
**NATIONAL CANCER INSTITUTE
CLINICAL TRIALS AND TRANSLATIONAL RESEARCH
ADVISORY COMMITTEE (CTAC)**

**GASTRIC AND ESOPHAGEAL CANCERS
WORKING GROUP**

**WORKING GROUP REPORT
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INTRODUCTION

Cancers of the stomach and esophagus are deadly with poor survival rates. Combined they are the second most common cause of cancer mortality worldwide resulting in more than 1.3 million deaths in 2020.¹ In the United States, it is estimated that these cancers will account for more than 45,000 new cases of cancer and 27,000 deaths in 2022.^{2,3} The incidence of both cancers is greater in males and increases with age peaking in the seventh and eighth decades. Although these malignancies are relatively uncommon in the United States, they are often diagnosed at later stages resulting in significant morbidity and high mortality.

Gastric adenocarcinoma (also known as gastric cancer) is the most common type of stomach cancer accounting for more than 95% of cases.⁴ Risk factors for gastric cancer include *Helicobacter pylori* (*H. pylori*) infection, Epstein-Barr virus (EBV) infection, chronic gastritis, certain diets, tobacco smoking, pernicious anemia, and a family history.⁵ Approximately 10% of gastric cancers are associated with one of several hereditary genetic syndromes. Gastric cancer typically is classified based on anatomic location (cardia or proximal stomach versus non-cardia), histology (intestinal versus diffuse), and molecular features (four major subtypes).⁶

Esophageal cancer consists of two major histologic types, squamous cell carcinoma and adenocarcinoma, which differ in their risk factors, tumor location, and molecular features.⁷ The incidence of esophageal squamous cell carcinoma has been declining in the US over the past several decades, while new cases of esophageal adenocarcinoma have been progressively increasing such that it is now the predominant type of esophageal cancer.⁸ Esophageal squamous cell carcinoma is associated with tobacco and alcohol use and has a higher incidence in males and Blacks. It is thought to arise from squamous dysplasia and is more commonly found in the middle or upper esophagus. Esophageal adenocarcinoma is more frequently found in the distal esophagus, associated with obesity, chronic acid reflux, and in most cases, develops from Barrett's esophagus, a condition where the normal esophageal cells are replaced by intestinal cells with varying degrees of dysplasia. Recent molecular characterization indicate that esophageal adenocarcinoma is very similar to the intestinal type of gastric adenocarcinoma occurring in the proximal stomach and gastroesophageal junction.⁹

It has been over two decades since the [NCI's Stomach and Esophagus Cancers Progress Review Group report](#) was released in 2002. In the intervening years, the overall incidence and mortality rates for esophageal cancer in the United States have declined modestly while those for stomach cancer have declined more substantially.^{10,11} However, there has been a worrisome increase in the incidence of gastric cancer in young non-Hispanic White females.¹² Despite advances in cancer science and clinical practice, five-year relative survival rates for both diseases remain distressingly low (20.6% for esophageal cancer and 33.3% for stomach cancer).^{2,3} Disease- and treatment-associated morbidity remain major challenges and

substantial disparities remain across populations in some measures of disease burden.¹³ There remains a compelling need for further progress.

WORKING GROUP FORMATION AND APPROACH

In December 2021, NCI convened the Clinical Trials and Translational Research Advisory Committee (CTAC) *ad hoc* Gastric and Esophageal Cancers Working Group to advise the NCI Director and CTAC on translational research strategies to most effectively advance the field. The Working Group was co-chaired by Dr. Karyn Goodman, Professor, Radiation Oncology, Icahn School of Medicine and Associate Director of Clinical Research, Tisch Cancer Institute at Mount Sinai and Dr. Anil Rustgi, Irving Professor of Medicine and Director, Herbert Irving Comprehensive Cancer Center at Columbia University. Members comprised a broad range of stakeholders in the field including individuals with expertise in medical, surgical, and radiation oncology, gastroenterology, cancer screening and prevention, imaging, epidemiology, pathology, and advocacy. The membership of the Working Group is provided in Addendum 1.

The Working Group recommendations presented in this report were developed through a sequential process, beginning with a first virtual plenary meeting on December 13, 2021. During this initial meeting, then-NCI Director Dr. Norman Sharpless charged the Working Group with the following mission:

- Identify translational research knowledge gaps related to gastroesophageal cancer
- Identify the most provocative and impactful translational research questions to advance the prevention, diagnosis, and treatment of gastroesophageal cancer
- Examine and identify the most important opportunities for application of new technologies to gastroesophageal cancer translational research.

In defining the scope of this charge, the term ‘gastroesophageal cancer’ referred to gastric adenocarcinoma and the two major types of esophageal cancer. Certain rare cancers including gastrointestinal stromal tumors, neuroendocrine tumors, and lymphomas were not included because of their substantively different cellular origins and different approaches to treatment.

Following the charge, the Working Group was presented with overviews of the extramural portfolio of NIH-funded research grants and a landscape analysis of clinical trials addressing gastric and esophageal cancer. (See Appendix 1 and 2.) In addition, a new NCI program dedicated to the origins of gastric and esophageal adenocarcinomas ([RFA-CA-21-026](#) and [RFA-CA-21-027](#)) was introduced and its scope described. Subsequent to the initial meeting, advocacy organizations including Debbie’s Dream Foundation, DeGregorio Family Foundation, and Esophageal Cancer Action Network were invited to share their portfolios of funded projects and research with the Working Group. Additionally, a portfolio analysis of non-NIH funded

gastroesophageal research was conducted using the International Cancer Research Partnership database.

For purposes of its deliberations, the Working Group was organized into subgroups around four topics:

- “-Omic” technologies, including functional genomics, transcriptomics, proteomics, metabolomics, microbiomics, etc.
- Experimental model systems, including mouse, 2D and 3D organoids, patient-derived xenografts, human tissues, and animal/human imaging
- Prevention, screening, surveillance, and early detection
- Treatment, correlative studies, and additional enabling technologies including big data, radiomics, and biobanking.

Each subgroup held a series of virtual conferences to assess the status of each research or technology domain, identify key knowledge gaps limiting progress, and propose priority initiatives to address those gaps. At a second and final virtual plenary meeting on June 29, 2022, the Working Group received reports on each subgroup’s deliberations and discussed and approved a unified set of recommendations encompassing both an overall research strategy and a set of initiatives for implementation to advance the prevention, diagnosis, and treatment of gastroesophageal cancer. These recommendations with their associated rationale are presented in this report.

RECOMMENDATIONS

Reflecting the compelling unmet need for clinical advances that will have a material impact on the lives of patients with gastric and esophageal cancers, the Working Group charge highlighted the importance of translational research, which seeks to advance insights that have emerged from fundamental research to the point where they are embodied in novel modalities that are ready for evaluation in clinical trials. Throughout its deliberations, the Working Group gave close attention to the availability of promising translational opportunities – specific clinical challenges for which there are novel insights in hand that are judged likely to lead relatively quickly to readiness for clinical testing if pursued with a focused developmental effort.

However, it was the consensus of the Working Group that the impact so far on gastric and esophageal cancers of the targeted and immunotherapeutic agents that have shown promise in other tumor types has been modest, and that material progress is likely to require new insights, candidate agents and regimens, and predictive biomarkers. In addition, the Working Group noted the challenges of applying today’s costly and invasive assessment modalities to the tasks of population-level screening, detection and surveillance, and the absence of practical concepts for preventive interventions beyond those associated with the

prevention and management of *H. pylori* infection.¹⁴ Accordingly, the Working Group recommends a strategy aimed at building a more robust pipeline of translational opportunities. This strategy addresses both the strengthening of key enabling resources and tools and their application to fundamental research to identify new markers, targets, interventions, and population-level strategies with sufficient promise to justify focused translational efforts.

Overarching Research Strategy Recommendation

Develop precision approaches for the prevention, screening, detection, surveillance, and treatment of gastric and esophageal cancers by:

- Building repositories of well-characterized biospecimens and model systems that embody key stages in gastric and esophageal carcinogenesis and progression across diverse populations
- Further developing analytic tools and computational methods to characterize gastric and esophageal cancer pathophysiologic processes with greater clarity and insight
- Identifying actionable markers and targets within the processes of gastric and esophageal carcinogenesis and progression
- Developing novel clinical assessment tools and interventions for gastric and esophageal cancers based on those markers and targets.

Specific Recommendations

The specific recommendations detailed below are organized into two major topical areas: *Enabling Resources and Tools and Future Research Directions*.

1. ENABLING RESOURCES

A. Biospecimen Repositories

Clinically-annotated biospecimens with defined, disease-related characteristics are a critical enabling resource for the fundamental research needed to identify markers and targets specific to gastric and esophageal cancer. To date, collection strategies of existing general biorepositories, although not focused on gastric and esophageal cancer, have achieved modest representation of tissues from gastroesophageal cancers with a haphazard mix of attributes.¹⁵ Access hurdles for researchers who wish to make use of specimens from the repositories further limit the impact of these resources. Working Group deliberations highlighted several points:

- The importance of prospectively defining specimen attributes – clinical scenarios, tissue types and standardized processing methods – needed to enable prioritized lines of

research, and of implementing collection strategies that can efficiently gather specimens with these attributes

- The value of paired or grouped specimens (e.g., tumor and adjacent normal tissue, primary tumor and metastasis, specimens collected at diagnosis and at progression/relapse) that enable compare-and-contrast analyses
- The need for standardized methods for collection, processing, and characterization of specimens to assure validity, consistency, and comparability of data and insights derived from specimens
- The need for wider awareness of and access to collected specimens, if they are to have a broad impact on research progress.

The Working Group's recommendations related to **Biospecimen Repositories (BR)** address all of these considerations.

Recommendation BR-1: *Launch a concerted effort to overcome logistical obstacles and assemble repositories of clinically annotated biospecimens that embody key stages in gastric and esophageal carcinogenesis and progression across diverse populations.*

Recommendation BR-2: *Identify an initial set of high-priority biospecimens to be made available through a national repository that is accessible to all qualified researchers with meritorious proposals.*

Specific implementation strategies for these recommendations were offered by the Working Group as three sub-recommendations.

Recommendation BR-S1: *Collect specimens from both observational and interventional study cohorts, emphasizing paired, grouped, or sequential specimens that illuminate key events in carcinogenesis and progression as well as variations in these processes across populations:*

- *Longitudinal samples including normal tissue, precancers, early and late cancers, untreated and treated*
- *Specimens from responders and non-responders to therapy in gastric and esophageal cancer clinical trials, including exceptional responders*
- *Specimens pre- and post-emergence of gastric and esophageal cancer treatment resistance in clinical trials*
- *Specimens from hereditary risk groups and from diverse racial/ethnic populations, including international populations*
- *Grouped specimens of different types from the same individuals (e.g., solid tissue, blood, oral/stool/mucosal microbiome, breath).*

Recommendation BR-S2: *Devise strategies for identifying and, where necessary, creating observational and interventional study cohorts that lend themselves to efficient collection of specimens with desired characteristics.*

Recommendation BR-S3: *Drawing on existing best practices and, where necessary, on new consensus-development initiatives, promulgate standards for collection, processing, and characterization of tissue specimens needed to enable different types of analyses.*

The Working Group envisions a centralized biospecimen repository that encompasses solid tissues, blood, and other body fluids, and provides a platform for standardization of biospecimen procurement, processing, and storage. Investigators who utilize the repository should be required to commit to a data sharing plan. This would greatly facilitate the incorporation of emerging insights into validation studies, the generation of new hypotheses and lines of research, limit redundant effort, and accelerate progress. Adequate informatics support will be critical to realizing these benefits. Also important will be a concerted effort to identify specimen types that optimally embody key stages in gastric and esophageal carcinogenesis and progression across diverse populations. Advice from a broadly representative steering committee can assure that collection strategies, operational standards, specimen access procedures, and reporting requirements are optimized for repository objectives.

The Working Group acknowledged the logistical challenges that increased specificity of requirements can impose on specimen collection. Not all specimen types that would ideally be desired for prioritized lines of research will be straightforward or even practical to collect.

Collection of pre-cancerous tissues has been especially challenging in the United States in the absence of population screening programs, though the expansion of screening for Barrett's esophagus may provide new opportunities to collect specimens addressing esophageal and gastroesophageal junction carcinogenesis. International collaborations, particularly in areas where screening programs have been active, may provide opportunities to collect specimens addressing the emergence of gastric cancer, while posing distinctive logistical hurdles in specimen handling.

Collection of specimens within clinical trials is critical to better understanding the effects of interventions; support for this collection is important.

Collection of longitudinal specimens with associated annotation poses operational burdens on clinical sites beyond those associated with isolated individual specimens. Consideration should be given to the pros and cons of collecting specimens from a large number of centers versus providing infrastructure support for a smaller, coordinated network

to sustain more intensive patient follow-up and better-standardized longitudinal specimen collection. To avoid competing claims that may arise on specimens collected in interventional trials, consideration should also be given to the creation of a non-interventional protocol dedicated to tissue collection for the envisioned national repository.

To increase the efficiency and cost-effectiveness of the recommended repository effort, where possible, NCI should build on infrastructure and technical capabilities developed under existing efforts such as the [Cancer Moonshot Biobank](#). Similarly, the development and establishment of standards for specimen collection and handling should, where possible, take advantage of the staff expertise and information resources – best practices, evidence-based practices, and research database – developed by NCI’s Biorepositories and Biospecimen Research Branch.

B. Research Tools

The importance of novel research tools for opening new lines of inquiry and generating novel, actionable insights was a consistent theme in the Working Group’s deliberations. The recommendations highlight three tool categories: model systems, laboratory analytic methods, and computational methods. Emerging methods in these domains, applied individually and especially in combination, offer the potential to serve as a powerful engine for generating novel insights into the natural history of gastric and esophageal cancer and identifying candidate markers for surveillance and detection purposes as well as possible targets for preventive and therapeutic interventions. Each approach, however, requires further development to achieve its full potential.

The Working Group made one general recommendation related to **Research Tools (RT)** and several specific recommendations related to model systems, laboratory analytic methods, and computational methods, which are outlined in this section.

Recommendation RT-1: *Develop and refine research tools to further enhance our ability to derive insight into the biology of gastric and esophageal cancer from patients, biospecimens, and model systems.*

a. Model Systems

The Working Group’s deliberations on model systems identified three aspects for which a concerted effort is required to maximize impact on target identification and translational progress: physiologic realism, production and distribution efficiency, and robustness and consistency.

Discussions highlighted the importance of organoids – *ex vivo* models that incorporate multiple cell types in two- or three-dimensional structures that recapitulate

key aspects of tumor architecture, function, and microenvironment. Organoids represent a robust opportunity to elucidate molecular mechanisms and test standard of care and novel therapies. As well, organoids offer the potential of more rapid deployment and lower cost compared to animal models. Organoid models have been created for both gastric and esophageal cancer,^{16, 17} including co-cultures of gastric organoids with *H. pylori*, demonstrating proof of concept for the general approach and providing a foundation for further efforts. However, defining optimal combinations of cell types and sources and culture conditions for answering various research questions remains a challenge.¹⁸

Working Group members called out a range of aspects into which tailored organoid models may be able to provide specific insight:

- Disease sites – e.g., gastric antrum / corpus, distal esophagus / gastric cardia
- Stages of disease progression – e.g., normal, gastric intestinal metaplasia, dysplasia, carcinoma
- Populations – e.g., underrepresented high-risk populations as well as autoimmune-driven models to reflect the increase in gastric corpus tumors in young women
- Models that can sustain anaerobic bacteria and other fastidious components of the microbiome
- iPSC-derived organoids
- Animal model-derived organoids

While several robust animal models exist,^{19, 20, 21} areas for improvement highlighted during the discussions included:

- Improved patient-derived xenograft and humanized animal models, including more immunologically-faithful animal models
- Animal models representing precancerous physiologic states

The Working Group noted that the full potential of these model systems to advance fundamental and translational research can be achieved only if the models are widely available to researchers. Collaborative efforts to refine, replicate, and disseminate novel model systems will be important.

The Working Group offered four specific recommendations related to **Research Tools - Model Systems (RT-MS)** that highlight these concepts.

Recommendation RT-MS1: *Develop, optimize, and validate preclinical and animal models that more faithfully recapitulate gastroesophageal carcinogenesis*

and progression in humans and that represent diverse populations, prioritized clinical situations, and scientific questions. Initiatives in this area should highlight improved organoid and immunocompetent animal models while remaining open to scientifically compelling proposals for development of novel models of other types.

Recommendation RT-MS2: *Recruit and collaborate with bioengineers, medical physicists, and technical specialists from other disciplines to develop model systems with greater complexity and biological realism for gastric and esophageal cancer.*

Recommendation RT-MS3: *Collaborate with bioengineers, chemical engineers, and technical specialists from other disciplines to lower the barriers to broader use of model systems by developing more economical synthetic reagents and culture systems and more efficient ways to replicate and distribute the models.*

Recommendation RT-MS4: *Promulgate standardized methods for generating and replicating uniform, well-characterized model systems for gastric and esophageal cancer.*

The Working Group highlighted examples of specific model systems that might be fruitful not for the purpose of designating them exclusively for prioritized funding but rather to encourage investigators to propose novel ideas across a broad scope and reviewers to assess proposals for creativity in bringing novel tools to bear in addressing unsolved problems.

The envisioned cross-disciplinary collaborations can be encouraged by including language in relevant Funding Opportunity Announcements that explicitly requires it. In addition, NCI should explore the potential for shared interest in model systems development with the National Institute of Biomedical Imaging and Bioengineering.

As with biospecimen repositories, standardization and validation of model systems are critical requirements for replicability and interpretability of work based upon them.

b. Laboratory Analytic Methods

Ongoing advances in laboratory analytic methods have enabled a broad range of approaches for molecular characterization of tissues. Data types now available include DNA mutations, chromatin accessibility, histone modification, DNA methylation, transcriptomics, proteomics, lipidomics, microbiomics, and metabolomics; for several of these, multiple analytic methods are available, each with its own strengths and limitations. Several of these methods can be applied not only to bulk tissues but also at

the single-cell level.²² Multiplex imaging of intact tumor tissues has enabled spatial characterization of cellular heterogeneity and interactions.²³ Radiomic data can be correlated with molecular or cellular characterization to extend insight to the macro scale, while tracer imaging can add a temporal dimension to the analysis.^{24,25} Further refinement and broad application of these tools will be essential to building the foundation for a renewed translational effort in gastric and esophageal cancer.

The Working Group offered one recommendation related to **Research Tools – Analytic Methods (RT-AM)** incorporating these concepts.

Recommendation RT-AM1: *Develop and refine biological, chemical, and physical analytic methods, including incorporation of the spatial domain, to complement the growing variety of -omics tools and further enhance our ability to derive insight into the biology of gastric and esophageal cancer from patients, biospecimens, and model systems.*

While cautioning against neglect of other methods, the Working Group highlighted the potential for increased insight through the combined application of molecular characterization and advanced imaging methods in both patients and model systems, as well as the potential of this approach to help characterize and validate model systems relative to humans. The following potential lines of work were discussed as examples without prejudice against other possibilities that may be proposed by investigators:

- Further develop imaging methods for assessment of immune activation *in vivo*, including novel probes of the immune environment, immune activation, and inflammation
- Develop improved optical imaging and radiotracer techniques to quantify additional physiologic components that contribute to carcinogenesis and progression, such as host cellular metabolism, microbiome composition, cell proliferation, hypoxia, and DNA damage
- Build on insights from metabolomic analyses to develop radiomic labels/markers with improved sensitivity at both microscopic and macroscopic scales

c. Computational Methods

Working Group discussions encompassed both the enormous potential of machine learning methods to facilitate recognition of previously unappreciated, physiologically important associations among observed phenomena, and the risk that black-box methods may generate false signals that lead investigators astray. Close collaboration between researchers with deep biological and clinical knowledge and

analysts with a deep understanding of machine learning algorithms, their validation, and failure modes are essential.

Achieving the full potential of machine learning methods will also require attention to the assembly, cleaning, and integration of data sets providing complementary perspectives on the biological phenomena of interest. Multidimensional -omics characterizations, diverse imaging modalities, and classical clinical and pathological observations, including outcomes data, will all be important inputs.

Funding for routine collection of specified -omics data, for example in clinical trial settings, could greatly increase the quantity and value of relevant data resources. As with biospecimens and model systems, standardization of methods for data collection and formatting is essential for both the feasibility of data integration and the validity and commensurability of the resulting analyses. Similarly, policies and procedures should be established to enable ready access to data resources for qualified investigators with approved research proposals.¹⁴

The Working Group incorporated these concepts into one recommendation related to **Research Tools – Computational Methods (RT-CM)**.

Recommendation RT-CM1: *Collaborate with bioengineers, medical physicists, bioinformatics specialists, and other disciplines to develop and validate machine learning approaches for assessing patterns within and across diverse -omics and other data types to infer interventional targets for prevention or treatment of gastric and esophageal cancer.*

2. FUTURE RESEARCH DIRECTIONS

A. Biological Insights and Fundamental Research

The Working Group's recommendations on biological insights and fundamental research are central to the proposed strategy. The goal is to “harvest” the many advances that continue to be made in analytic technologies and research methods by applying them to biological questions specific to gastric and esophageal cancer in order to build a more robust pipeline of translational opportunities.

The Working Group acknowledges that NCI's recent issuance of [RFA-CA-21-026](#) and [RFA-CA-21-027](#), Program on the Origins of Gastroesophageal Cancers, is a significant step forward and urges NCI to build on this important initiative by adding support for complementary investigations of downstream phases of disease and treatment. In addition, the Working Group

urges NCI to monitor efforts by biomedical research funding agencies in other countries, private foundations, and patient advocacy groups to assure that available resources are channeled to most effectively fill gaps and strengthen the overall research effort. Where appropriate, NCI should engage in collaborative efforts to apply complementary resources and capabilities to greatest effect.

The Working Group offered one recommendation and three associated sub-recommendations related to **Biological Insights (BI) and Fundamental Research** to further elucidate the biology of gastroesophageal carcinogenesis and progression.

Recommendation BI-1: *Apply -omics and other emerging analytical tools and computational methods to characterize gastric and esophageal cancer pathophysiologic processes with greater clarity and insight and identify translationally actionable markers and targets within the processes of gastroesophageal carcinogenesis and progression.*

Recommendation BI-S1: *Improve the molecular characterization of gastric and esophageal precancer and disease progression from emergence of precancer states through early-stage cancer to disease recurrence and advanced disease and across diverse racial/ethnic populations, hereditary risk groups, and cancer subtypes. Seek an integrated understanding of how genomic, molecular, clinical, environmental, and behavioral factors interact to determine the risk of gastric and esophageal cancer initiation and progression.*

Recommendation BI-S2: *Elucidate the functional significance for gastric and esophageal cancer of genomics, proteomics, metabolomics, microbiomics, and tumor microenvironment and characterize associated targets that may be susceptible to intervention.*

Recommendation BI-S3: *Investigate the biology of exceptional responders in gastric and esophageal cancer and of acquired and de novo resistance to immunotherapies and targeted therapies.*

B. Treatment

The need for better treatments for gastroesophageal cancers was a recurring theme throughout Working Group discussions. Surgical resection is potentially curative for the few patients with localized disease. Multimodality treatment is the most common approach for patients with locally advanced esophageal or stomach cancer. Chemotherapy has been the mainstay of treatment for recurrent or metastatic disease, but current regimens only yield survival of a little over a year, highlighting the need for improved therapies. Targeted therapies to date have been disappointing with the exception of trastuzumab which provides modest benefit for tumors expressing the human epidermal growth factor receptor 2 protein (HER-2).

Immunotherapy agents have emerged as promising new therapies for gastroesophageal cancers.²⁶ One challenge to broader application is that a substantial number of tumors are immunologically “cold” and derive no benefit from immunotherapy.

Recently, the Cancer Genome Atlas (TCGA) research network proposed four genomically distinct gastric cancer subtypes based on a comprehensive genome-wide analysis: Epstein-Barr virus positive, microsatellite instable, genomically stable, and chromosomal unstable.⁶ The full clinical utility of this classification has yet to be realized.

There is still much research needed to identify immune targets, novel combinations of treatment, and patients that will respond best to current treatments. Working Group recommendations and observations on translating biological insights to make therapeutic advances are outlined in this section. One general recommendation was made related to **treatment (T)** with sub-recommendations further delineating needs for **clinical assessment tools** and **therapeutic regimens**.

Recommendation T1: *Apply -omics and other emerging analytical tools and computational methods to translate emerging biological insights on gastric and esophageal cancer into improved clinical assessment tools and therapeutic regimens, tailored more effectively to the distinctive characteristics of each patient’s disease process.*

a. Clinical Assessment Tools

Recommendation T-S1: *Develop improved methods for predicting and monitoring response and resistance of gastric and esophageal cancer to therapy, particularly for guiding treatment of patients receiving front-line therapy and immunotherapy combinations.*

Recommendation T-S2: *Develop surrogate markers of therapeutic effect in gastric and esophageal cancer to enable rapid assessment of new agents and accelerate clinical trials.*

The Working Group noted the substantial current interest in the use of liquid biopsies including circulating tumor DNA (ctDNA) as a measure of treatment response and a potential early endpoint for clinical trials.²⁷ Promising initial validation studies of ctDNA use in non-small cell lung cancer²⁸ and other tumor types should be extended to gastric and esophageal cancer, but the Working Group urges NCI to continue to support other lines of research such as development of more rapid and sensitive imaging markers as well.

b. Therapeutic Regimens

Recommendation T-S3: *Develop improved treatments for gastric and esophageal cancer, particularly for patients with refractory disease, including optimized and novel:*

- *Immunotherapy and immune-oncology combination regimens*
- *Targeted therapies*
- *Cell-based therapies.*

Recommendation T-S4: *Identify targets and develop methods for image-guided treatment in gastric and esophageal cancer.*

The field of image-guided treatment was highlighted in Working Group discussions as an area that is seeing rapid advances in technological capability through integration of progress across different research domains. The use of targeted optical agents to delineate tumor tissues offers the potential for increasing therapeutic effectiveness while reducing the morbidity associated with surgical procedures and radiation therapy.

Recommendation T-S5: *Develop new approaches to preventing or mitigating adverse effects associated with gastric and esophageal cancer and/or its treatment.*

The Working Group took a broad view of the morbidity associated with gastric and esophageal cancer and its treatment rather than singling out particular adverse effects for attention. A key common pathway to morbidity is the effects of both disease and treatment on nutritional adequacy, while nutritional inadequacy in turn can limit the patient's ability to endure physiologically-challenging therapeutic and supportive interventions. While the most fundamental need in treatment is for therapeutic interventions with greatly improved efficacy, the devastating effects of gastric and esophageal cancer and its treatment on quality of life point as well to the importance of seeking and following up on any novel physiologic insights that may enable more effective supportive care interventions.

C. Prevention

The Working Group took a broad approach to applying multi-omic and experimental model systems to prevention. The relative ease and safety of sampling the esophagus and stomach provide an opportunity to apply emerging technologies to biological specimens for rapid translation. One general recommendation relating to **prevention (P)** was made with sub-

recommendations further delineating research directions for **screening, detection, and surveillance** as well as **prevention interventions**.

Recommendation P1: *Apply -omics and other emerging analytical tools and computational methods to translate emerging biological insights into improved practical tools and strategies for risk stratification, screening, early detection, and surveillance of both precancerous lesions and gastric and esophageal cancers, as well as practical and effective preventive interventions tailored to the characteristics of specific populations.*

a. Screening, Detection, and Surveillance

Screening and surveillance pose an especially difficult challenge: modalities for use in population-scale programs must be not only technologically feasible but also logistically and economically practical. Working Group deliberations highlighted the need both for less-invasive detection modalities – for example, the [EsoCheck™](#) / [EsoGuard™](#) system for detecting Barrett’s esophagus, developed with support from [NCI’s BETRNet](#) program – and for risk assessment models that integrate biological, clinical, and social factors to guide the efficient and cost-effective deployment of various detection modalities in population screening and surveillance programs.

The Working Group discussed the potential value of liquid biopsies²⁵ as well as volatile markers²⁹ and other biological indicators assessed via less-invasive modalities but noted the varying sensitivity of such indicators at different stages of the disease process, and in particular the limitations of current versions of these technologies in detecting disease at sufficiently early stages to inform preventive interventions. Accordingly, the Working Group recommends research across a broad front to identify and validate new, minimally-invasive detection modalities for use in screening and surveillance, rather than concentrating resources solely on existing modalities.

Recommendation P-S1: *Develop more sensitive and accurate assessment tools for screening and early detection of gastric and esophageal cancer.*

Recommendation P-S2: *Develop more sensitive and accurate assessment tools to characterize gastric and esophageal cancer risk. Evaluate the use of endoscopy findings, including innovative molecular probes and AI/machine learning approaches, as a risk stratifier.*

Recommendation P-S3: *Develop more sensitive and accurate assessment tools for gastric and esophageal cancer disease surveillance.*

b. Prevention Interventions

Recommendation P-S4: *Develop novel preventive interventions for gastric and esophageal cancer.*

Preventive interventions for gastroesophageal cancers tested in clinical trials to date have not yielded promising results with the exception of endoscopic ablative therapy and proton pump inhibitors for Barrett's esophagus and antibiotic therapy for *H. pylori* infection.^{30, 31, 32, 33}

Recommendation P-S5: *Apply state-of-the-art vaccine development technologies to advance the development of *H. pylori* vaccines.*

Recommendation P-S6: *Define optimal antibiotic stewardship practices for *H. pylori* eradication, including surveillance systems for antibiotic resistance.*

The association of *H. pylori* infection with gastric cancer suggests that an effective vaccine against *H. pylori* infection would present a rare opportunity to have a large impact on the global burden of gastric cancer. However, Working Group discussions illuminated the complexity of the epidemiology and pathophysiology of *H. pylori* infection, noting the wide geographical variation in infection rates and trends, disease associations, and antibiotic susceptibility patterns, as well as evidence suggesting an inverse relationship between *H. pylori* infection and the risk of other cancers such as esophageal adenocarcinoma and gastric cardia cancer. Accordingly, the Working Group endorsed a broad-based research program to advance a range of interventions and supporting evidence with the goal of enabling optimal matching of interventions with specific patients and populations.

The Working Group noted the increasing weight of esophageal cancer within the overall morbidity and mortality burden of gastric and esophageal cancer in the US population and recommends support for research on preventive interventions for non-*H. pylori*-related gastric and esophageal cancers as well.

CONCLUSION

The epidemiologic and clinical realities of gastric and esophageal cancer define a compelling need for substantial advances in prevention, detection, surveillance, and treatment. Reviewing progress over the past couple of decades, including the extent to which emerging therapeutic strategies that have been successful for other tumor types have only had a modest impact on gastric and esophageal cancers to date, the Working Group concluded that a

concerted and sustained effort is needed to build a more robust pipeline of translational opportunities.

Recognizing the national and global problems underlying gastric and esophageal cancer, there is no one intervention or priority that will serve as a panacea. Instead, the Working Group recommends a broad-based, interdisciplinary approach that spans prevention, screening/surveillance/early detection, risk, and therapy. Rapid and continuing advances in laboratory analytic methods and computational approaches applied to existing and novel model systems offer great promise for generating biological insights that can provide the foundation for translational development. Establishing the biospecimen repository envisioned by the Working Group, as well as the further development and propagation of model systems tailored specifically to the biological questions raised by gastric and esophageal cancer are critical. These resources will be essential to achieving the ultimate goals of identifying risk factors, prognostic and predictive biomarkers, and identifying effective new interventions to prevent and treat these diseases.

Such a broad-based approach in turn requires a focus on collaborations between federal agencies, public and private universities/institutes, industry, patient advocacy, and philanthropy. Progress is feasible, at times incremental and at other times more dramatic, all converging to have impact upon gastric and esophageal cancer incidence and mortality.

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Addendum 1 – Working Group Roster

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Addendum 2 – Summary of Recommendations

CLINICAL TRIALS AND TRANSLATIONAL RESEARCH ADVISORY COMMITTEE (CTAC) GASTRIC AND ESOPHAGEAL CANCERS WORKING GROUP SUMMARY OF RECOMMENDATIONS

OVERARCHING RESEARCH STRATEGY

Develop precision approaches for the prevention, screening, detection, surveillance, and treatment of gastric and esophageal cancers by:

- Building repositories of well-characterized biospecimens and model systems that embody key stages in gastric and esophageal carcinogenesis and progression across diverse populations
- Further developing analytic tools and computational methods to characterize gastric and esophageal cancer pathophysiologic processes with greater clarity and insight
- Identifying actionable markers and targets within the processes of gastric and esophageal carcinogenesis and progression
- Developing novel clinical assessment tools and interventions for gastric and esophageal cancers based on those markers and targets.

SPECIFIC RECOMMENDATIONS

1. ENABLING RESOURCES

A. Biospecimen Repositories (BR)

Recommendation BR-1: Launch a concerted effort to overcome logistical obstacles and assemble repositories of clinically annotated biospecimens that embody key stages in gastric and esophageal carcinogenesis and progression across diverse populations.

Recommendation BR-2: Identify an initial set of high-priority biospecimens to be made available through a national repository that is accessible to all qualified researchers with meritorious proposals.

Recommendation BR-S1: Collect specimens from both observational and interventional study cohorts, emphasizing paired, grouped or sequential specimens that illuminate key events in carcinogenesis and progression as well as variations in these processes across populations:

- Longitudinal samples including normal tissue, precancers, early and late cancers, untreated and treated Specimens from responders and non-responders to

therapy in gastric and esophageal cancer clinical trials, including exceptional responders

- Specimens pre- and post-emergence of gastric and esophageal cancer treatment resistance in clinical trials
- Specimens from hereditary risk groups and from diverse racial/ethnic populations, including international populations
- Grouped specimens of different types from the same individuals (e.g., solid tissue, blood, oral/stool/mucosal microbiome, breath).

Recommendation BR-S2: Devise strategies for identifying and, where necessary, creating observational and interventional study cohorts that lend themselves to efficient collection of specimens with desired characteristics.

Recommendation BR-S3: Drawing on existing best practices and, where necessary, on new consensus-development initiatives, promulgate standards for collection, processing and characterization of tissue specimens needed to enable different types of analyses.

B. Research Tools (RT)

Recommendation RT-1: Develop and refine research tools to further enhance our ability to derive insight into the biology of gastric and esophageal cancer from patients, biospecimens and model systems.

a. Model Systems (MS)

Recommendation RT-MS1: Develop, optimize, and validate preclinical and animal models that more faithfully recapitulate gastroesophageal carcinogenesis and progression in humans and that represent diverse populations, prioritized clinical situations and scientific questions. Initiatives in this area should highlight improved organoid and immunocompetent animal models while remaining open to scientifically compelling proposals for development of novel models of other types.

Recommendation RT-MS2: Recruit and collaborate with bioengineers, medical physicists, and technical specialists from other disciplines to develop model systems with greater complexity and biological realism for gastric and esophageal cancer.

Recommendation RT-MS3: Collaborate with bioengineers, chemical engineers, and technical specialists from other disciplines to lower the barriers to broader use of model systems by developing more economical synthetic reagents and culture systems and more efficient ways to replicate and distribute the models.

Recommendation RT-MS4: Promulgate standardized methods for generating and replicating uniform, well-characterized model systems for gastric and esophageal cancer.

b. Laboratory Analytic Methods (AM)

Recommendation RT-AM1: Develop and refine biological, chemical, and physical analytic methods, including incorporation of the spatial domain, to complement the growing variety of -omics tools and further enhance our ability to derive insight into the biology of gastric and esophageal cancer from patients, biospecimens and model systems.

c. Computational Methods (CM)

Recommendation RT-CM1: Collaborate with bioengineers, medical physicists, bioinformatics specialists, and other disciplines to develop and validate machine learning approaches for assessing patterns within and across diverse -omics and other data types to infer interventional targets for prevention or treatment of gastric and esophageal cancer.

2. FUTURE RESEARCH DIRECTIONS

A. Biological Insights (BI) and Fundamental Research

Recommendation BI-1: Apply -omics and other emerging analytical tools and computational methods to characterize gastric and esophageal cancer pathophysiologic processes with greater clarity and insight and identify translationally actionable markers and targets within the processes of gastroesophageal carcinogenesis and progression.

Recommendation BI-S1: Improve the molecular characterization of gastric and esophageal precancer and disease progression from emergence of precancer states through early-stage cancer to disease recurrence and advanced disease and across diverse racial/ethnic populations, hereditary risk groups and cancer subtypes. Seek an integrated understanding of how genomic, molecular, clinical, environmental, and behavioral factors interact to determine the risk of gastric and esophageal cancer initiation and progression.

Recommendation BI-S2: Elucidate the functional significance for gastric and esophageal cancer of genomics, proteomics, metabolomics, microbiomics, and tumor microenvironment and characterize associated targets that may be susceptible to intervention.

Recommendation BI-S3: Investigate the biology of exceptional responders in gastric and esophageal cancer and of acquired and de novo resistance to immunotherapies and targeted therapies.

B. Treatment (T)

Recommendation T1: Apply -omics and other emerging analytical tools and computational methods to translate emerging biological insights on gastric and esophageal cancer into improved clinical assessment tools and therapeutic regimens, tailored more effectively to the distinctive characteristics of each patient's disease process.

a. Clinical Assessment Tools

Recommendation T-S1: Develop improved methods for predicting and monitoring response and resistance of gastric and esophageal cancer to therapy, particularly for guiding treatment of patients receiving front-line therapy and immunotherapy combinations.

Recommendation T-S2: Develop surrogate markers of therapeutic effect in gastric and esophageal cancer to enable rapid assessment of new agents and accelerate clinical trials.

b. Therapeutic Regimens

Recommendation T-S3: Develop improved treatments for gastric and esophageal cancer, particularly for patients with refractory disease, including optimized and novel:

- Immunotherapy and immune-oncology combination regimens
- Targeted therapies
- Cell-based therapies.

Recommendation T-S4: Identify targets and develop methods for image-guided treatment in gastric and esophageal cancer.

Recommendation T-S5: Develop new approaches to preventing or mitigating adverse effects associated with gastric and esophageal cancer and/or its treatment.

C. Prevention (P)

Recommendation P1: Apply -omics and other emerging analytical tools and computational methods to translate emerging biological insights into improved practical tools and strategies for risk stratification, screening, early detection, and surveillance of both precancerous lesions and gastric and esophageal cancers, as well as practical and effective preventive interventions tailored to the characteristics of specific populations.

a. Screening, Detection, and Surveillance

Recommendation P-S1: Develop more sensitive and accurate assessment tools for screening and early detection of gastric and esophageal cancer.

Recommendation P-S2: Develop more sensitive and accurate assessment tools to characterize gastric and esophageal cancer risk. Evaluate the use of endoscopy findings, including innovative molecular probes and AI/machine learning approaches, as a risk stratifier.

Recommendation P-S3: Develop more sensitive and accurate assessment tools for gastric and esophageal cancer disease surveillance.

b. Prevention Interventions

Recommendation P-S4: Develop novel preventive interventions for gastric and esophageal cancer.

Recommendation P-S5: Apply state-of-the-art vaccine development technologies to advance the development of *H. pylori* vaccines.

Recommendation P-S6: Define optimal antibiotic stewardship practices for *H. pylori* eradication, including surveillance systems for antibiotic resistance.

Appendix 1 – Portfolio Analysis of NIH-Funded Gastric and Esophageal Cancers Research:

See separate document on website.

Appendix 2 – Landscape of NCI-Supported Gastric and Esophageal Cancers Clinical Trials

See separate document on website.