for broad dissemination to health care providers, advocates, and patients via informatics links to each partner's existing Web sites, as well as by other methods of communication.

Therapy and Therapeutic Targets.

SENTRNet can provide an integrated, comprehensive tissue-based approach to clinical trials that is beyond the capacity of any single cancer center. SENTRNet's gastroenterologists can obtain endoscopic biopsies before and after treatment. This collection provides a valuable tissue repository to be used by SENTRNet molecular biologists and epidemiologists in an effort to investigate host and tumor characteristics predictive of positive and negative responses to existing and novel therapies. Furthermore, comprehensive genomic expression array and proteomic analyses of these tissues can identify novel therapeutic targets that can be investigated in SENTRNet tumor models and used to identify promising new interventions. The interventions then can be tested in clinical trials in an effort to improve the efficacy and safety of available therapeutic options. Ultimately, SENTRNet will evaluate contributions of different treatment modalities for esophageal and gastric cancers as well as the proper integration and sequencing for optimal treatment outcomes.

Some therapeutic targets and treatment modalities are on the verge of breakthroughs, and they can be accelerated in clinical trials organized by SENTRNet. For example, exciting new agents that selectively modulate the behavior of cancer cells (i.e., cytostatic anti-cancer drugs) promise to be less toxic and more effective than current drugs. The effectiveness of these agents, particularly in early phases of drug development, can best be demonstrated by evaluating key biologic parameters before and after treatment in gastro-

esophageal tissues. In addition, the effectiveness of traditional interventions is less than optimal, but additional research on patients and their tumors before and after intervention may better explain the mechanisms underlying response and resistance, thereby providing insights to guide the development of new, more effective combinations.

Thus, SENTRNet provides a translational research model from the laboratory to standard practice. First, SENTRNet will determine which patients and tumors are most likely to respond to existing therapies. Second, SENTRNet will develop novel therapeutic approaches based on the molecular pathways of gastroesophageal carcinogenesis (interacting with established NCI programs such as the Chemoprevention Agent Development Program and the Drug Therapeutics Program). Finally, SENTRNet will evaluate the most effective therapies in clinical trials and move them efficiently into standard practice.

Markers and Molecular Profiling.

SENTRNet will have an unparalleled repository of normal, premalignant, pretreatment malignant, and posttreatment malignant tissues that can be used for molecular marker development ranging from exploratory preclinical investigations to marker validation to risk stratification and treatment response studies. Many of these activities may create synergy with existing NCI initiatives and services, including the Specimen Resource Locator, Tissue Expediter, and the EDRN. This partnership platform will allow laboratory experts on stomach and esophageal carcinogenesis in one institution to collaborate with other clinical and population-based research at other institutions. These collaborations can support other S/E PRG priorities, including population studies, prevention, therapy and therapeutic targets, host-environmental interactions, and preclinical models. By

providing characterization of tissues at multiple stages of carcinogenesis, including its treatment, SENTRNet may create synergy with the Cancer Genome Anatomy Project.

Outcomes. SENTRNet's multi-institutional, multidisciplinary team can facilitate a rich understanding of how people use health information and access communication technologies of all kinds. SENTRNet can evaluate clinical and outcomes data related to symptoms, quality of life (QoL), and quality of care (QOC) in people with gastric and esophageal cancers and in those at risk for these conditions. Cross-sectional studies using existing databases can then provide a more formal assessment. SENTRNet can utilize and adapt current esophageal and gastric-specific QoL and QOC instruments to measure disease stage and treatment-related outcomes. SENTRNet's infrastructure may best address the following:

- Many patients with stomach and esophageal cancers present at a late stage that reduces their chance of survival, leaves little opportunity for non-surgical interventions, fosters surgical treatment that renders potential disabilities, and increases their likelihood of co-morbidity. SENTRNet's research initiatives can address important questions related to communication of health messages, treatment decisions, QOC, long-term follow-up, and QoL.
- The number of cancer survivors is expected to increase as more people undergo cancer screening, as screening technologies improve, and as new therapies are introduced. While some of these cancer survivors are cured of their original malignancies, they may have health-limiting impacts and related side effects that remain poorly documented or understood. In addition, many of these

individuals may be at risk for the development of new tumors. The length of time projected for survival and the risk of co-morbid conditions often exert an impact on both cancer treatment and posttreatment follow-up care. Thus, there is a need for more research on the identification, prevention, treatment, post-therapeutic surveillance, and care of the broad spectrum of conditions experienced by survivors of stomach and esophageal cancers.

- Evidence suggests that some patients with cancer do not receive newer, more effective treatments. Moreover, in some cases, there remains substantial disagreement or uncertainty about what constitutes optimal care, especially from the patient's perspective. Clearly, too many patients face significant financial difficulties and other barriers to obtaining appropriate and timely care. As society wrestles with how to make health care more accessible to more people, it is critically important to advance a comprehensive research agenda that includes finding ways to improve outcomes and the quality of the cancer care. Additionally, a greater understanding of the factors that impede access, regardless of race/ethnicity, income and geographic location, is needed. Stomach and esophageal cancers provide an opportunity for such studies.

Host/Environment Interactions. Early efforts to discover how genes and environmental factors interact to cause cancer are showing promise, but they also highlight the complexity of the puzzle. SENTRNet's research in this area can uncover elements of gene-environment interactions that lead to improvements in preventing and controlling stomach and esophageal cancers. SENTRNet's research platform will accelerate discovery and translation because all necessary elements

are involved. For example, endoscopic biopsies with standardized pathology interpretations from patients with known environmental exposures can be evaluated by comprehensive genomic, expression array, and proteomic methods. These complex tissue-based data then can be analyzed in the analytic center, and the resulting hypotheses can be clinically tested. These studies might define strategies either to avoid or reduce adverse exposures, to identify genetic susceptibility far in advance of clinical disease, to identify appropriate treatment regimes, and to take special precautions for people at high risk. SENTRNet's research infrastructure provides a means to create synergy between host/environmental interaction research advances and other S/E PRG priorities, including population studies, prevention, patient/provider education, therapy and therapeutic targets, markers and molecular profiling, and preclinical models.

Technologies for Screening/Surveillance. Although endoscopic visualization and biopsy offer the potential for early detection, existing methods are not cost effective. Advances in imaging technology and molecular biopsy characterization have the potential to improve risk stratification, and the development of serum assays can make population-based screening possible. However, such advances have typically been suggested in single-center studies without rapid translation into more definitive, multi-center investigations that would be necessary to define the risks and benefits of these technologies. Current funding mechanisms through NCI or NIDDK do not match the developmental potential of these new technologies, nor do they provide for adequate comparisons between novel and existing approaches that have a direct impact on patient care and the public's health.

SENTRNet will dramatically improve the rapid translation of research observations

into clinical and public health interventions. Collaborations among SENTRNet's clinical research centers, translation laboratories, pathology center, and analytic center can collectively offer what is not possible now. The collaborations can develop a menu of markers for stomach and esophageal cancers and their precursor states. They can conduct multicenter, multidisciplinary studies for validation of existing and novel biomarkers. Finally, they can provide specified standards of performance for tissue and blood collections, quality control, database tracking, prioritization, and specimen distribution.

SENTRNet clinical research centers also can develop, compare, and validate novel imaging techniques, including ultrathin endoscopes, colorimetric devices, optical detection of dysplasia, autofluorescence, Raman spectroscopy, light-scattering spectroscopy, and synchronous luminescence. These devices can have a profound impact on identifying the true incidence of both esophageal and gastric cancers by identifying patients at risk for the disease and interrupting such conditions as the "dysplasia-carcinoma" sequence far in advance of cancer. As serum markers become available, SENTRNet's virtual tissue and serum repository will provide the best means available to rapidly validate and compare them to imaging and tissue-based markers in phase III studies. SENTRNet's components will allow for the rapid comparison of endoscopic, imaging, and molecular risk stratification for translation to improved patient care in phase IV studies. SENTRNet is the only potentially available vehicle by which imaging and molecular screening and surveillance can be evaluated in definitive biomarker studies to demonstrate reduction in mortality in patients who have stomach and esophageal cancers.

Preclinical Models. Valid preclinical models of gastroesophageal carcinogenesis

can facilitate the achievement of many S/E PRG priorities. However, esophageal and gastric tumor models face many challenges, which have been discussed previously. In spite of these challenges, there have been limited successes in animal models. These include transgenic and knockout mice with alterations in APC, SMAD-4, TFF-1, TGF-beta 1, RUNX3, CDX 2 cyclin D1 and EGFR, as well as animal models of *H. pylori* infection, Barrett's esophagus, and esophageal adenocarcinoma, and primary cell cultures of Barrett's esophagus.

SENTRNet can work with NCI's Mouse Models of Human Cancer Consortium to create robust mouse models, using hybrid techniques (genetic approaches, surgery, *H. pylori* infection) to define underlying molecular mechanisms of esophageal or gastric carcinogenesis, as well as to allow for preclinical evaluation of novel chemoprevention and therapeutic agents. Additionally, SENTRNet can develop and characterize primary cells, immortalized cells, transformed cells, organ cultures, and organotypic cultures for studying stem-cell biology, intestinal metaplasia, and cancer in esophagus and stomach, as well as develop immunocompetent rodent models of advanced disease. SENTRNet also can define the genetic factors that regulate epithelial cell responses to injury that lead to esophageal and gastric cancers, but which are difficult to study directly in humans.

Conclusion

The S/E PRG has identified 10 recommendations essential to making progress in understanding and treating stomach and esophageal cancers. The best approach to achieve those recommendations is through a multi-institutional and multidisciplinary group employing unique strategies to enhance effectiveness, collaboration, and quality in a translational research enterprise

that fluidly moves advances between the lab, the clinic, and the population. SENTRNet is necessary to advance the scientific priorities of the S/E PRG.

References

¹Ferlay J, Bray F, Pisani P, Parkin DM. GLOBOCAN 2000: Cancer incidence, mortality, and prevalence worldwide; ed Version 1.0, International Agency for Research on Cancer Press, 2001, vol 2002.

²Jemal A, Thomas A, Murray T, Thun M. Cancer statistics, 2002. *CA Cancer J Clin* 2002; 52:23–47.

³Ries LAG, Eisner MP, Kosary CL, Hankey BF, Miller BA, Clegg L, Edwards BK. *SEER Cancer Statistics Review, 1973–1999*. Bethesda, MD: National Cancer Institute, 2002.

Appendix A

About the National Cancer Institute's Progress Review Groups

Appendix A: About the National Cancer Institute's Progress Review Groups

The National Cancer Institute (NCI) supports basic, clinical, and population-based research to elucidate the biology, etiology, early detection, prevention, and treatment of cancers of various organ sites. These research efforts have produced a substantial base of knowledge that, while providing a wealth of new scientific opportunities that can further advance our knowledge and progress against these diseases, also requires that the Institute determine the best uses for its resources.

To help ensure the wise use of resources, NCI has established Progress Review Groups (PRGs) to assist in assessing the state of knowledge, reviewing the Institute's research portfolio, and identifying scientific priorities and needs for its large, site-specific research programs.

CHARGE TO THE PRGS

Each PRG is charged to:

- Identify and prioritize scientific research opportunities and needs to advance medical progress against the cancer(s) under review.
- Define the scientific resources needed to address these opportunities and needs.
- Compare and contrast these priorities with the current NCI research portfolio.
- Prepare a written report that describes findings and recommendations.
- Discuss a plan of action with NCI leaders to ensure that the priority areas are addressed.

The following section details the process used to execute these charges.

THE PRG PROCESS

PRG members are selected from among prominent members of the scientific, medical, and advocacy communities and from industry to represent the full spectrum of scientific expertise required to make comprehensive recommendations for the NCI's cancer research agenda. The membership is also selected for its ability to take a broad view in identifying and prioritizing scientific needs and opportunities that are critical to advancing the field of cancer research.

The leadership of each PRG finalizes an agenda and process for a PRG Planning Meeting. At the Planning Meeting, participants are identified to take part in a subsequent Roundtable meeting. Topics are identified for Roundtable breakout sessions to which participants will be assigned and for which the PRG members will serve as co-chairs.

A PRG Roundtable brings together in an open forum approximately 100–180 leading members of the relevant cancer research, medical, industry, and advocacy communities to formulate key scientific questions and priorities for the next 5–10 years of research on specific cancers. As part of the process, the NCI provides the PRG Roundtable with an analysis of its portfolio of cancer research in the relevant organ site. This analysis is intended to enable the Roundtable to compare and contrast identified scientific priorities with the research currently being done under the Institute's auspices. Input from the Roundtable is used by the PRG in delineating and prioritizing recommendations for research, related scientific questions, and resource and infrastructure needs. At its discretion, the

PRG may solicit additional input from the research and advocacy communities through workshops, ad hoc groups, or by other means. The PRG also may consider the deliberations of previously convened expert groups that have provided relevant cancer research information.

THE PRG REPORT

After the Roundtable, the PRG's recommendations are documented in a draft report, multiple iterations of which are reviewed by the PRG leadership and PRG members. The final draft report is then submitted for deliberation and acceptance by the NCI Advisory Committee to the Director. After the report is accepted, the PRG meets with the NCI Director to discuss the Institute's response to the report, which

is widely disseminated and integrated into the Institute's planning activities. At this meeting, the PRG and NCI identify the research priorities that ongoing NCI initiatives and projects do not address. Then the PRG and NCI discuss a plan for implementing the highest research priorities of the PRG. This plan becomes a blueprint for tracking and hastening progress against the relevant cancer.

PRG reports on breast cancer; prostate cancer; colorectal cancer; pancreatic cancer; lung cancer; brain tumors; leukemia, lymphoma, and myeloma; gynecologic cancers; and kidney/bladder cancers, in addition to this PRG report on stomach/esophageal cancers are available online at <http://planning.cancer.gov>.

Appendix B
Breakout Reports

Guiding Principles Biology

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Overview/Background Information/Barriers

The biology of squamous and columnar epithelia is of critical importance in understanding their transition to stomach and esophageal cancers. The carcinogenic process is driven by three main influences: (1) an injurious chemical or infectious agent; (2) host factors that modulate the response to the injurious agent(s), such as immune responses (IL-1 beta), protective molecules (MUC-1), and adhesion molecules (E-cadherin); and (3) environmental factors that determine the host response to the carcinogenic agents. The carcinogenic process appears to be closely related to chronic active inflammation, which may lead to a neoplastic or a nonneoplastic outcome.

Gastroesophageal carcinogenesis consists of a series of events that can be viewed as those that initiate and subsequently mediate genetic changes within epithelial cell DNA. These genetic changes then provide a survival advantage for affected cells, resulting in malignancy. An underlying theme that unifies stomach and esophageal cancers is that both develop in response to chronic inflammation or injury. Another common theme, exclusive of initiating factors that may not always be identifiable, is that the mediation of disease progression may be via inflammation-induced DNA damage, due to the production of superoxide radicals and other products of oxidation.

Described below are some of the molecular and cellular changes triggered by infection with the bacterium *H. pylori*. These will be used as a model to explore other pathways of carcinogenesis in the esophagus and stomach that occur within the context of inflammatory states. The example of *H. pylori* infection provides a paradigm of a known initiator that, through induction of an inflammatory response, leads to neoplastic transformation.

Gastric adenocarcinoma is the second leading cause of cancer mortality worldwide. Infection with *H. pylori* significantly increases the risk of the two predominant histologic subtypes of gastric adenocarcinoma. The more common type is intestinal-type gastric cancer. The other form is diffuse gastric cancer, which originates within a background of superficial gastritis and may occur spontaneously without well-defined glandular structures. Intestinal-type gastric cancer progresses through well-defined histologic steps, including atrophic gastritis, intestinal metaplasia and dysplasia, which are followed by frank adenocarcinoma. The first stage is the transition from normal mucosa to chronic superficial gastritis.

The relationship between *H. pylori* infection and gastric cancers stems from interactions between the bacterium and the host. Some of the genetic components of *H. pylori* that increase the risk of cancer include the *cag* pathogenicity island and the vacuolating

cytotoxin VacA, the effects of which are less well understood. Components of the *cag* pathogenicity island induce (1) increased release of the proinflammatory cytokine IL-8, and (2) profound morphologic derangements of gastric epithelial cells following bacterial attachment. The molecular pathways that underlie these events are (1) activation of NF kappa B and MAP kinase signaling; and (2) translocation of the CagA protein into the host cell, which induces the morphologic derangements of the cells themselves. The latter phenotype mirrors mitogenic stimulation with growth factors. More virulent strains of *H. pylori* (e.g., *cag*-positive strains) may increase the risk of cancer by inducing a more intense inflammatory response and by mimicking the effects of growth factor stimulation.

Host polymorphisms within immune-response genes, including IL-1-beta and TNF-alpha, also influence disease risk. Specifically, the IL-1 gene cluster contains several informative polymorphisms that can be correlated with either increased or decreased IL-1-beta production. Studies have shown that persons who possess polymorphisms associated with high levels of IL-1-beta production have an increased risk of atrophic gastritis and gastric cancer, but these relationships only hold sway in *H. pylori*-infected persons. Therefore, a synergism exists between *H. pylori* infection and host genotype. A consequence of long-term *H. pylori* infection is the development of hypochlorhydria, which allows the overgrowth of non-*H. pylori* pH-sensitive bacteria, conversion of ingested nitrites to N-nitrosamines, and an increased risk of gastric cancer.

Chronic *H. pylori* infection also leads to hypergastrinemia, which can stimulate epithelial cell growth. Thus, multiple factors contribute to the survival of the mutagenic cell in an environment of genetic instability: hyperproliferation in the presence of

inflammation, and production of oxygen-free radicals that induce DNA damage over time. Animal models may mimic aspects of the process that occur in humans. For example, after *H. pylori*-induced inflammation, intestinal metaplasia may result from overexpression of *Cox-2* (in mice), which hastens the progression from atrophic gastritis to intestinal metaplasia. Other mediators of intestinal-type gastric cancer include exogenous causes of hypochlorhydria and hypergastrinemia, such as vagotomy and acid-suppression therapy.

The paradigm for *H. pylori*-induced inflammation in the stomach can also be applied, in principle, to esophageal squamous cancer and adenocarcinoma, although the initiating factors are distinctly different. The initiators of squamous cancer include achalasia, which results in stasis of ingested food; infection with human papillomavirus (HPV); and environmental factors such as high alcohol intake, smoking, and lye ingestion. Genetic risk factors also play a role in squamous carcinoma, including the inherited disorder, tylosis, which results in squamous cell hyperproliferation. The initiation of esophageal adenocarcinoma is primarily through reflux esophagitis-induced Barrett's metaplasia.

Strategies for cancer protection include removal of the initiating events (where identified) and/or inhibition of one or more of the inflammatory mediators, such as *Cox-2*, IL-1, and/or NF kappa B activation. However, these relationships are complex, because while infection with *H. pylori* increases the risk of distal gastric cancer, it may protect against the development of esophageal adenocarcinoma. This complexity underscores the importance of precisely identifying the mechanisms through which inflammation can induce the carcinogenic cascade.

Future Research Directions

Future research in stomach and esophageal cancers should include the following:

- Identification and appropriate eradication (where possible) of initiating factors.
- Identification of novel means to suppress the inflammatory response. For example, inhibition of NF kappa B activation may be an important strategy for cancer prevention, either by disrupting the inflammatory process or normalizing imbalances in cell-cycle dynamics.
- Suppression of the hyperproliferative response, irrespective of its initiating and mediating events.
- Identification of additional strain-specific *H. pylori* virulence determinants, which may in turn identify persons at increased risk for gastric cancer.
- Identification of specific bacterial strains in conjunction with a particular host background to allow focused therapeutic interventions, rather than indiscriminately treating all persons who are colonized with *H. pylori*, because in some persons the bacterium may protect against the development of esophageal adenocarcinoma.
- Identification of biomarkers in Barrett's metaplasia to serve as predictors of cancer risk.
- Characterization of the biology of Barrett's metaplasia as it relates to its origination and protection against reflux-induced esophageal injury.
- Establishment of animal models to study the pathogenetic pathways for both squamous and adenocarcinoma of the esophagus.

Three Scientific Priorities and Rationales

Priority 1: Define the genetic bacterial and host factors that regulate epithelial cell responses to injury that lead to esophageal and gastric cancer.

Rationale: It is essential to understand the underlying genetic factors and molecular mechanisms that regulate progression to cancer, because only a minority of patients with identifiable risk factors progress to develop esophageal or gastric cancers. For gastric carcinoma, *H. pylori* genotypes that may augment the risk of neoplastic transformation need to be identified. This will help identify specific patient cohorts for screening and treatment in the future.

Priority 2: Define the environmental and host factors that regulate inflammatory responses to epithelial cell injury in esophageal and gastric mucosa that lead to cancer.

Rationale: There is increasing recognition that inflammatory responses play a central role in progression to cancer. In addition, targeting inflammation may be an effective method of preventing the development of malignancy.

Priority 3: Develop more relevant animal model systems for understanding upper GI carcinogenesis, including squamous and adenocarcinomas of the esophagus and stomach.

Rationale: Animal models are essential to understanding the development of gastric and esophageal cancers and identifying host-factor interactions that increase disease risk. Studies of these models are a key step in the process of translating basic research into more effective methods for screening and treatment.

Infrastructure Needed To Accomplish Priorities

Partnership Platforms

Gastric and esophageal cancers are a global problem and account for a high proportion of cancer deaths worldwide. International collaborations in high-prevalence populations will facilitate a more efficient and more complete understanding of the disease and the development of more effective interventions and treatments.

Partnership platforms for these studies include investigations of all age groups, including children (NICHD), immunologic studies (NIAID), and collaborative studies of basic biology, specimen collection, and development of screening and prevention (NIDDK). Specific recommended initiatives include:

- Multi-institutional funding initiatives
- Dual-investigator RO1's

- Development of SPORES—the establishment of tissue banks and cell lines that are available to all investigators.

Expected Resources To Overcome Limitations of Previous Research and To Capitalize on Existing Opportunities

- Development of gerbil and other animal models
 - Establish cell lines that represent normal cells as well as all stages of cancer progression
 - Develop specific reagents, such as antibodies, to be employed in gerbil studies
 - Establish *H. pylori* strain repositories
 - Establish tissue-specimen banks, including blood banks, to identify genetic factors, having as a goal the development of a nationwide tissue bank.

Etiology

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Overview/Background Information/Barriers

Non-cardia gastric adenocarcinoma, esophageal adenocarcinoma, and esophageal squamous cell carcinoma are each a distinct entity with its own uniquely identified causes. Although they share a superficial anatomical relationship, each is distributed in different populations in differing amounts.

Gastric cancer remains the second most common cancer worldwide, although a decline over the past 30–40 years has decreased the age-specific incidence of this cancer in most western countries by 50%. Due to the aging of the world's population, and a steep gradient in occurrence among the elderly, the actual numbers of victims are increasing. Efforts to improve treatment have had only limited success, and the age-specific decrease is likely attributable to decreased exposure to causal factors. Most prominent among these is infection by *H. pylori*, now identified as the strongest and most important risk factor.

Squamous cell carcinomas comprise the majority of esophageal cancers in the world, with the majority of cases occurring in developing countries. Areas of China, central Asia, and southern Africa have extremely high mortality, but with large variations in occurrence over short distances. In the U.S., the occurrence of squamous cell carcinoma is low by

comparison and has changed little in recent years. Many studies, but not all, have shown a correlation between the prevalence of esophagitis and esophageal squamous cell carcinomas, but the importance of esophagitis remains poorly defined.

The increased incidence of adenocarcinoma has been recognized since the mid-1980s. Gastroesophageal reflux is identified as a key risk factor: people with weekly reflux symptoms demonstrate a 5- to 8-fold higher risk of developing this cancer. Even more striking is that persons with Barrett's esophagus, estimated to develop in 10–15% of people with chronic reflux, are recognized as having at least 30–40 times the incidence as in the general population.

In considering major secular factors in cancer etiology and distribution, the following relationships are of interest:

- Fruits and vegetables (anti-oxidants) are protective in all three types of cancers. In the stomach, nearly 85% of studies have revealed a decreased risk of gastric cancer with a high intake of raw vegetables, and the evidence is similarly strong for the beneficial effects of citrus fruit. The preventive effect of fruit and vegetable intake is also strong in esophageal cancer. A strongly reduced risk of squamous cell carcinoma has been reported along with intake of vegetables, fresh fruits, and vitamin C. Although the data are less plentiful, studies have also

identified an inverse relationship between fruit and vegetable consumption and esophageal adenocarcinoma.

- A review of literature through the early 1990s revealed no substantial effect of alcohol consumption on the risk of stomach cancers. By contrast, alcohol consumption has been identified as a major cause of squamous cell carcinoma. That cancer is more frequent in people who drink alcoholic beverages, with the risk depending more on mean daily intake than on the length of the habit. The risk of esophageal cancer returns to the level for abstainers only after 10 years without drinking alcohol. Alcohol consumption has no significant effect on the risk of adenocarcinoma.
- Smoking tobacco contributes to the risk of these cancers, with a 1.5–2.5-fold increase in the risk of stomach cancer among current smokers. Several studies have shown increasing risk with longer and heavier tobacco use. For squamous cell carcinoma, tobacco use is one of the major causative factors. The life-time duration of cigarette smoking is a significant variable. For adenocarcinoma, smoking increases the risk

that remains at its increased level until more than 20 years after smoking cessation.

- All three cancers are more common in men than in women.
- Low socioeconomic status correlates with increased frequency of all three cancers. The strength of this effect is strongest for squamous and weakest for adenocarcinoma.
- All three cancers are rare before the age of 50. Their incidence then rises with age but never reaches a plateau.
- In the U.S., gastric cancer is more common in non-whites than in whites. Squamous cell carcinoma occurs 6 times more frequently in blacks than in whites; adenocarcinoma occurs 5 times more frequently in whites than in blacks.
- The incidence of gastric and squamous cell carcinoma co-vary, while adenocarcinoma is often reciprocal in its occurrence.

A summary of many of these secular factors in cancer etiology appears in Table 1.

Table: Etiology-1

Risk/protective factor	Direction and Magnitude of the Association		
	Gastric (a)	Squamous	Adeno (a)
Fruits/vegetables	↓↓	↓↓	↓↓
Alcohol (b)	--	↑↑↑	--
Smoking	↑	↑↑↑	↑↑
Male sex (c)	↑	↑↑	↑↑↑
Low Socioeconomic Status	↑↑↑	↑↑↑	↑
Age (d)	↑↑↑	↑↑↑	↑↑↑
Ethnicity (e)			
Black	↑↑	↑↑↑	↓↓↓
Hispanic	↑↑	--	--
Asian	↑↑↑	↑↑	↓↓↓
Native American	↑↑	Unknown	Unknown

- (a) Excludes cardia.
- (b) There may be an inverse association with wine.
- (c) Squamous and adeno may be closer.
- (d) Over age 50, no plateau with age, typical of epithelial cancer.
- (e) Compared with whites.

Three Scientific Priorities and Rationales

Priority 1: Identify and explore the relationship of *H. pylori* to gastric cancer and esophageal adenocarcinoma in terms of physiology, premalignant lesions, and interaction with other factors (e.g., age of acquisition, strain differences, ethnicity, host susceptibility, and exogenous exposures).

Rationale: There is a wide body of evidence that *H. pylori* is the single most important risk factor identified for gastric cancer; however, because of its high prevalence, it is clearly not sufficient to explain these cancers. Therefore, a deeper understanding of the steps from *H. pylori* acquisition to development of these cancers must be determined, including the relationship with modifying factors.

Conversely, there is preliminary evidence that the presence of *H. pylori* is associated with protection against adenocarcinoma of the esophagus and precursor lesions. This point needs clarification because the implications are opposite to those for gastric cancer.

Priority 2: Identify the causation, normal variation, and pathophysiologic consequences of reflux, and its interrelationship with BMI, fat distribution, and other factors in the development of esophageal and gastric cardia adenocarcinomas and their precursors.

Rationale: There is a wide body of evidence that reflux and anthropometric measures are very important risk factors for adenocarcinoma of the esophagus. Despite this importance, our knowledge base is insufficient. There are important

definitional questions and questions about natural history and mechanisms.

Priority 3: While independent etiologic factors have been identified in the development of esophageal and gastric cancers and their precursors, the priority is to understand how these factors interact in affecting the disease continuum and explaining patterns of incidence in the population.

Rationale: Existing evidence suggests that these cancers are multifactorial diseases, and reliance on approaches directed toward single risk factors are unlikely to be sufficient to provide a complete explanation of etiology.

Infrastructure Needed To Accomplish Priorities

Partnership Platforms

Large, collaborative cohort studies could be coordinated through such agencies as NCI and NIDDK.

Expected Resources To Overcome Limitations of Previous Research and To Capitalize on Existing Opportunities

- Investment in/improvement of databases with emphasis on enrollment of minority populations
- Archival specimen and tissue banking

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Overview/Background Information/Barriers

Many molecular alterations have been described in gastric and esophageal carcinogenesis. The genetic features of these cancers can potentially be used to develop ways of assessing risk, improving detection, identifying prognostic markers, and stratifying therapies. However, such advances will require careful prioritization of strategies in order to discover and validate both inherited and acquired molecular alterations in these cancers and their precancerous states. Three research areas adequately describe approaches to advancement in this field: laboratory research, technology, and goal setting. Each area is described in detail below.

Laboratory Research

The first area—laboratory research into the genetics of gastric and esophageal cancers— involves investigation into several categories of genetic alterations. For example, genetic instability is a hallmark of cancer. This category of abnormality includes two subcategories: chromosomal instability (aneuploidy) and deficient DNA mismatch repair (microsatellite instability). This latter mechanism involves targets that occur downstream in the pathway of disordered mismatch repair, such as TGF-beta1 RII, *MSH-3*, *MSH-6*, *BAX*, and *ActRII*. Genetic activation also involves several mechanisms, such as point mutation and DNA ampli-

fication. Examples of genes activated in gastric and/or esophageal cancers include *c-myc*, *c-erbB-2*, and those encoding cyclin D and EGF-R. DNA amplification occurs at the chromosomal loci 7q, 17q, and 20q. Inactivation, another category of genetic alteration, is exemplified by E-cadherin, p53, p16, *APC*, *hMLH1*, and by genetic loci showing allelic loss, such as 4q, 5q, 8p, 9p, 17p, 18p, and 18q. Mechanisms of gene inactivation include point mutation, allelic loss, and hyper-methylation. For example, hyper-methylation of the *hMLH1*, E-cadherin, and *APC* genes has been reported in gastric epithelia and tumors (Tamura et al., *JNCI*, 2000; Fleisher, A.S. et al., *Cancer Research*, 1999, *Oncogene*, 2000; Tamura et al., *Oncogene*, 2000). Finally, further research is needed on altered gene expression in order to establish the clinical or biological significance of global gene expression patterns as well as to advance understanding of the role of aberrant expression of individual genes. Genes already known to be important in these cancers include those encoding Cox-2, iNOS, growth factors and their receptors, and the proline-rich differentiation gene esophagin.

Another important area of laboratory research is studying the molecular genetics of gastric and esophageal cancers to distinguish hereditary from somatic gene alterations. Although most abnormalities that have been described are somatic, some are altered in the germ line. One prime

example of germ line alteration is E-cadherin in familial gastric cancer. Similar alterations in germ line abnormalities of esophageal cancer still need to be investigated.

Finally, laboratory research is also needed to assess the role of infection on the advent of gastric, esophageal adenocarcinoma, and esophageal squamous cancers. For example, *H. pylori* infection is very common, yet less than 2% of those infected ultimately develop gastric cancer. El-Omar, et al. (*Nature*, 2000) determined that common polymorphisms that exist in the population for the Interleukin I (IL-1) gene strongly influence, either positively or negatively, the gastric response to *H. pylori*. Other studies in Portugal and UK/Poland have confirmed and extended this concept for TNF- α , IL-10, and the IL-1 receptor. Thus, the pro/anti-cancer risk is related not only to the type of bacterium, but to the genetically determined response to the bacterium.

Technology

Technological advances, the second research area to advance gastric and esophageal cancers, have changed both basic research and clinical investigation. Some techniques have been perfected, while others have only recently been developed, but all deserve consideration as emerging approaches to the genetic understanding of gastric and esophageal cancers. These technologies include genomics, proteomics, bioinformatics, flow cytometry, immunohistochemistry, comparative genomic hybridization (CGH), single nucleotide polymorphisms (SNPs), fluorescent *in situ* hybridization (FISH), microarray, DNA mutational screening, imaging technologies (e.g., endoscopic/whole body), methylation discovery platforms, and systems biology approaches (i.e., multidisciplinary integration). For example, bioinformatics studies based on cDNA microarray data

suggest that esophageal cancers and their premalignant precursor lesions can be accurately diagnosed based on molecular phenotyping (Selaru et al., 2002; Xu et al., 2002).

A second technologic advance, instabilotyping, has been used to show that gastric and other cancers have a unique profile of mutations. This technique has also resulted in the discovery of several novel candidate tumor suppressor genes (Mori et al., 2001; 2002).

One technology in particular, SNPs, can be used to assess risk of upper gastrointestinal cancers. Although studies of risk related to SNPs have been limited, SNPs hold promise as potential risk factors themselves and as factors that influence environmental exposures. SNPs under study include those for carcinogen activation (P450s) and metabolism (glutathione *s*-transferase), nutrient metabolism (folate, selenium, and proteins), and alcohol metabolism.

Goal Setting

Goal setting defines the third research area and qualifies as an approach to advance the understanding of gastric and esophageal cancers by focusing investigation and generating collaborations. In particular, the discovery of new genes and biomarkers should be emphasized and priorities set for their further study. The function of novel genes should be determined by using *in vitro* and *in vivo* models. Noninvasive or minimally invasive “bedside” assays need to be developed in order to translate bench discoveries to the clinic. Importantly, putative or potential genetic markers must be validated, because the clinical utility and “generalizability” of these markers have not been definitively established. These markers need to be assessed for clinical utility, technical reliability, translation into high throughput assays, and recognition of their general importance in other cancers.

Future Research Directions

Gastric, esophageal Adenocarcinoma, and esophageal Squamous (GAS) cancers are relatively underresearched, are much more lethal than other cancers, have had relatively fewer candidate genes identified, and have had fewer opportunities for intellectual sharing than have other types of cancer. Only a small portion of the genome has been investigated, and the identified genes have not been translated to the clinic. Current funding for these cancers has not provided sufficient incentives for sharing resources across disciplines and institutions. Traditional funding mechanisms have encouraged single-center academic institutional studies, thereby limiting community patient enrollment and participation. Therefore, a novel guiding principle to address these needs is proposed:

VIDA: Validate, Identify/Discover, and Adapt.

To form a large, multi-institutional, trans-disciplinary, patient-centered, academic and community-based consortium of basic, translational, and clinical investigators to achieve the following priorities in gastric, esophageal adenocarcinoma, and squamous esophageal (GAS) carcinogenesis.

Three Scientific Priorities and Rationale for Each

Priority 1: Validate genetic alterations in GAS neoplasia.

Rationale: In GAS and their precursor conditions, no previously identified genetic alterations of early detection, prognostic, or diagnostic biomarkers have been reliably validated. Currently, validation strategies have been predominantly applied to small, geographically localized patient populations. Current technology permits following subjects endoscopically and longitudinally, so the clinical significance of genetic and

epigenetic alterations in GAS malignant and premalignant lesions can be determined.

Priority 2: Identify and discover novel genes and biomarkers in GAS neoplasia.

Rationale: In GAS cancers and their precursor conditions, little is known of the genome for genetic and epigenetic abnormalities. The majority of alterations remains to be discovered. This situation stands in stark contrast to that in other cancers, where many more viable candidate genes have already been identified and characterized. Moreover, many of the candidate genes identified in other cancer types have been found to be uninvolved or clinically insignificant in GAS lesions. A broader palette of genetic alterations and candidate genes in GAS neoplasia would not only increase the basic understanding of these diseases but also yield potential biomarkers for validation and adaptation (priorities 1 and 3).

Priority 3: Adapt current and future technologies and biomarkers to the clinical arena.

Rationale: In GAS cancers and their precursor lesions, both current and future markers must be clinically measurable. One unique advantage of GAS premalignant tissues is that they remain *in situ*, in contrast to preneoplastic lesions arising in other organ systems. Thus, proposed technologies and biomarkers should utilize this unique advantage.

Infrastructure Needed To Accomplish Priorities

Partnership Platforms

A SWOG-like structure needs to be formed as an incentive to cross-institutional and cross-disciplinary fertilization and collaboration in GAS studies. This structure, known as VIDA (Validation, Isolation,

Discovery, and Adaptation), would be composed of a large network of gastroenterologists, epidemiologists, pathologists, bioinformaticists, and experts in other appropriate disciplines. VIDA's purpose would be to promote large-scale cooperation, patient enrollment, and biomarker validation.

Expected Resources To Overcome Limitations of Previous Research and To Capitalize on Existing Opportunities

- A specified line item, Southwest Oncology Group-like, cooperative group mechanism for this consortium of gastroenterologists and other specialists studying GAS neoplasia.
- Cooperative mechanisms that produce incentives for sharing of resources among community-based or academic investigators. GAS carcinogenesis is uniquely suited to make use of this mechanism because of the ability to serially access these lesions longitudinally, as well as with detailed spatial mapping, to improve the understanding of neoplastic progression in these diseases.
- Research strategies devolving from this GAS human model may be applicable to cancers arising in other organ sites.

References

¹Tamura G, Yin J, Wang S, Fleisher AS, Zou T, Abraham JM, Kong D, Smolinski KN, Wilson KT, James SP, Silverberg SG, Nishizuka S, Terashima M, Motoyama T, Meltzer SJ. E-Cadherin gene promoter hypermethylation in primary human gastric carcinomas. *J Natl Cancer Inst.* 2000; 92(7):569–573.

²Fleisher AS, Esteller M, Wang S, Tamura G, Suzuki H, Yin J, Zou TT, Abraham JM, Kong D, Smolinski KN, Shi YQ, Rhyu MG, Powell SM, James SP, Wilson KT, Herman JG, Meltzer SJ. Hypermethylation of the

hMLH1 gene promoter in human gastric cancers with microsatellite instability. *Cancer Res.* 1999; 59(5):1090–1095.

³Tsuchiya T, Tamura G, Sato K, Endoh Y, Sakata K, Jin Z, Motoyama T, Usuba O, Kimura W, Nishizuka S, Wilson KT, James SP, Yin J, Fleisher AS, Zou T, Silverberg SG, Kong D, Meltzer SJ. Distinct methylation patterns of two APC gene promoters in normal and cancerous gastric epithelia. *Oncogene* 2000; 19(32):3642–3646.

⁴Selaru FM, Zou T, Xu Y, Shustova V, Yin J, Mori Y, Sato F, Wang S, Oлару A, Shibata D, Greenwald BD, Krasna MJ, Abraham JM, Meltzer SJ. Global gene expression profiling in Barrett's esophagus and esophageal cancer: a comparative analysis using cDNA microarrays. *Oncogene* 2002; 21(3):475–478.

⁵Xu Y, Selaru FM, Yin J, Zou TT, Shustova V, Mori Y, Sato F, Liu TC, Oлару A, Wang S, Kimos MC, Perry K, Desai K, Greenwald BD, Krasna MJ, Shibata D, Abraham JM, Meltzer SJ. Artificial neural networks and gene filtering distinguish between global gene expression profiles of Barrett's esophagus and esophageal cancer. *Cancer Res.* 2002; 62(12):3493–3497.

⁶Mori Y, Yin J, Rashid A, Leggett BA, Young J, Sims L, Kuehl PM, Langenberg P, Meltzer SJ, Stine OC. Instabilotyping: comprehensive identification of novel cancer-related genes by large-scale probing for mutations in coding region microsatellites. *Cancer Res.* 2001; 61(16):6046–6049.

⁷Mori Y, Sato F, Selaru FM, Oлару A, Perry K, Kimos MC, Tamura G, Matsubara N, Wang S, Xu Y, Yin J, Zou T-T, Leggett B, Young J, Nukiwa T, Stine OC, Abraham JM, Shibata D, Meltzer SJ. Instabilotyping reveals novel unique mutational spectra in microsatellite-unstable gastric cancers. *Cancer Res.* 2002; 62(13):3641–3645.

Imaging/Technologies

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Overview/Background Information/Barriers

There is a dramatic, ongoing increase in the incidence of adenocarcinoma of the esophagus and gastric cardia. For both tumors, precursor lesions have been identified and are identifiable endoscopically. In the past 20 years, remarkable advances in imaging and technologies in esophageal and gastric cancers have occurred. Advances in endoscopic technology, non-endoscopic optical imaging techniques, radiological techniques, and other new technologies provide opportunities to affect the course of esophageal and gastric cancers.

Advances in endoscopy include new ultrathin endoscopes capable of being used clinically without sedation. New high-magnification endoscopes with or without the use of exogenous dyes (chromoendoscopy) provide high-resolution images of gastrointestinal mucosa, which correlate, in many cases, with histopathological diagnosis. New endoscopic staging technologies have advanced in just the past 10 years to become the state-of-the-art for esophageal and gastric cancers. Endoscopic ultra-sonography (EUS), which combines the benefits of medical ultrasound with the access of endoscopy, provides unparalleled imaging and staging accuracy. The advent of EUS-guided fine needle aspiration provides a tissue diagnosis in the case of metastatic regional lymph nodes in patients with esophageal and gastric cancer. Adjuncts to

tissue cytopathology include immunocytochemistry and PCR amplification.

A number of studies have demonstrated the feasibility and safety of endoscopy, without sedation, using a variety of instruments including narrow diameter endoscopes. Early instruments were relatively unsatisfactory in terms of the resolution and illumination. Newer technology has made these small diameter instruments equivalent or nearly equivalent to standard endoscopes. However, the sensitivity and specificity of these instruments for the detection of Barrett's esophagus and cardia cancer is not fully established. At the same time, the technology has advanced more quickly than data can be accumulated from clinical trials, primarily because most published data from trials have been from single centers, both within and outside of the United States.

Another difficulty with using endoscopy without sedation is that expert endoscopists have not acquired all of the available screening data. It is not known whether this imaging method can be used by primary care physicians as an office-based procedure. This would require the development of additional cost-effective technology largely related to the processing and disinfecting of the instruments.

A number of high-resolution adjuncts to endoscopy are currently under development and are the focus of intense research. Referred to collectively as "optical biopsy,"

these techniques include laser-induced fluorescence spectroscopy, reflectance spectroscopy, light-scattering spectroscopy, trimodal spectroscopy, Raman spectroscopy, optical coherence tomography, and confocal microendoscopy. The precursor for esophageal and cardia cancers is one proposed target for imaging by these highly advanced techniques. Preliminary reports suggest that one or more of these imaging techniques may be capable of detecting mucosal dysplasia. This could have a profound impact on the incidence of both esophageal and gastric cancers by identifying patients at risk for the disease and interrupting the “dysplasia-carcinoma” sequence.

High-resolution spiral computed tomography scans, magnetic resonance imaging, and FDG-Positron Emission Tomography (PET) scanning represent nonendoscopic advances in imaging. The latter technology may rival the sensitivity and specificity of EUS as a staging tool for patients with advanced disease. With the use of neoadjuvant therapy, assessment of response has been very important. However, the conventional imaging modalities are quite limited in prediction of response to therapy or in monitoring therapy. PET with Flourine-18-fluoro-2 deoxy-D-Glucose (FDG), which localizes rapidly to many human cancers following intravenous injection, has been shown to have potential for use in this setting.

Contrast agents have the potential to be a powerful adjunct to current radiological imaging techniques. Contrast agents under development for use in conjunction with nuclear and magnetic resonance imaging are capable of quantifying tissue metabolic processes, angiogenesis, apoptosis, hypoxia, receptors, enzymes, and the degree of cellular proliferation. Stomach and esophageal cancers offer a unique opportunity, because oral delivery of contrast agents is possible to target molecular markers expressed on

precancerous and cancerous cells. Capsule “endoscopy” is the newest non-endoscopic, non-radiological imaging technique capable of imaging the stomach. Sometimes referred to as a “remote” or “wireless” endoscopy, the system is a pill-sized unit containing a camera, battery, and telemetry unit. Images from within the GI tract are transmitted to a receiver worn as a harness by the patient. Currently in development, advanced capsule devices are capable of real-time imaging and propulsion within the stomach so that a complete gastric examination may be performed.

Three Scientific Priorities and Rationales

Priority 1: Develop and implement improved screening modalities that do not require sedation for esophageal and gastric cancers.

Rationale: Available data from studies indicate that a screening endoscopy without sedation is well-tolerated and acceptable to patients. However, these studies also indicate that as many as 40% of patients decline to undergo unsedated screening endoscopy. This problem needs to be addressed through the development of improved screening modalities and educational programs for physicians and patients. Ultimately, screening of large patient populations for esophageal and gastric cancers will enable improved identification of the risk factors associated with progression to cancer, and a better understanding of the molecular, biochemical, and morphological changes associated with the progression or regression of esophageal and gastric cancers.

Priority 2: Develop improved imaging techniques and contrast agents specific to stomach/esophageal cancers.

Rationale: Using imaging, it is possible to define a signature of cancerous and

precancerous cells. Various optical imaging techniques are in development for imaging stomach and esophageal cancers; these include trimodal spectroscopy, optical coherence tomography, and confocal microendoscopy. In the future, clinical comparisons and evaluations will need to be conducted. Due to cost and the high level of technology required, it will be necessary to partner with industry to continue the development of suitable instruments and equipment.

Priority 3: Develop and evaluate imaging techniques to define or predict responses to new therapies.

Rationale: Using imaging, it is possible to predict therapeutic response soon after initiating therapy or to tailor dosimetry to the physiology of the individual patient to optimize its effectiveness. Early diagnosis will avoid the morbidity and expense associated with ineffective treatments. As new therapies evolve, innovative probes and techniques would be adopted for monitoring therapy.

As examples:

- In the case of esophageal cancer, persistent FDG uptake in a lesion after treatment with radiation could represent either residual tumor or inflammation induced by radiation. Development of an agent to distinguish between these states would be a major advance.
- Local and systemic disease evaluation. Specifically, the use of PET with FDG (or new radiotracers) as a tool to evaluate the effectiveness of new therapeutic strategies.
- Local disease evaluation. Optical techniques such as Optical Coherence Tomography (OCT), which provides cross-sectional images of tissues *in situ*,

may have application in a specific group of patients in a similar way that PET is currently being used.

- Imaging can be used to define doses of therapeutic agents. For example, optical techniques can be used to define therapeutic doses of agents for photodynamic therapy based upon the activity of the optical agent. Therapeutic drugs can be labeled with optical or nuclear probes, and the pharmacokinetics of uptake and biological effect can be quantified prior to determining the dosing of the therapeutic agent.

Infrastructure Needed To Accomplish Priorities

Partnership Platforms

- Partnerships must be developed between the various groups developing imaging techniques and applying them.
- Individuals developing optical probes and agents (in gastroenterologists and engineers) need to partner with radiologists and imaging scientists in developing CT, MRI, and PET techniques and probes.

Expected Resources To Overcome Limitations of Previous Research and To Capitalize on Existing Opportunities

- Current advances in imaging have been largely due to ad hoc collaborations between physician scientists and physicist/engineers. Such interdisciplinary collaborations should be encouraged.
- Establish and fund imaging centers of excellence for laboratory and clinical research.
- Foster interdisciplinary research by creating RFAs that support research

conducted by collaborations between radiologist/molecular biologists, gastrointestinal endoscopists/engineers, and/or applied physicists and other scientists.

- Support the training and education of patients and physicians regarding the benefits of screening for precursors of esophageal and gastric cancers in patients at risk for the disease.
- Encourage increased collaboration between scientists in academia and industry in the development of imaging instrumentation and probes. One method to encourage such collaboration is through the SBIR/STTR grant mechanisms.

Outcomes/Education/Communication/Quality of Life

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Overview/Background Information/Barriers

Each year in the United States, there are 21,600 new cases of gastric cancer and 12,400 deaths. Survival rates for esophageal cancer are worse, with 13,100 new cases annually and approximately 12,600 deaths. While studies of diagnosis and treatment have focused on the traditional outcomes of disease-free survival and tumor progression, there have been few studies focusing on patient-centered outcomes directed toward health-related quality of life (HRQoL), patient care experiences, symptom management, and total economic burden. Education for the public and professional sectors regarding both cancers in regard to their presenting symptoms, interventions, and treatment options has been inadequate. Furthermore, since many patients are diagnosed in late stages of stomach and esophageal cancers, there are virtually no outcome studies in patients identified in premalignant phases.

There is an increased symptom burden resulting from both disease and treatment in advanced stages of stomach and esophageal cancers. Currently, only two well-validated disease-specific instruments exist for measuring HRQoL in stomach and esophageal cancers: the EORTC QLQ-C30 instrument and the FACT-Gastric and FACT-Esophageal instruments. The European Organization for Research and Treatment of

Cancer (EORTC QLQ-C30) consists of a core module covering physical, emotional, and social aspects, accompanied by a disease-specific set of questions for esophageal (OES24 module) and gastric (STO 22 module) cancers. The Functional Assessment of Cancer Therapy – General (FACT-G), the U.S. counterpart to the EORTC, addresses both generic and disease-specific issues. The disease-specific issues are investigated through the esophageal and gastric subscales. For both instruments, the general components are relevant to a broad range of patients with cancer. Both instruments have provided rich information in the general core areas through a large number of studies. However, few studies have used these instruments in patients with stomach and esophageal cancers, so disease-specific information on HRQoL is severely lacking. Additionally, HRQoL issues, including the ability to perform activities of daily living, to work, and to attend school, as well as common symptoms resulting from disease and treatment have not been among outcome variables in large-scale clinical trials and observational studies.

Currently, a range of validated symptom identification and management instruments exists for measuring pain, nausea, fatigue, anxiety, depression, and dysphagia, but none of these instruments has been studied specifically for stomach and esophageal cancers. Nor do these instruments address differences in terms of ethnicity, culture,

race, gender, or health literacy, which would potentially influence responses to HRQoL questions. These instruments have generally been used in studies for palliative care as opposed to earlier stages of care, and they have been used for multiple cancer sites but not specifically for gastric and esophageal cancers. Additionally, these instruments have not been integrated into clinical trials and observational studies on a large-scale basis. Thus, little is known about symptom management for stomach and esophageal cancers.

A number of evidence-based interventions have been tested for the management of symptoms (e.g., pain, dysphagia) associated with disease and treatment of gastric and esophageal cancers. However, few clinical trials have employed these interventions in patients with these specific cancers. Additionally, a body of science building on HRQoL issues is nonexistent. Thus, information on best practice interventions and management of symptoms is lacking.

In terms of education, the evidence and consensus-based treatment guidelines for esophageal and gastric cancers have not been uniformly disseminated and implemented. Thus, the quality of care (QOC) varies widely by geographic region, socioeconomic level, and provider preferences. In addition, there has been a lack of an interdisciplinary approach that includes not only chemotherapy, radiation, and surgery, but also nutrition management, pain control, counseling, and concern for psychological, social, existential, and spiritual issues. For those patients who survive for longer periods, there has not been adequate attention to physical and psychosocial rehabilitation measures.

For the general public, there is a lack of public awareness of the scope and magnitude of stomach and esophageal cancers, and their premalignant and preventive aspects. Specifically, there has been a lack of focus on educating high-risk groups including

those with Barrett's esophagus, GERD, and *H. pylori* infection. For others, the possible role of alcohol, tobacco, and diet in these cancers has not been emphasized.

Furthermore, public education on risk factors, common presenting symptoms, and interventions has been inadequate to motivate the public to seek early diagnosis. Finally, the public has not received information about the possible treatment options available for premalignant disorders.

Barriers to the study of patient-centered outcomes in stomach and esophageal cancers relate to the small number of cases, the high mortality rate, and the consequent need for multidisciplinary, multicenter studies to generate an adequate sample size. Studies are also constrained by changes in the incidence and demographic characteristics of patients who develop these cancers. In addition, patient-centered issues are very different across the spectrum of disease stages, from premalignant to late malignant. Finally, there is a lack of evidence-based information on the efficacy of early diagnosis and treatment of these cancers. These factors all serve as barriers to public education.

TWO SCIENTIFIC PRIORITIES AND RATIONALES

Priority 1: Evaluate clinical and patient/family data available for patient-centered outcomes related to symptoms, HRQoL, and QOC in gastric and esophageal cancer. This should include assessment of the aggregate economic burden of these cancers considering years of productive life lost, negative impacts on survival, cost of care and caregiving, and other factors. Then conduct a cross sectional study using existing databases to provide a more formal assessment. Importantly, all clinical trials and observational studies should include patient-centered outcomes for HRQoL and QOC.

Rationale: There is a lack of data on patient-centered outcomes related to symptoms, HRQoL, and QOC.

Priority 2: Utilize and adapt current esophageal and gastric-specific HRQoL and QOC instruments to measure disease stage and treatment-related outcomes.

Tools for developing and testing care experiences—including pain control, treatment options, effects of therapy, and others—are critical for measuring patient-centered outcomes. Ensure that patient advocates are involved in all aspects of evaluation and development of measures of patient-focused issues and QOC.

Rationale: Current instruments have not been widely used and tested in observational studies and clinical trials. Patients bring a unique perspective regarding their experiences and responses concerning these diseases.

Infrastructure Needed To Accomplish Priorities

Partnership Platforms

- New health Web sites
- Pharmaceutical firms
- Academic and high-volume institutions

- ASCO symptom management to add modules
- Partnering among agencies
- American Cancer Society
- Quality of Cancer Care Committee
- Professional organizations—thoracic surgeons, general
- Recommend that patient advocates be involved across the spectrum
- Foundations (e.g., The Robert Wood Johnson Foundation, Pew Memorial Trust, Kaiser Family Foundation, and others)
- Veteran’s Health Administration

Expected Resources To Overcome Limitations of Previous Research and To Capitalize on Existing Opportunities

- Multimodality and multicenter clinical trials and observational studies
- Well-defined cohorts
- Availability of databases (e.g., SEER, Medicare, etc.)

Predictive and Prognostic Markers

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Overview/Background Information/Barriers

A predictive marker is an indicator of response to therapy, preferably defining a patient's survival after treatment. A prognostic marker is an indicator of the natural history of the disease, and it is used to help define patients with high and low risks of death that result from the inherent heterogeneity of the disease process.

These markers are applicable to screening patient populations with normal risk, surveillance of patient populations at increased risk, diagnosing symptomatic patients, determining disease stage, and prevention strategies. These principles are applicable to adenocarcinomas of the esophagus, the esophagogastric junction, and the stomach as well as to esophageal squamous cell carcinoma. These principles also are applicable to premalignant conditions, such as Barrett's metaplasia.

The era of molecular biology has yielded a plethora of potential predictive and prognostic markers, but none has achieved routine clinical use because methods for assessing response or prognosis are neither standardized nor correlative. Applying individual predictive markers is complicated by the use of multimodality therapies, which employ chemotherapeutic agents with differing mechanisms of action, biological effects, and radiotherapy. In addition, these therapies often cause substantial damage to

normal tissue. Molecular markers may help alleviate the problem of widespread tissue damage by allowing physicians to test tumors for susceptibility to these toxins. In addition, biological modulators of toxicity are becoming clinically available by identifying prognostic markers and integrating them into clinical staging for better prediction of the natural history of carcinomas and premalignant conditions.

There are currently no well-defined pathways for validating predictive and prognostic markers and incorporating them into routine clinical practice. Gene arrays of Barrett's esophagus tissue indicate that the number of molecular pathways and targets are limited. Since esophageal tumors are similar to other cancer tumors, esophagus cancers could finally provide a window on these markers. Finally, a clear infrastructure does not exist that permits multicenter routine molecular correlative studies of predictive and prognostic markers in clinical trials of esophageal and gastric cancers. Gastric and esophageal cancers affect many; however, there is little information from multicenter trials.

Three Scientific Priorities and Rationale for Each

Priority 1: Develop rapid, flexible, and adequate funding mechanisms for cooperative groups and institutions conducting clinical trials. They will focus on engaging in real-time collaborative

studies of existing markers for validation of laboratory methodologies, tissue and blood collection, quality control, database tracking, prioritization, and specimen distribution, with minimum standards of performance.

Rationale: The NCI research portfolio heavily emphasizes clinical trials and biologic studies. Large numbers of patients with esophageal or stomach cancers are enrolled in therapeutic trials, but translational studies of correlative markers are not constant features of the protocols. Current funding mechanisms for such translational studies are out of phase with clinical trial development and implementation. There is an urgent need to support cooperative groups and institutions conducting clinical trials for marker studies.

Priority 2: Development and validation of novel methods for both clinical and operative molecular staging, particularly by means of molecular markers and imaging techniques (molecular and/or functional).

Rationale: Despite curative surgery and adjuvant therapy, the majority of patients with gastric and esophageal cancers suffer from both local and distant recurrence. Conventional staging techniques, particularly T and N, do not adequately predict heterogeneity of patient outcomes. An integrated molecular staging might predict patient outcomes more accurately. Novel molecular staging techniques may assist in guiding operative treatment, (e.g., extent of surgery/lymphadenectomy, use of intraperitoneal chemotherapy and/or biologic therapy) as well as the use of appropriate adjuvant chemotherapy, radiation therapy, and biologic therapy. This advance will establish a novel panel of prognostic markers that will supersede the current parameters.

Priority 3: Identify specific and quantitatively valid molecular pathways involved in oncogenesis, tumor response, tumor progression, and normal tissue tolerance.

Rationale: Premalignant and malignant progression can be identified for squamous and adenocarcinoma of the esophagus and of the stomach, and these organs allow for access to tissue both preoperatively and after therapy. Insights would be valid for much of adult cancer, amplifying the impact for understanding and treating cancer. In malignant tumors, targets for therapy (such as enzymes, receptors, genes, and proteins) have also been described; however, their clinical implementation and validation of methodology is lagging. Additionally, reducing toxicity should be a major goal, given the limited success of existing therapies.

Infrastructure Needed To Accomplish Priorities

Partnership Platforms

- Multicenter trials
- Partner with insurance companies to explore endoscopic screening as a preventative measure, similar to Japan

Expected Resources To Overcome Limitations of Previous Research and To Capitalize on Existing Opportunities

- Coordinator for multicenter trials
- Tissue banks need to be reorganized to include untreated tissue
- Expedited grant process

Prevention

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Overview/Background Information/Barriers

The decline in gastric cancer has been viewed as a public health triumph in the United States, yet it is still an important cause of death for high-risk groups. Although the incidence of esophageal cancer in the United States is even lower than stomach cancer, it accounts for slightly more deaths each year due to dismal survival rates. Thus, consideration of prospects for prevention is warranted. Specifically, have the high-risk groups been appropriately and fully identified, and what are the most effective means for reducing their risk?

Prevention research on stomach and esophageal cancers in the last decade has focused on four disease subtypes: non-cardia and cardia adenocarcinoma of the stomach; adenocarcinoma; and squamous cell carcinoma of the esophagus. Nearly all stomach cancers are adenocarcinomas; however, recent research has revealed potentially different etiologies according to whether the site is the cardia or more distal (“non-cardia”). Adenocarcinomas of the esophagus and gastric cardia have been increasing in some population groups at alarming rates. Some studies group esophageal adenocarcinomas with cardia adenocarcinomas, in part because the available number of cases is often small. Emerging epidemiologic evidence suggests that esophageal and cardia adenocarcinomas may have a common etiology; however, this

is difficult to confirm when studies do not report results separately for these two types. Difficulties in determining whether a cancer in this region originated in the stomach or esophagus may contribute to this problem. Little research in the United States has focused on the two major subtypes of gastric carcinoma, intestinal and diffuse, perhaps because the distinction may not be recorded routinely and is therefore frequently unavailable. There has been minimal investigation of rare subtypes such as gastric lymphoma.

The more common stomach and esophageal cancer subtypes (non-cardia gastric carcinoma and esophageal squamous cell carcinoma) occur most frequently in populations of low socioeconomic status. Esophageal, and perhaps cardia, adenocarcinomas appear to be increasing in more affluent populations. The major shared risk factors for non-cardia gastric carcinoma and esophageal squamous cell carcinoma are low intake of fruits and vegetables and tobacco smoking (although the effect of smoking appears stronger for esophageal cancer).

Other major risk factors for esophageal squamous cell carcinoma are alcohol consumption and nutrient deficiencies. Suspected modifiable risk factors, for which current evidence is less convincing, include hot food and drink, pickled vegetables, moldy food (mycotoxins), nitrosamines, and human papillomavirus. Other major risk

factors for non-cardia gastric carcinoma are *H. pylori* infection and a high intake of preserved (salted, pickled) foods.

Risk factors for cancers of the gastroesophageal junction are beginning to emerge from recent research. These subtypes are associated with gastroesophageal reflux. Suspected modifiable risk factors for adenocarcinoma of the esophagus include obesity, high intake of fat and vitamin A, low intake of fiber, smoking, and perhaps alcohol intake. Suspected modifiable risk factors for cardia adenocarcinoma are similar. The evidence for risk factors specific to cancers of the gastroesophageal junction comes from a small body of studies; therefore, the risk patterns need to be confirmed in more extensive research.

Squamous cell carcinoma of the esophagus is considered preventable through reductions in smoking and alcohol consumption, and improvements in basic nutrition. For non-cardia gastric carcinoma, perhaps the greatest promise is in interventions aimed at eliminating *H. pylori* infection through treatment or immunization. However, research suggests that a vaccine will not be available in the near future. Meanwhile, studies have focused on evaluating the cost-effectiveness of screening for *H. pylori* infection and treating those who are positive. Given concerns about potential adverse consequences of *H. pylori* treatment of asymptomatic individuals, there have been calls for intervention trials to assess benefits relative to adverse effects. Chemoprevention trials also need to be evaluated for cost-effectiveness. Most are aimed at preventing progression of premalignant lesions through combinations of micronutrient supplementation and *H. pylori* eradication. Recent studies have shown that aspirin and garlic may have protective effects.

Gastric carcinoma of the intestinal type is associated with identifiable premalignant lesions, such as atrophic gastritis, intestinal metaplasia, and dysplasia. Diffuse-type gastric carcinoma has not been linked to identifiable premalignant lesions. Population screening for detection of premalignant gastric lesions or early invasive cancers is not considered cost-effective for low-risk populations. This approach has not been advocated in the United States, where there has been little evaluation of its cost-effectiveness in high-risk groups. Population screening has been used successfully in Japan, where gastric cancer rates are high.

Squamous cell carcinoma of the esophagus is associated with identifiable premalignant lesions such as chronic esophagitis, atrophy, and dysplasia, but the predictive value of cytology has not been considered adequate for population screening. Screening trials in high-risk populations in China have had equivocal results. Esophageal adenocarcinomas are generally preceded by reflux esophagitis and Barrett's esophagus.

Currently, more than 26 NCI projects are related to the prevention of stomach and esophageal cancers. These include projects on dietary interventions for general cancer prevention (2 projects); cancer awareness for minority populations (5 projects); screening for early detection of esophageal cancer in China (1 project); dietary intervention for preventing disease progression in Barrett's esophagus patients (1 project); laboratory research focused on mechanisms of carcinogenesis and potential chemotherapeutic agents (4 projects); human chemoprevention trials for the esophagus and stomach in China (1 project) and for the stomach alone in Colombia and Mexico (2 projects); improving cost-effectiveness of strategies for early detection of esophageal adenocarcinoma (1 project); identification of biomarkers of risk of disease progression in Barrett's esophagus (1 project); identifying

prognostic markers and improving treatment outcomes in stomach and esophageal cancer patients (3 projects); and observational studies to identify modifiable risk factors or potential preventive agents (5+ projects).

There are three major barriers. First, there are small numbers of cases of these cancers, which limits subgroup analysis. Second, there is a lack of uniformity in classifying neoplasms by subsite/subtype, particularly regarding the location of adenocarcinomas proximal to the gastroesophageal junction. Finally, sampling variability in ascertaining intermediate endpoints leads to classification errors.

Three Scientific Priorities and Rationales

Priority 1: Develop risk profile(s) for stomach and esophageal cancers that serve as a basis for subsequent intervention (similar to the GAIL model for breast cancer).

Rationale: Some known risk factors can be used to develop preliminary risk profiles. However, more etiological and epidemiological information is needed. The goal is to define the populations at risk so prevention efforts can be targeted effectively. Due to the relatively low incidence of these cancers, accurate estimates of risk require research efforts that involve a broad collaborative network across institutions and geographic regions to develop and maintain a comprehensive exposure database, to increase the statistical power of studies, and to develop uniform questionnaires and diagnostic classifications.

Priority 2: Develop a menu of biomarkers of risk for stomach and esophageal cancers and their precursor states.

Rationale: Intermediate disease endpoints should be established that can (a) inform the

appropriateness of plans for screening and treatment (within the context of risk-profile models), and (b) provide guidelines for assessing effectiveness of prevention measures in low-, middle-, and high-risk groups.

Priority 3: Develop cost-effective prevention strategies for reducing mortality of stomach and esophageal cancers.

Rationale: Prevention research needs to weigh the costs and benefits of intervention at three levels: preventing disease onset by modifying risk factors, early detection of asymptomatic disease, and minimizing potential adverse consequences of treatment. Again, without increasing the power of studies through broad collaborative networks, the cost-effectiveness of screening and treatment plans cannot be assessed accurately. In particular, controversy over the need for and effectiveness of *H. pylori* screening and treatment cannot be resolved until research examines the costs, including adverse effects, and benefits of such an approach.

Infrastructure Needed To Accomplish Priorities

Partnership Platforms

- Partnership with NIDDK (National Institute of Diabetes and Digestive, and Kidney Diseases)
- Pharmaceutical companies (these already share some structures for collaborative networks, but what is missing is uniting under a common agenda)
- Academic centers
- Patient advocacy groups

Expected Resources To Overcome Limitations of Previous Research and To Capitalize on Existing Opportunities

- Infrastructure: All of the priorities and collaborative efforts outlined above depend on establishing a broad collaborative network for increasing the power of research through large, multicenter studies. Given that numbers of cancer cases at any given institution are low, potentially useful information about risk factors, surveillance, and outcomes is dispersed and isolated rather than aggregated. Existing data about screening, early detection, intervention, and social, behavioral, dietary, microbiological, or genetic predictors must be aggregated for increased statistical power.
- The validity of new prevention research efforts will be maximized through collaborations that allow the use of uniform methods in study design, conduct, and analysis.
- The development and maintenance of shared databases will maximize the efficiency of the research.
- Patient advocacy group stimulation can support research efforts. Such groups capitalize on patient involvement to provide information for databases. Many patients with Barrett's esophagus are motivated and compliant. Creative approaches are needed to stimulate advocacy for stomach and esophageal cancer subtypes that occur primarily in hard-to-reach populations.

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Overview/Background Information/Barriers

Intestinal metaplasia is the premalignant lesion for adenocarcinoma of the esophagus and stomach. In the United States, esophageal adenocarcinoma has the most rapidly rising incidence of all cancers in White males. Current screening and surveillance for esophageal adenocarcinoma is based on endoscopic biopsies and the histologic confirmation of Barrett's metaplasia. If Barrett's metaplasia is diagnosed, follow-up endoscopic biopsy surveillance for evidence of dysplasia and/or early adenocarcinoma is warranted. No prospective evidence exists that shows that screening and surveillance of Barrett's esophagus reduces the mortality from adenocarcinoma of the esophagus. Most patients who develop esophageal adenocarcinoma are unaware that they have Barrett's esophagus, and they are not in a surveillance program.

Barriers to effective screening and surveillance of Barrett's esophagus include the expense of screening the at-risk population for the presence of Barrett's esophagus; the expense of endoscopy with biopsy in low-risk Barrett's patients; the technical difficulties of performing intensive systematic biopsy protocols and targeting small areas of endoscopically invisible dysplasia or cancer; the inter-observer disagreement in the reading of dysplasia; and the large numbers of patients and long

duration of follow-up necessary to document effective screening and surveillance.

Compared to esophageal adenocarcinoma, the incidence of gastric adenocarcinoma is at least twofold higher. The incidence of proximal gastric cancer was rising rapidly before recently leveling off. Barrett's esophagus is associated with and may be the premalignant lesion for this cancer. The incidence of distal gastric cancer has decreased dramatically as has the prevalence of *H. pylori* infection. *H. pylori* infection results in a sequence of mucosal changes, including intestinal metaplasia, which can lead to gastric adenocarcinoma.

The overall incidence of esophageal squamous carcinoma is approximately the same as that of esophageal adenocarcinoma, but it is at least twice as high in Black males than in White males. A premalignant lesion for esophageal squamous cell carcinoma is not recognized in the United States; however, in China, dysplasia, diagnosed by non-endoscopic brush cytology, is commonly recognized prior to the development of squamous cell cancer as part of mass population screening.

The major barrier to screening and surveillance of these cancers is the lack of a well-defined, precancerous condition that is endoscopically visible. An important need is to identify patients at risk for gastric adenocarcinoma and esophageal squamous cell carcinoma who might benefit from

screening and surveillance procedures. There is the global issue of what magnitude of increased cancer risk warrants screening and surveillance.

NCI funding addresses two areas that may improve the clinical effectiveness and cost-effectiveness of screening and surveillance strategies for Barrett's esophagus. These areas include the optical detection of dysplasia by such methods as autofluorescence, RAMAN spectroscopy, light-scattering spectroscopy, and synchronous luminescence. Development of biomarkers in tissue samples—including array analysis, peptides, DNAploidy, p53 mutation, Cox-2 expression, angiogenesis factors, retinoic acid receptor, iNOS, and telomerase—are being evaluated. NCI is also supporting an epidemiologic study of Barrett's esophagus.

Three Scientific Priorities and Rationales

Priority 1: Establish a clinical research infrastructure with multispecialty and multi-institutional centers to perform surveillance to determine the natural history of the premalignant disease states.

Rationale: Current studies do not allow risk stratification of patients with premalignant disease (epidemiologic and biomarkers), given the lack of validated prognostic markers. They do not provide statistical power for hypothesis testing, given the lack of sufficiently large sample sizes with adequate clinical outcomes. Finally, current tissue repositories are not linked to the clinical databases and actively managed patient populations in an effort to translate basic research into clinically relevant information. An infrastructure of this magnitude and detail would correct for all of these.

Priority 2: Conduct population-based screening to identify patients at high risk for premalignant disease states.

Rationale: The prevalence of premalignant disease states in the general population is currently undefined. Therefore, risk stratification criteria to increase cost-effectiveness of screening have not been developed. Endoscopy is currently the screening method of choice; however, newer technologies that are more effective, more cost-effective, better tolerated, and safer need to be developed and promoted.

Priority 3: Establish or merge databases for hypothesis generation and disease modeling to understand the natural history of these diseases.

Rationale: More detailed databases will improve the identification of at-risk populations as well as assist in assessing costs of disease management and impacts on the quality of life of patients with premalignant conditions and cancer. Access to greater information can help guide the development of methodologies for clinical trials and protocols. Finally, more information from more sites will increase the generalizability of the findings.

Infrastructure Needed To Accomplish Priorities

Partnership Platforms

- Link independent research centers for expanding the databases
- Take advantage of multidisciplinary expertise for research on natural history of disease, new technologies for screening, and surveillance
- Validate prognostic markers

**Expected Resources To Overcome
Limitations of Previous Research and To
Capitalize on Existing Opportunities**

- Patient cohorts
- Multidisciplinary expertise (intellectual synergies)
- Centralized tissue banks, pathology readings, and biomarker assessment
- Standardized disease classification, data, and tissue collection

Therapeutics

Co-Chairs: Castell, Donald O; Hundahl, Scott and Rothenberg, Mace

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Overview/Background Information/Barriers

Even though the esophagus and stomach share close proximity, cancers of these organs are distinct diseases. They differ both in etiology and in their reaction to therapy. In addition, esophageal cancer comprises two different types: squamous and adenocarcinoma. Nevertheless, both esophageal and gastric cancers require a coordinated, interdisciplinary approach to therapy.

Stomach cancer. Worldwide, stomach cancer accounts for 9.9% of all reportable cancers, ranks as the second most frequently reported neoplasm, and is responsible for 12.1% of all cancer deaths (Parkin et al., 1999¹). In the United States, stomach cancer was the most common solid tumor in the early 1900s, but it is now relatively uncommon, accounting for less than 2% of reported cancers (Greenlee et al., 2001²).

The median age of afflicted patients in the United States is 68 years, and the impact of co-morbid disease on treatment selection must be considered. As many as 25% of gastric cancer patients receive no surgical treatment despite presenting in a treatable stage (Hundahl et al., 2000³). Surgery, the mainstay of current treatment, carries notable morbidity and mortality. For example, in-hospital surgical mortality in New York State for gastrectomy for cancer is 6.2%, with a clear volume-to-mortality relationship.

Further, sub-optimal surgical treatment appears common. Clearly, strategies are needed to enhance the safety and efficacy of surgical treatment.

Recently, the use of adjuvant postoperative chemoradiation resulted in about 40% survival, double the survival rate of surgery alone (Macdonald et al., 2001⁴). A recent surgical analysis (Hundahl et al., 2002⁵) revealed that most cases had a high likelihood of residual regional disease that could have been addressed by the surgeon; an index of residual regional nodal disease proved a significant independent predictor of survival. Patients with a low residual-disease index displayed a 60% survival rate compared with 25% for the rest of the group. Importantly, adjuvant chemoradiation appeared to improve survival in all surgical-pathologic subgroups. Enhanced local-regional treatment appears to enhance survival, and chemoradiation increases survival for all subgroups. Nonetheless, at least 40% of the cases with apparent local-regional disease still recur. Also, the optimal sequence of systemic treatment (biological or chemotherapeutic) and local-regional (surgical or radiotherapeutic) treatments remains undefined.

For patients with metastatic disease being treated with multi-agent chemotherapy regimens, relative response rates of 50–60% are common. However, the complete response rate remains less than 10%, and survival remains brief (8 to 10 months).

There is no consensus regarding the optimal chemotherapeutic regimen for these patients.

Esophageal cancer. One of the remarkable characteristics of esophageal cancer during the past 30 years has been the change in predominant histologic subtype from squamous cell carcinoma to adenocarcinoma. There has been a 10- to 20-fold increase in the incidence of esophageal adenocarcinoma over the past 20 years, which represents the largest increase of any solid tumor during this period. Currently, the incidence of adenocarcinoma exceeds that of squamous cell carcinoma. The site of the primary lesion has migrated down from mid-esophagus to the lower esophagus/GE junction. All of these changes have definite therapeutic implications.

Historically, surgery has been the cornerstone of treatment for patients with local (stage I) or locally advanced (stages IIA to III) cancer. However, the high rate of unresectability, coupled with the high rate of extra-regional disease, has challenged the notion of single-modality treatment of esophageal cancer. During the past 15 years, studies of combined chemoradiotherapy generated encouraging results in phase II and phase III trials. Combined chemoradiotherapy is a valid alternative to surgery for patients with stage II or III (T3) disease. Whether long-term survival is increased through the use of trimodality therapy is an area of active investigation. In addition, the preferred timing of chemoradiotherapy in relation to surgery remains unknown.

Esophageal cancer is highly symptomatic: 90% of patients have dysphagia and weight loss at presentation. Fifty percent have odynophagia (pain on swallowing). Because many patients are symptomatic, symptom palliation is an important goal of therapy.

Given the ease of access to the esophagus, therapeutic trials should make every attempt

to include pre- and post-tissue collection and analysis. This could provide important predictive and prognostic information to guide future research directions.

Three Scientific Priorities and Rationale for Each

Priority 1: Develop meaningful anatomic and biological subsets of esophageal and gastric cancers.

Rationale: There are at least four major anatomic subsets of gastroesophageal neoplasms. Overall similarity of outcomes belies the biological heterogeneity of these malignancies and the potential for differential sensitivity to newer therapies.

Priority 2: Evaluate contributions of different treatment modalities for esophageal and gastric cancers and their proper integration and sequencing for optimal treatment outcomes.

Rationale: Existing predictive models for gastric cancers based on clinicopathologic features may help in selection of optimal surgical treatment. In addition, molecularly based models could be developed to predict response, survival, and long-term outcomes to specific therapeutic interventions. Different treatments have different outcomes in mortality and morbidity. For example, surgery avoids adverse events associated with chemoradiotherapy, whereas chemoradiation avoids surgical-associated mortality.

Priority 3: Expand a clinical trials network for these diseases to include multispecialty representation.

Rationale: Low accrual makes it difficult to test new therapies. Trials should be expanded to include participation from gastroenterologists, epidemiologists, surgeons, pathologists, basic scientists, diagnostic

radiologists, nutritionists, statisticians, specialists in outcome measures, and representatives of industry.

Infrastructure Needed To Accomplish Priorities

Partnership Platforms

- Practitioner-focused tissue-acquisition programs oriented toward outcome-linked integrated research.
- Clinical trial network explicitly to bring in all the different types of specialists.

Expected Resources To Overcome Limitations of Previous Research and To Capitalize on Existing Opportunities

Central office to coordinate and facilitate attracting interested practitioners to contribute tissue and to collaborate in clinical trials

References

¹Parkin DM, Pisani P, Ferlay J. Global cancer statistics. *CA Cancer J Clin* 1999; 49(1):33–64.

²Greenlee RT, Hill-Harmon MB, Murray T, Thun M. Cancer statistics 2001. *CA Cancer J Clin* 2001; 51(1):15–36.

³Hundahl SA, Phillips JL, Menck HR. The National Cancer Data Base Report on poor survival of U.S. gastric carcinoma patients treated with gastrectomy: Fifth edition, American Joint Committee on Cancer staging, proximal disease, and the “different disease” hypothesis. *Cancer* 2000; 88(4):921–932.

⁴Macdonald JS, Smalley SR, Benedetti J, Hundahl SA, Estes NC, Stemmermann GN, Haller DG, Ajani JA, Gunderson LL, Jessup JM, Martenson JA. Chemoradio-therapy after surgery compared with surgery alone for adenocarcinoma of the stomach or gastroesophageal junction. *N Engl J Med* 2001; 345(10):725–730.

⁵Hundahl SA, Macdonald JS, Benedetti J, Fitzsimmons T, for the Southwest Oncology Group and the Gastric Intergroup. Surgical treatment variation in a prospective, randomized trial of chemoradiotherapy in gastric cancer: the effect of undertreatment. *Ann Surg Oncol* 2002; 9(3):278–286.

Tumor Models

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Overview/Background Information/Barriers

Models of esophageal and gastric cancers are necessary for dissecting biological, biochemical, and genetic pathways and for applying innovative diagnostic and therapeutic strategies.

Historically, the vast majority of models have been based on carcinogen application in rodents, especially rats. A number of carcinogen-based animal models for upper-GI cancers have been described in the past with respect to stomach cancer. The carcinogen MNNG has been used in the rat; and in the mouse, NMU has been used with variable success. In recent years, greater attention has been paid to *H. pylori* species as the more relevant and physiologic carcinogen for inducing stomach cancer. *H. pylori* has been shown to induce gastric cancer in mouse, ferret, and Mongolian gerbil models.

With respect to esophageal cancer, DMBA and NMBA have been used in the rat, and to a lesser extent in the mouse, for inducing squamous papillomas and squamous cell carcinoma. These lesions are accentuated in the setting of various mineral deficiencies.

From a surgical viewpoint, rats have been subjected to esophageal jejunostomy with resulting Barrett's esophagus and esophageal adenocarcinoma. These lesions are accelerated in a p53-deficient background in the mouse.

The mouse offers multiple opportunities for genetic approaches to understanding molecular mechanisms underlying esophageal and gastric cancers. Mutations in a number of genes have led to the development of premalignant or malignant tumors of the stomach. These include mutations in APC, SMAD-4, TFF-1, TGF-beta 1, and RUNX3. The Cdx2 gene can induce intestinal metaplasia in the stomach. Perturbations in cyclin D1 or EGFR have been demonstrated to induce esophageal squamous dysplasia in transgenic mice. When cyclin D1 mice are bred into a p53-deficient background, there is development of esophageal squamous cancer. However, genetic models that recapitulate Barrett's esophagus are lacking. Apart from these considerations, *in vitro* or cell-culture based models are in a nascent stage.

Currently, primary mouse and human esophageal squamous epithelial cells have been established in culture. Recently these cells were placed in organotypic culture to recapitulate the stratified squamous epithelium. However, the role of oncogenes and tumor-suppressor genes in these cell-culture models requires elucidation. There has been limited success in maintaining primary cultures of Barrett's esophageal specimens. These particular cultures maintain the genotypic profile of the original tissues. There has been a wealth of utilization of transformed esophageal cancer cell lines.

With respect to stomach cancer, there has been considerable work with transformed and non-transformed cell lines in culture and in nude mice and some recent work with gastric cancer spheroids. There are no cell lines representative of intestinal metaplasia of the stomach.

Barriers to esophageal and gastric tumor models include a lack of identification of stem cells and markers for esophagus and stomach, a lack of stem-cell-specific promoters for use in animal models, a lack of centralized core facilities for cell lines and animal models, a lack of uniform criteria in mouse histopathology, and a lack of physiologic tools and approaches to animal models.

Three Scientific Priorities and Rationale for Each

Priority 1: Create robust mouse models using hybrid techniques (genetic approaches, surgery, H. pylori infection) to define underlying molecular mechanisms of esophageal and gastric carcinogenesis.

Rationale: Defining underlying molecular mechanisms would assist in elucidating biological and genetic mechanisms as well as in developing surrogate biomarkers. There is a strong need to test the efficacy of chemoprevention and therapeutic agents.

Priority 2: Develop and characterize primary cells, immortalized cells, transformed cells, organ cultures, and organotypic cultures for studying stem-cell biology, intestinal metaplasia, and cancer in esophagus and stomach.

Rationale: There is strong need to test biological mechanisms, investigate stem-cell biology, investigate stepwise progression to

cancer, and test chemoprevention and therapeutic agents. Cooperative groups that share resources in these investigations would decrease duplicate efforts.

Priority 3: Develop an immunocompetent rodent model of advanced disease.

Rationale: There is a need to develop biomarkers for diagnosis and treatment stratification as well as to test targeted therapeutic agents.

Infrastructure Needed To Accomplish Priorities

Partnership Platforms

Core facilities for the following:

- Mouse models: Surgery, *H. pylori* infection, breeding
- Morphology: Histology interpretation, microdissection
- Technology (devices) and imaging
- Genomics/proteomics
- Drug prioritization for testing

Expected Resources To Overcome Limitations of Previous Research and To Capitalize on Existing Opportunities

- NCI (UO1, SPORE, PO1)
- AACR, AGA, ASCO, ACS
- Industry (biotechnology, pharmaceutical, animal labs)
- Cooperative oncology groups

Disease Sites

Adenocarcinomas

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Overview/Background Information/Barriers

Barrett's esophagus, a metaplastic change in the esophageal lining from normal squamous epithelium to columnar intestinal-type epithelium, is recognized as a common sequela of gastroesophageal reflux disease (GERD), developing in approximately 10–15% of persons with reflux disease. Because people with Barrett's esophagus display 30–40 times the incidence of esophageal adenocarcinoma found in the general population, GERD and Barrett's esophagus have been identified as major risk factors predictive of esophageal adenocarcinoma. Each year, approximately 0.5% of patients with Barrett's esophagus develop esophageal adenocarcinoma. The tumors occur predominantly among White males, and the incidence has quadrupled since the mid-1970s. During the same period, the incidence of adenocarcinomas of the gastric cardia (upper stomach) has also increased dramatically.

With the increased occurrence of both esophageal and gastric cardia adenocarcinomas, it is important to identify these tumors as either esophageal or gastric in origin for both diagnostic and therapeutic reasons. The distinction between tumors of the proximal stomach or the distal esophagus is frequently a difficult one, especially when a tumor straddles the gastroesophageal (GE) junction. For glandular cancers that cross the GE junction, this situation is even more complex, because glandular elements may arise from either side of the GE junction. To date, no test is able to determine unequivocally where the tumor arose. A major problem confounding investigations of tumors of the GE junction is the lack of standardized anatomic landmarks that could clearly delimit the extent of the gastric cardia. The gastric cardia has been variously described as comprising a rim as wide as 1-2 cm to as little as 1-4 mm adjacent to the GE junction. Factors such as hiatal hernia or the distortion accompanying a lesion make anatomical localization even more difficult.

The common precursor lesion to these three anatomic areas (distal esophagus, GE junction, and gastric cardia) is intestinal metaplasia. However, the pathways to intestinal metaplasia differ depending on its site of origin. In the esophagus, GERD appears to be a key in the development of intestinal metaplasia. In addition to GERD and Barrett's esophagus, factors that increase the risk of developing intestinal metaplasia include obesity, diet, and perhaps smoking. The roles of other potential environmental exposures are yet to be evaluated.

Despite the strong evidence of a relationship between GERD and adenocarcinomas, 40% of patients diagnosed with these tumors give no history of GERD or Barrett's esophagus. Large gaps in current epidemiological data about GERD and Barrett's esophagus have resulted from difficulties in defining, recognizing, and verifying both conditions. In addition, environmental risk factors remain ill defined. An effective screening protocol has yet to be developed, because it is difficult to identify those actually at risk.

Most clinical trials fail to distinguish among adenocarcinomas from the esophagus, GE junction, cardia, or distal gastric cancers. In fact, even the most recent staging system does not distinguish between these cancers. As a result, very little data exist on either single or combined modality therapies focused on this entity. Incorporating chemotherapy and radiation into primary treatments has made some progress, but the benefits of platinum-based therapies have reached a plateau. Both screening and therapies present significant quality of life issues as they can cause patient morbidity. Further improvements in outcomes will require a major change in strategy, such as incorporating molecular characterization of the adenocarcinomas in order to optimize both diagnostic and therapeutic protocols.

Three Scientific Priorities and Rationale for Each

Priority 1: Elucidate the mechanisms by which host and environmental factors interact in the development of metaplasia in the stomach and esophagus and its progression to cancer, and apply this knowledge to develop prevention strategies, improve therapeutics, and diagnostics.

Rationale: These cancers represent a multidecade process, and they progress in an orderly fashion from intestinal metaplasia to dysplasia and invasive disease. Preliminary studies implicate disorders involving gastric acid, bile, exposure to nitrosamines, and possibly a protective effect of *H. pylori* colonization in the development of these conditions. Ascertainment of mechanisms, especially at the molecular level, may allow preventive steps.

Priority 2: Develop a molecular characterization of adenocarcinoma of the esophagus, GE junction, and cardia for classification and staging, and compare with other foregut malignancies to help define causation and to develop and apply novel and specific therapies.

Rationale: The mortality rates for these adenocarcinomas remain unacceptably high compared to many other cancers for which major therapeutic advances have occurred. Currently, the clinical management of adenocarcinomas of the distal esophagus, GE junction, and cardia has not been distinguished from that of squamous cancers and distal gastric cancers. These tumors are arbitrarily classified as either gastric or esophageal cancers. This arbitrary categorization impairs knowledge of causation and true incidence, as well as making it difficult to define differences that could be important in the development of

novel therapeutics. There is an urgent need to identify potential markers of response or resistance to therapy and molecular pathways that could be targeted by specific therapies.

Priority 3: Target screening to populations at greatest risk by first defining the prevalence of premalignant lesions and associated risk factors in populations of diverse ethnicity not seeking medical attention, and then defining the natural history of these lesions.

Rationale: The vast majority (95%) of patients presenting with adenocarcinoma of the esophagus were not known to have any premalignant lesions. Thus, there is a need to detect more quickly individuals at increased risk. In particular, knowledge of the extent of these lesions in members of minority groups is limited, and there is good reason to suspect that important differences exist. Understanding the natural history of these lesions is important to develop strategies for appropriate interventions. Better knowledge of risk factors should lead to improved diagnostics for identification of at-risk individuals.

Infrastructure Needed To Accomplish Priorities

Partnership Platforms

- Develop a multidisciplinary consortium to identify the epidemiological, molecular, and clinical/pathologic parameters of esophageal, GE junction/ cardia adenocarcinoma development and translate them into clinical trials
- Partner with industry
- Create interinstitutional cooperation with NIAID, NIDDK, NIA, Department of Veterans Affairs, DOD, and CDC

Expected Resources To Overcome Limitations of Previous Research and To Capitalize on Existing Opportunities

- Support for tissue acquisition, classification, and storage
- Bioinformatics and biostatistical core
- Imaging facilities

Gastric

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Overview/Background Information/Barriers

Gastric cancer will occur in 21,900 patients this year and cause 13,500 deaths in the United States. Worldwide, gastric cancer will occur in 798,000 patients. The most common known antecedent to the development of gastric cancer is prior infection with *H. pylori* with subsequent development of chronic gastritis. Host and environmental factors modulate the process of carcinogenesis. *H. pylori* infection is not inevitably associated with the development of gastric cancer, and it is unknown whether the eradication of *H. pylori* will decrease the risk of gastric cancer.

The conventional therapy of primary gastric cancer is based upon en bloc surgical resection of the stomach tumor and the draining lymph nodes. In the United States, overall 5-year survival after gastric resection is approximately 20%. Because of the high relapse rate after gastric resection, extensive studies of adjuvant chemotherapy have been performed. There is no solid evidence that patients benefit from this approach. However, a recent NCI intergroup phase III trial of postresection chemoradiation versus

surgery alone demonstrated significant improvement in disease-free and overall survival. In the United States, postoperative chemoradiation is now considered a standard of care for patients at risk for recurrence following resection.

The use of preoperative chemotherapy or chemoradiation therapy (neoadjuvant therapy) produces objective responses in as many as 50% of patients with primary gastric cancer. This therapeutic approach has not been evaluated in phase III trials and, thus, must be considered investigational in the management of gastric cancer.

Conventional staging techniques (particularly T and N) do not adequately predict the heterogeneity of patient outcomes. Novel molecular staging techniques may assist not only in more accurately predicting outcome but also in guiding treatment decisions, including extent of surgery, use of adjuvant chemotherapy, radiation therapy, and/or biologic therapy.

Current measurements of outcome in patients treated for gastric cancer are inadequate. Assessment of tumor- and treatment-related morbidity is critical, and

data measuring quality of life (QoL) are scant. There is a need to disseminate guidelines for optimal treatment in this disease.

Three Scientific Priorities and Rationale for Each

Priority 1: *Use multidisciplinary research approaches to understand the interactions of various strains of *H. pylori*, host factors, and other lifestyle/environmental factors in gastric carcinogenesis.*

Rationale: Chronic inflammatory states are commonly associated with carcinogenesis. *H. pylori* infection is recognized as a common precursor to gastric cancer. The availability of human, animal, and *H. pylori* genomics offer a unique opportunity to study the mechanisms of gastric carcinogenesis. This type of approach may evolve into a template for the study of other cancers.

Priority 2: *Develop novel methods, using molecular profiling of gastric neoplasia, to stratify patients into risk groups to help direct therapeutic decision-making. This would include sequential and anatomic mapping of alterations in tumor compared to adjacent nonmalignant tissue. It would also include genomic and bioinformatic approaches to create comprehensive profiles of these lesions.*

Rationale: Conventional staging is inadequate for assessing prognosis and optimizing treatment decisions. The application of current therapies is largely empiric. The opportunity to understand molecular profiles may lead to the identification of new targets and new therapies.

Priority 3: *Measure outcomes of diagnostic and treatment strategies, including early detection, response to treatment, survival, QoL, and quality and cost of care in patients with gastric cancer. This would*

include the application and/or development of disease-specific QoL instruments.

Rationale: While the clinical endpoints of relapse and death are often reported, there are very few tools to measure the functional outcome and QoL of patients treated for gastric cancer. Tumor and treatment-related morbidity is substantial and often affects not only relapse/survival rates, but also treatment decisions. QoL tools and functional measurements become imperative as increasing numbers of patients are cured of disease, as a result of early detection or multimodality therapy. Long-term functional sequelae in patients treated for gastric cancer are undefined.

Infrastructure Needed To Accomplish Priorities

Partnership Platforms

- Establish close interactions with the NCI Office of Communications to use the resources of the Federal Government to distribute uniform information in a thoughtful and effective way.
- Emphasize interactive relationships and incentives to encourage adherence to guidelines.
- Establish partnerships with other NIH institutes, Department of Defense, and Veterans Administration, and industry. International collaborations in high-prevalence populations will facilitate more efficient and complete understanding of disease and the development of more effective interventions.

Expected Resources To Overcome Limitations of Previous Research and To Capitalize on Existing Opportunities

- Explore the development of an international, interactive,

interdisciplinary, multi-institutional consortium for gastric cancer, possibly joining with other gastrointestinal disease.

- Establish an international *H. pylori* species bank.

Squamous

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Overview/Background Information/Barriers

Esophageal squamous cancer is uncommon in the U.S. population, accounting for 6,000 cases each year, with the incidence decreasing. The histopathologic subtype of squamous cell carcinoma is now less common than esophageal adenocarcinoma. However, the occurrence of esophageal squamous cell carcinoma is known to relate to well-recognized socioeconomic, lifestyle, and demographic factors that identify high-risk groups. The vast majority of cases occur in males, and the incidence is about 15 per 100,000 population in non-White males, as contrasted with about 2 per 100,000 in White males.

Few cases occur in the absence of known predisposing conditions that include tobacco use (in common with other upper-aerodigestive squamous cell carcinomas), alcohol consumption, a history of caustic injury to the esophagus, human papilloma virus infection, or tylosis and other rare genetic syndromes. Nonsteroidal anti-inflammatory drugs and a diet rich in fruits and vegetables are reported to have protective benefit, giving additional clues to possible prevention strategies but without

evidence for the phase of initiation and progression at which the effects may occur.

Also, the incidence rate is nearly equaled by the mortality rate, and medical care for patients with advanced disease is complex and expensive, indicating that improvements in therapy and end-of-life care are needed. The NCI funding portfolio for esophageal squamous cell carcinoma is small and heavily weighted toward treatment research, especially clinical trials that also include patients with esophageal adenocarcinoma. In terms of absolute dollars and as a proportion of research funding, there is a much lower allocation of NCI funds dedicated to the biology of squamous esophageal cancers than other tumor types (7% versus 24%). The characteristics of esophageal squamous cell carcinoma and the current research environment suggest opportunities for initiatives to attempt to improve population incidence, morbidity, and mortality of individuals with the disease.

Three Scientific Priorities and Rationale for Each

Priority 1: Further define the molecular events involved in the multistage process of squamous cell carcinoma development in

the human esophagus with a focus on different ethnic groups and geographic locations. Clarify the similarities and differences in development of esophageal adenocarcinoma.

Rationale: To elucidate the process of oncogenesis in squamous cell esophageal cancers, the molecular genetic events involved in this process must be defined. This opportunity is afforded by the esophageal mucosa because it can be targeted for serial biopsies over time. Consequently, this characteristic enables serial examination of the molecular processes in oncogenesis, tumor prevention (environmental risks and chemoprevention), and tumor progression before and after treatment.

Priority 2: Characterize the molecular, cellular, and epidemiological features of squamous cell carcinoma of the esophagus, with the goal of using these findings to identify diagnostic, prognostic, predictive, and therapeutic targets.

Rationale: Intratumoral markers and targets are essential to developing molecular and physiological imaging and diagnostic strategies that are less invasive, and treatment strategies that are more efficacious and less toxic than existing modalities. Therapeutic programs should be developed to enhance quality of life (QoL) considerations for the affected patient population.

Priority 3: Develop clinically relevant human or genetically defined animal models of established squamous cell carcinoma and its premalignant phase.

Rationale: Few clinically relevant animal models of esophageal squamous cell carcinomas exist. Animal models are essential to understanding the development of esophageal cancers and to identifying host interactions with various environmental

agents that increase disease risk. Consequently, study of animal models is key in the process of translating basic research into effective clinical methods for prevention, screening, and treatment. Moreover, in this low-prevalence disease, cell line xenografts, and animal models provide an economic use of resources from which valuable material can be obtained to study diagnostic, therapeutic, and chemopreventive approaches.

Infrastructure Needed To Accomplish Priorities

Partnership Platforms

Develop consortia of investigators who treat patients with squamous cell esophageal carcinoma to collaborate in studies of its epidemiology and natural history. Collaborative groups should collect cancer and premalignant tissue, and contribute to the conduct of the genetic and biology studies outlined in the above priorities.

- Establish a clinical research infrastructure with multispecialty and multiinstitutional centers to perform surveillance in an effort to determine the natural history of the premalignant state.
- Minorities and high-risk populations should be targeted for prevention efforts. The QoL issues in cancer survivors and predictors of survivorship in patients who have esophageal cancer should be studied. Public education programs should be developed to publicize the links between esophageal cancer, smoking, and alcohol.
- Continue the clinical trials of esophageal squamous carcinoma as a feature of GI Committees of the existing Cooperative Oncology Groups.

Expected Resources To Overcome Limitations of Previous Research and To Capitalize on Existing Opportunities

- Increased funding from a variety of sources to support human and animal tissue banks as well as databases.
- Rapid, flexible, and adequate funding mechanisms for cooperative groups and institutions conducting clinical trials to enable them to engage in real time, collaborative studies to validate existing markers based on levels of evidence. These resources should be applied to validation of laboratory methodologies,

tissue and blood collection, quality control/quality assurance of research materials, database tracking, prioritization, and specimen distribution with established minimum standard of performance in the clinical trials setting.

- Development of consortia of investigators, NCI, and local agencies where these cancers are prevalent.
- Sponsorship of nationwide workshops for investigators and public health personnel to highlight the relationship between smoking and squamous cell carcinomas of the esophagus and other organs.

Population Management At Risk

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Overview/Background Information/Barriers

Currently, there is no way to identify everyone who is at risk for gastric cancer, esophageal adenocarcinoma, and esophageal squamous cancer. The mortality rate of approximately 95% indicates that a majority of patients are not presenting with early-stage cancer. Moreover, adequate markers are not available to predict which patients will develop Barrett's esophagus, gastric intestinal metaplasia, or squamous dysplasia.

To the best of our knowledge, existing markers have only been tested in patients with Barrett's esophagus or gastric cancer, esophageal adenocarcinoma, and esophageal squamous cancer, and have not been tested in the general population, which includes the at-risk population. For example, inactivation of the tumor-suppressor gene *p53* is known to occur early in esophageal adenocarcinogenesis, but it has never been studied in asymptomatic patients without Barrett's esophagus. Similarly, hypermethylation of the familial polyposis gene *APC* occurs in the tissues of 92% of tumors and 25% of sera from patients with esophageal adenocarcinoma.

Little accurate information on gastric cancer, esophageal adenocarcinoma, and esophageal squamous cancer is readily available to the general public. With the advent of an enormous array of information on the Internet, many patients who are diagnosed with Barrett's esophagus quickly obtain erroneous or misleading information, or none at all. They need tools to effectively evaluate this information, to learn about their options, and to make informed decisions. In addition, some general practitioners, other primary care physicians, and gastroenterologists have insufficient knowledge of gastric cancer, esophageal adenocarcinoma, and esophageal squamous cancer, or their precursors, due to the rarity of these diseases. Providing information to practitioners as well as to educational media that can best meet the needs of those at risk is important.

Our understanding of host/environment interactions in gastric cancer, esophageal adenocarcinoma, and esophageal squamous cancer is limited. For example, we know that acid and *H. Pylori* induce cyclooxygenase (Cox)-2 expression *in vitro*. However, we know little about other pathways or genes involved in the host's response to environmental risk factors. An improved understanding of these interactions would

generate new biomarkers to identify patients at risk for premalignant and malignant lesions. Moreover, insights into the biology of these interactions could have far-reaching ramifications for other human premalignant syndromes, particularly those related to chronic inflammatory states.

Many millions of dollars currently are spent on treating both premalignant and malignant gastric and esophageal lesions. For example, proton pump inhibitors are used widely (and perhaps indiscriminately) to treat a broad array of symptoms. More precise diagnosis and disease classification could result in more discriminate use of these agents, yielding significant cost savings.

Several barriers to identifying the at-risk population exist. First, no uniform classification system is available for the different cancer subtypes. Moreover, interventions affect the natural history of these diseases at both the testing (e.g., *H. pylori*) and treatment levels (e.g., proton pump inhibitors, antibiotics, nonsteroidal anti-inflammatory agents). In addition, with the decreasing prevalence of *H. pylori* and the relatively low prevalence of gastric cancers, esophageal adenocarcinomas, and esophageal squamous cancers, studies with large numbers of patients are difficult to conduct. International collaborations would be instrumental in addressing this need. Finally, the genomic diversity of populations within the United States and in other countries makes population studies challenging.

Three Scientific Priorities and Rationale for Each

Priority 1: Implement broad-based, integrated, population-based, endoscopic, multi-institutional studies to define environmental, clinical, and laboratory markers in an effort to identify groups at risk for gastric cancer, esophageal

adenocarcinoma, and esophageal squamous cancer.

Rationale: A study of this magnitude would assist in defining lifestyle, dietary, environmental, and genetic factors affecting risk, which is important because cancers of the esophagus and stomach often present at a late stage. With improved screening procedures to identify patients at risk, more patients could be treated earlier. Additionally, a large study could determine whether endoscopy reduces mortality, which, in turn, would help better define risk factors as a platform for stratifying who should and should not be screened.

Priority 2: Educate health care professionals and the general public regarding risk for gastric cancer, esophageal adenocarcinoma, and esophageal squamous cancer and their precursor states.

Rationale: Presumably, more at-risk patients would self-identify and seek treatment earlier if a risk profile were disseminated to the public and health care professionals. Mortality and morbidity could decrease with well-developed tools to establish an educational infrastructure and disseminate information.

Priority 3: Identify, define, and validate biomarkers (genetic, biochemical, biological) that stem from interactions between host and environmental factors specific to esophageal and gastric carcinogenesis (e.g., H. pylori, acid, bile, nitrosamines), using appropriate in vivo and in vitro models.

Rationale: Genomics and proteomics could assist in discovering novel genes and biomarkers, which, in turn, could assist in developing strategies for more effective risk stratification and prevention of cancer in the stomach and esophagus.

Infrastructure Needed To Accomplish Priorities

Partnership Platforms

- Form a national consortium of gastroenterologists, epidemiologists, pathologists, bioinformatics specialists, and other related specialists to conduct multicenter, interdisciplinary studies. A proposed name for this consortium is Validate, Identify, Discover, and Adapt (VIDA).
- HMO Research Network.
- Tap into existing professional societies and advocacy groups, and encourage the creation of new advocacy groups, where a need exists.
- Industrial partnerships to move new technologies forward.
- Enhance and expand large-scale studies by incorporating community hospitals as well as multiple academic centers.

Expected Resources To Overcome Limitations of Previous Research and To Capitalize on Existing Opportunities

- Attract more researchers to the field of gastric cancer, esophageal

adenocarcinoma, and esophageal squamous cancer.

- Use information technology to increase awareness.
- Develop tissue banks (esophagus, stomach) for large, multicenter studies.
- Develop blood banks (DNA, RNA, *H. pylori* genotyping) for large multicenter studies, as well as host/environment interactions.
- Develop questionnaires for demographics, dietary factors, environmental factors.
- Linkages to existing and new databases.
- Develop common data elements.
- Provide incentives for collaboration.
- Bioinformatics and statistics core (medical and genomic) to support priority 1.
- Identify the minority of patients with known risk factors who develop esophageal and gastric cancers.

Premalignant

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Overview/Background Information/Barriers

There are well-described and identifiable premalignant lesions that precede esophageal squamous cell carcinoma, esophageal adenocarcinoma, and gastric adenocarcinoma: squamous dysplasia, Barrett's esophagus, and gastric intestinal metaplasia. These premalignant lesions are well described in part because they remain *in situ* for long periods, which allows them to be identified and studied. Some groups, such as African American males, are at higher risk for developing esophageal squamous cell carcinoma, and other contributing exposures, such as alcohol consumption and smoking, have been linked to these diseases. Other groups, such as Caucasian males, are at higher risk for developing esophageal adenocarcinoma, a cancer that has been linked to gastro-esophageal reflux disease. Of particular interest, esophageal adenocarcinoma is the cancer with the most rapidly rising incidence in the United States. *Helicobacter* infection is strongly associated with gastric adenocarcinoma across ethnic groups.

Barriers exist to the identification of premalignant lesions. Endoscopic biopsy

histology is required for diagnosis of these lesions that cannot be detected by a routine history and physical examination. Another barrier to early identification of these diseases is that gastric and squamous precursor lesions cannot be seen in a routine endoscopic screening examination, and symptoms related to these lesions or their associated etiologic conditions can overlap broadly with other diseases. For example, many patients visit their physicians for reflux, and approximately 12% of these patients have Barrett's esophagus; however, cancer is rarely identified at this early stage, and many of those with adenocarcinoma do not have reflux. Conversely, 95% of those with adenocarcinoma have not been diagnosed previously with Barrett's esophagus.

Little is known regarding the natural history of these lesions. As yet, it is unclear whether current screening or surveillance strategies are effective in preventing malignant transformation or reducing mortality from these cancers. Many other factors regarding these lesions also remain unknown, including who is and is not at risk for acquiring them, their biology, including the process of carcinogenesis, the optimal management of individuals at risk, and what

can be done to reduce their risk. What we know is limited because precancer is not always a reportable disease; existing cancer registries rarely include these premalignant lesions; and burdening physicians with recording more information is often viewed as an additional barrier.

Clinical issues include whom, when, and how often, or even whether, we should screen and survey individuals at risk.

- What technologies are applicable for improving screening and surveillance strategies?
- What is the optimal treatment of early neoplastic and nonneoplastic premalignant upper gut lesions?
- What is the natural history of these lesions?
- What are the outcomes of untreated and treated lesions?
- Are screening, surveillance, and treatment of these lesions cost-effective?

Without answers to these questions, it is difficult for us to focus on preventing the disease.

Currently, NIH funding for studies of the premalignant lesions that precede these cancers is very limited and includes one early detection project for squamous dysplasia in China; one risk stratification project for Barrett's esophagus in the United States; and two funded gastric preneoplasia studies in Mexico.

Three Scientific Priorities and Rationales

Priority 1: Establish the prevalence of preneoplastic lesions (squamous dysplasia, Barrett's esophagus, and gastric intestinal metaplasia) in the U.S. population for

esophageal squamous cell, adenocarcinoma, and gastric cancer by performing a population-based endoscopic screening study.

Rationale: Impact of cancer outcomes requires a better characterization of these cancers in their premalignant disease states. Additionally, there are large potential populations at risk for these cancers (GERD, *H. pylori*, alcoholism, smoking, obesity), thus lending credibility to population-based prevalence studies. Within these at-risk populations, high-risk and low-risk or no-risk subjects can be identified through endoscopic biopsy and stratified for longitudinal study, because the lesions are not typically removed, unlike other premalignant processes (e.g., the adenomatous polyp). Further adenocarcinoma of the esophagus remains the cancer with the most rapidly rising incidence in the United States, so an accurate estimate of the prevalence of its precursor lesions and evaluation of their population distribution are essential. Such a research initiative would allow for the establishment of risk stratification (molecular, environmental, and epidemiological) for these lesions. An additional benefit of this initiative is the potential to measure patient-centered issues, such as the impact of identifying these premalignant lesions on functional status and quality of life. Finally, establishment of risk stratification allows a concentration of resources directed at individuals and populations at risk of disease progression.

Priority 2: Establish risk stratification for these premalignant lesions by the formation of a multi-institutional cohort registry of patients drawn from screening studies and current surveillance practices.

Rationale: Establishment of a cohort of subjects with upper gastrointestinal premalignant lesions would provide opportunities for addressing the natural

history of these lesions, opportunities for further risk stratification of patients with these lesions, and opportunities for investigating the genetic and biologically controlling events in the carcinogenic process. This, in turn, would provide opportunities for intervention studies aimed at preventing disease progression and would serve as a resource for evaluating and developing novel invasive and noninvasive diagnostic technology applications. Importantly, the premalignant lesions of these cancers remain *in situ*, which allow them to be followed and studied over time. This makes them a good model for studying carcinogenesis in these and other cancers.

Priority 3: Establish noninvasive technologies, such as serum markers and imaging techniques, for screening and surveillance of these premalignant lesions.

Rationale: At present, there is little or no funding on a national level for development of new technologies that has enormous potential for identifying these early lesions. Accurate identification of these lesions, especially in asymptomatic people, would allow real population screening, which would give us true prevalence figures and let us see the geographic and population variability of these lesions. Unlike some other malignant processes, higher risk populations for these diseases are identifiable, and the malignancies are associated with larger organ field defects that can be more reliably studied (e.g., long-segment Barrett's esophagus). Additionally, the same new technologies can probably be used for earlier detection and treatment of these curable premalignant and early malignant lesions, which should reduce the morbidity and mortality of these cancers.

Infrastructure Needed To Accomplish Priorities

Partnership Platforms

- No single center possesses the resources necessary for addressing any of these three priorities. Moreover, single center studies, by nature, preferentially exclude community-based individuals with these lesions. Interinstitutional cooperation is mandatory.
- Development of imaging technologies capable of identifying premalignant lesions and indicators of neoplastic progression are likely to require funding and collaboration from industry as well as from NIH.

Resources Needed To Overcome Limitations of Previous Research and To Capitalize on Existing Opportunities

- All three priorities require coordination of cross-institutional, cross-disciplinary, multicenter studies designed by interested investigators in this field, including epidemiologists, gastrointestinal endoscopists, basic scientists, and pathologists.
- Central to this process is a multi-institutional registry that would include epidemiological and biological information, as well as a tissue repository of well-characterized individuals with these premalignant lesions. Without such an infrastructure, many testable hypotheses and recommended studies cannot be performed.

Localized Malignant

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Overview/Background Information/Barriers

Patients with localized malignancies of the stomach and esophagus have a wide variety of biologic and anatomic features at presentation. In addition to traditional staging for each tumor (based on characteristics of the primary tumor, lymph nodes, and distant metastases), there are at least three distinct anatomic sites (esophagus, GE junction, stomach) and two histologies (adenocarcinoma and squamous cell). This heterogeneity makes clinical research in patients with localized malignancies in these sites even more challenging.

Surgery is the mainstay of treatment for tumors of the upper gastrointestinal tract, with a wide variety of outcomes depending not only on tumor stage, surgical expertise, and technique, but also on the increasingly common application of multimodality treatments.

For esophageal cancer, surgery alone remains a standard for most patients, but with a low likelihood of cure, even in apparently localized disease. Chemoradiation may significantly

downstage tumors and cure some patients, and may be considered as sole treatment for patients when nonsurgical palliation alone is considered. Many patients treated with curative intent now receive chemotherapy, radiation, and surgery, although the relative contribution of each modality to ultimate outcome remains uncertain.

For patients with gastric cancer, cure rates vary widely, depending on the stage and site of tumor, with distal lesions having higher cure rates than proximal lesions with surgery alone. Based on the recent U.S. intergroup trial results, a standard of care for patients with gastric cancer who are at risk for recurrence following complete resection is postoperative adjuvant chemoradiation. Future trials are being designed to assess the optimal sequence of treatments (preoperative vs. postoperative) and the modifications of systemic treatment to reduce the risk of distant failure.

While the incidence of both squamous cell carcinoma of the esophagus and adenocarcinoma of the distal stomach appears to be decreasing, adenocarcinoma of the gastric cardia and gastroesophageal junction appear to be increasing more rapidly than any other human cancer. Some of the precursor lesions for this entity have been identified (gastric

intestinal metaplasia, esophageal Barrett's epithelium), but the host factors governing progression to malignancy are not fully characterized. Furthermore, once the carcinoma is diagnosed, long-term prognosis is poor, even after multimodality therapy for apparent localized disease. The effects of patient, tumor, and treatment-related factors in outcome are not well understood.

Patients with esophageal and gastric cancers are older and often present with significant medical comorbidities that can limit treatment options. These comorbidities often define a patient's tolerance of and recovery from intensive treatment programs. These patients often have unique functional problems arising from both disease and treatment-related morbidity. Long-term survival data do not adequately describe these outcomes of treatment in this group of patients.

Compared to clinical research in other tumors, there has been relatively little work in predictive and prognostic markers, even retrospectively, to select optimal therapy for individual patients or groups of patients. Barriers to clinical research in these tumors include the lack of biologic markers, strong biases on the part of both patients and physicians for or against certain therapies, and suboptimal mechanisms - beyond the national cooperative groups - for collection of data and for testing of hypotheses in this relatively uncommon malignancy.

Three Scientific Priorities and Rationales

Priority 1: Optimize available treatment modalities and promote the development of novel targeted therapeutics, e.g., radiosensitizing agents, systemic agents, and minimally invasive resection and ablation techniques. Develop predictors of response that may affect treatment selection, including molecular and imaging

predictors of partial or complete response to both conventional and novel therapies.

Rationale: Treatment approaches for esophageal and stomach tumors have become more complex, with more patients receiving surgery, chemotherapy, and radiation. However, it remains unclear whether all patients require such treatments. In particular, the role of nonsurgical local modalities (such as endoscopic mucosal resection, stenting and photodynamic therapy) in patients with esophageal cancer needs to be further evaluated. To understand which patients would best benefit from what are now considered standard treatments, the role of chemoradiation in gastric and esophageal cancers needs to be explored. Advances in biologic markers and imaging should be exploited to better help in patient selection and determining response to therapy. Some intermediate measures of success (including serial biopsy before, during, and after treatment as well as imaging) would enable clinical researchers to assess efficacy of traditional and targeted biologic therapies outside of the framework of large-scale randomized trials.

Priority 2: Apply and refine patient-centered methods to assess specific short and long-term tumor-and treatment-related quality of life issues in patients with localized esophageal and gastric cancer. These would include assessment of pain, nutrition, swallowing, fatigue, and diarrhea as well as quality and cost of care issues.

Rationale: Information characterizing long-term functional outcome is scant even though good data exist describing patterns of recurrence and survival of patients treated for localized gastric and esophageal cancers. These patients have unique functional problems related to both disease and treatment-related morbidity. While some data exist for quality of life outcomes,

additional organ-specific instruments need to be developed, validated, and applied. In addition, assessment of quality and cost of care as well as patient preferences should be incorporated into clinical trial design.

Priority 3: Define host and tumor characteristics to best predict relapse and survival for patients with localized cancer of the esophagus or stomach. These include genetic, molecular, biochemical, imaging, and other clinical factors, as well as patient sociodemographic characteristics. Unique characteristics of esophageal and stomach cancers permit the serial sampling of tumor before, during, and after treatment.

Rationale: Currently, the treatment patterns for large groups of patients with esophageal or gastric tumors are largely based on empirical data. The problem is that the different primary sites should be considered as distinct diseases. Molecular and genetic markers should be obtained to rationally select both the need for and type of therapy for the individual patient or subset of patients. With the introduction of new chemotherapeutic agents and targeted biologic therapies, predictive markers for response or resistance are important in designing treatment programs and in

predicting toxicity of therapy. Esophageal and stomach cancers offer ease of access for serial biopsies to assess the impact of therapy, which makes them unique for these purposes.

Infrastructure Needed To Accomplish Priorities

Partnership Platforms

Cooperative groups

- Collaboration with NIDDK
- Department of Defense; Department of Veterans Affairs, Research Wing

Expected Resources To Overcome Limitations of Previous Research and To Capitalize on Existing Opportunities

- Cooperative national database of patients with gastric and esophageal cancers
- National tissue bank for study of molecular profile of gastric and esophageal cancer
- National multi-institutional consortium for gastric and esophageal cancer

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Overview/Background Information/Barriers

Among the approximately 30,000 U.S. patients diagnosed annually with gastric or esophageal cancer, the vast majority will eventually face widespread metastatic disease, thereby confronting the prospect of an incurable cancer and a limited life. Curative therapy for these cancers can be achieved only rarely. The primary considerations for these cancers have been palliative therapies and treatments designed to extend survival.

Palliation. Palliative therapy for upper gastrointestinal tumors has focused on maintaining the patency of the lumen in order to allow nutrition, medications, and salivary secretions to pass. The most commonly applied methods of achieving this goal have been the placement of stents to alleviate severe dysphagia, as well as chemotherapy and radiation. Gastric cancers rarely obstruct because of the larger diameter of the lumen in the stomach. Modern stents can be made from flexible plastic materials, metallic expandable mesh, metallic stents that are coated with a plastic material, or metallic mesh stents that contain flaps to prevent reflux of ingested material. Metallic stents have become commonly used in the esophagus because of their ease of placement and longer-term palliation of

dysphagia. Thermal ablative therapies, such as Nd:YAG laser therapy or photodynamic therapy, have also been used to open the esophageal lumen and may be tolerated better, but often they do not offer durable palliation. Gastric and esophageal cancers also affect nutritional status, which can be enhanced by novel enteral access devices such as percutaneous jejunostomy and gastrostomy.

Chemotherapy. Chemotherapy has provided patients a survival advantage. In three previous trials, chemotherapy was compared to best supportive care, and although benefits were modest, a statistically significant survival advantage was observed among chemotherapy-treated patients in each of these trials.

This survival advantage has spawned renewed interest in testing other chemotherapeutic agents in this setting. However, recent studies suggest two recurrent and concerning themes. First, conventional chemotherapy appears to be reaching a plateau with respect to its efficacy. For example, a promising treatment regimen for stomach cancers is combined administration of epirubicin, cisplatin, and 5-fluorouracil. This regimen yielded a response rate as high as 70% in previous phase II trials. However, the treatment regimen provides only a modest

survival advantage over a previously used regimen of 5-fluorouracil, adriamycin, and methotrexate. The median survival times for these regimens were 8.9 versus 5.7 months, respectively.

Second, high toxicity rates remain a major problem. The testing of newer drugs, such as the taxanes and camptothecans, in combination with other agents, has provided response rates that approach 50%, but only at the cost of severe toxicity that also occurs in approximately 50% of patients. Thus, although the modest benefits of chemotherapy protect from nihilism, there is a clear mandate to explore other strategies to improve treatment efficacy and to reduce toxicity.

Patient Concerns. Patients with late stage esophageal or gastric cancer are experiencing the physical symptoms of poorly controlled disease such as anorexia, pain, bleeding, fatigue, and obstruction, and the recognition that therapies are not curative. This combination of physical and existential concerns (anxiety, depression, seeking of the meaning of life and death) lead to levels of distress that are substantial and are experienced not only by the patient, but by the family as well. While there has been increasing attention to the control of symptoms near the end of life, few studies have addressed the problems of patients with tumors of these two sites. The interruption of gastrointestinal function adversely affects nearly every aspect of daily living and limits meaningful social interactions with family and others, which often occur around food.

There is a range of assessment tools available that validly measure subjective symptoms: pain, nausea and vomiting, dysphagia, fatigue, anxiety, depression, and delirium related to treatment toxicities. It is important to review this body of information and its relevance to these tumors, particularly in relation to late stage disease,

when these symptoms are the most common. More importantly, it is critical that patients with esophageal and gastric tumors be studied in late stages to determine the complex distressing symptoms and to conduct symptom-control trials using the modalities currently available, while also exploring novel interventions.

Three Scientific Priorities and Rationale for Each

Priority 1: Develop specific, molecularly targeted therapies for late-stage gastroesophageal cancers based on knowledge of molecular pathways important in tumor progression, response to therapy, and normal tissue tolerance. Identify molecular markers that could be assessed by nationally available bioinformatics resources to define patients who would respond to nonsurgical treatments.

Rationale: Current therapies for late-stage gastroesophageal cancer are unsatisfactory. It is important to develop new therapies that decrease mortality and minimize damage to normal tissue. Molecular markers of susceptibility to these toxicities are being discovered, and biological modulators are becoming clinically available. Because of their accessibility, gastroesophageal cancers are ideal candidates for testing novel therapies and for identifying surrogate markers of response. The accessibility also means that tissue can be acquired serially, which would enhance the ability to establish tissue databanks to study these diseases.

Priority 2: Design and conduct clinical trials by multidisciplinary investigators to test the efficacy of new diagnostic and treatment modalities for late-stage gastroesophageal cancers. These should include measurements of QoL, cost-effectiveness, best supportive care, and patient education in the non-curative management of late disease.

Rationale: Currently, there are very few clinical trials for advanced-stage gastroesophageal cancers, and virtually no symptom management studies related to these cancers.

Priority 3: *Develop validated tumor models for late-stage gastroesophageal cancers to facilitate the development and testing of new drugs that would allow effective treatment of advanced tumors.*

Rationale: Tumor models of late-stage disease are necessary to elucidate biological and genetic mechanisms of cancer progression. They are needed to test the efficacy of therapeutic agents and permit the application of genomics and proteomics.

Infrastructure Needed To Accomplish Priorities

Partnership Platforms

Establish partnerships for research and education with other governmental agencies, cooperative groups, community oncologists, private foundations, relevant professional organizations, industry, and patient

advocacy groups—particularly the National Coalition of Cancer Survivorship.

Expected Resources To Overcome Limitations of Previous Research and To Capitalize on Existing Opportunities

- Investigate and define optimal information networks, including the NCI Office of Communication, to:
 - Inform patients
 - Educate physicians about the standards of care for advanced disease (e.g., physicians need to anticipate B12 deficiency, the need for bone-density scans, and the possibility of *H. pylori* infection). It may be possible to approach this objective by modifying widely disseminated Clinical Practice Guidelines.
- Develop an Internet-based information system for public distribution. It should include information about post-operative complications, nutritional needs, etc.

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Stomach/Esophageal Cancers PRG Members

Appendix C: Stomach/Esophageal Cancers PRG Members

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