

Stomach/Esophageal Cancers Progress Review Group

Co-Chairs:

Timothy Eberlein, M.D.

Brian Reid, M.D., Ph.D.

Executive Director:

Ernest Hawk, M.D., MPH

Stomach/Esophageal Cancers Progress Review Group

Planning Meeting

Jan 24/25, 2002

- **Classify Progress**
- **Identify Gaps**
- **Highlight Research Opportunities**

Roundtable Meeting

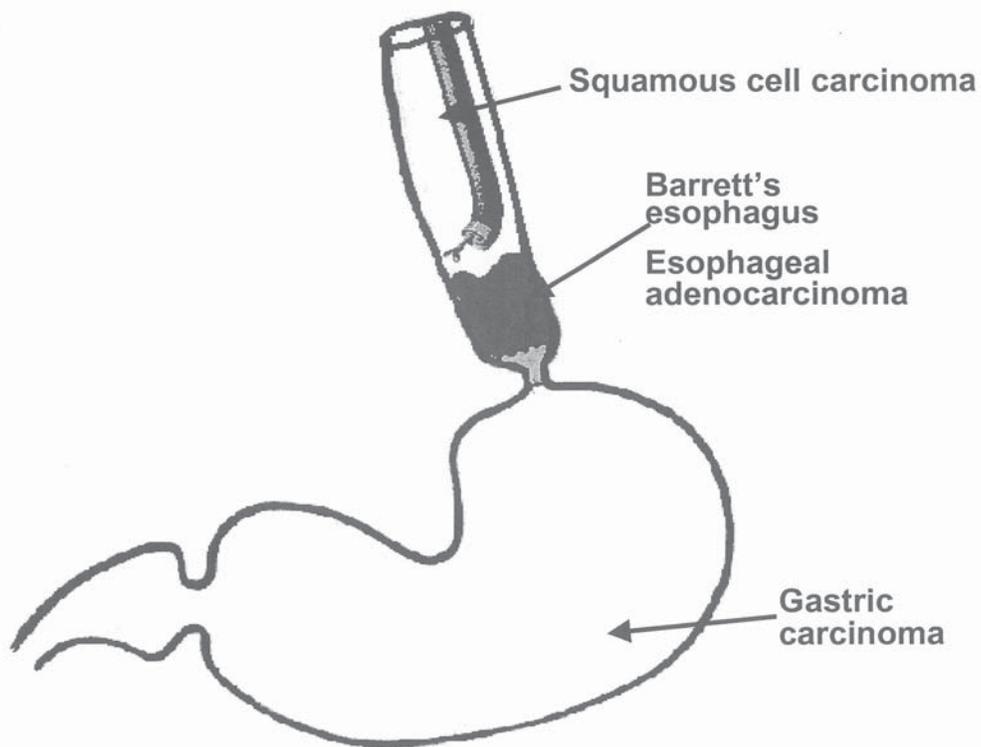
May 5-7, 2002

- **10 Scientific Guiding Principles**
- **Population Management**
- **Disease Site**

Consensus

- **10 Recommendations**

Stomach-Esophageal Cancers Progress Review Group



Special Issues

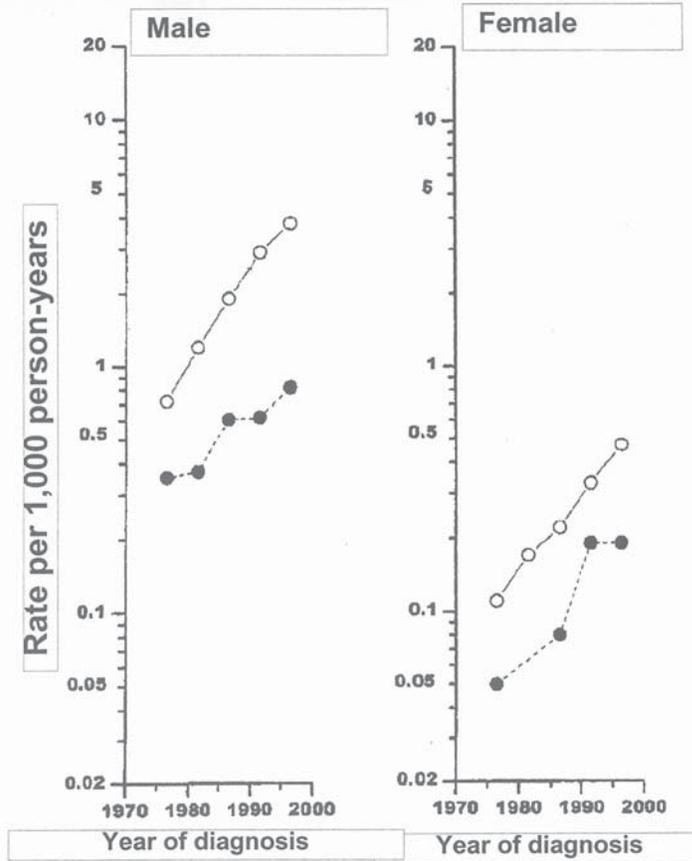
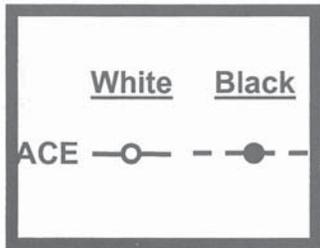
- **Low Incidence, High Morbidity and Mortality**
- **Incomplete Network Systems**
- **Lack of Awareness**
- **Lack of Advocacy**
- **Ability to Biopsy at all Stages of Disease**
- **Well Defined Pre-Malignant Lesions**

Scope of the Problem – 2002

	<u>U.S.</u>		<u>World</u>	
	<u>Incidence</u>	<u>Death</u>	<u>Incidence</u>	<u>Death</u>
Esophagus	13,900	13,000	412,327 (8)	337,501 (6)
Stomach	22,400	12,100	876,341 (4)	646,567 (2)



Rising Incidence of Adenocarcinoma of the Esophagus (ACE)

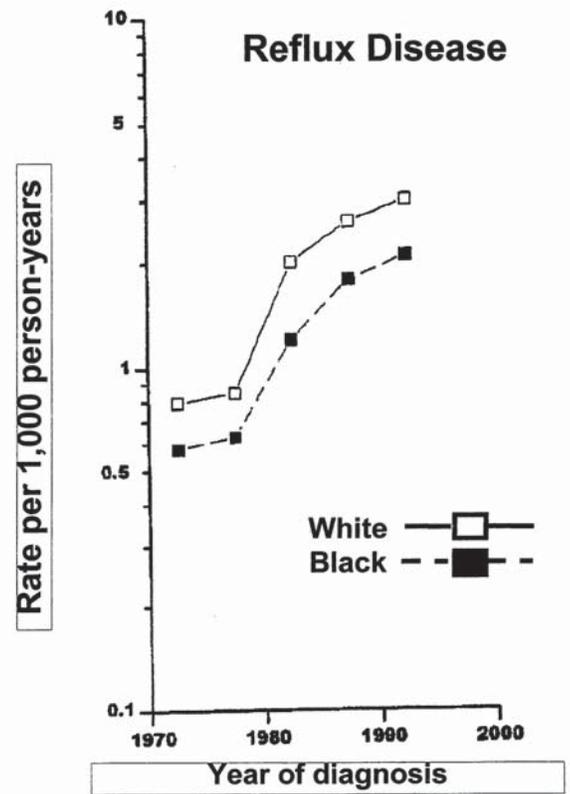
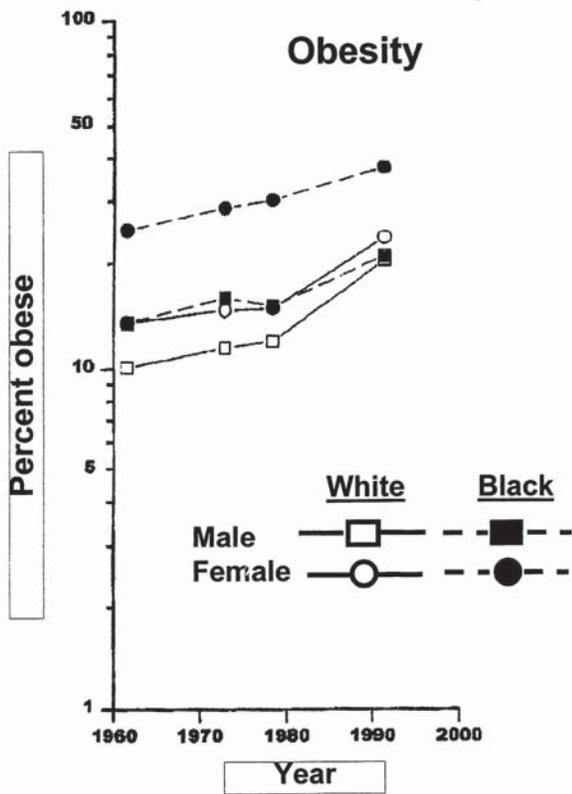


*Brown and Devesa,
Surg Oncol Clin N Am
2002; 11:235-256*

Obesity, Reflux Disease

Risk Factors for Esophageal Adenocarcinoma

Population Trends



Brown and Devesa, Surg Oncol Clin N Am 2002; 11:235-256

SEER Incidence Age-Adjusted Rates 1993-1999*

<i>Race</i>	<i>Esophagus</i>		<i>Stomach</i>	
	<i>Male</i>	<i>Female</i>	<i>Male</i>	<i>Female</i>
White	7.1	1.9	11.7	5.2
Black	12.9	4.4	19.6	9.9
Amer. Indian	2.8	0.5	9.8	5.9
Asian / PI	5.6	1.0	24.9	13.6
Hispanic	5.4	1.0	17.1	9.2

*cases per 10,000 population

Stomach/Esophageal Cancers Progress Review Group
Priority Recommendations

Population Studies:

Establish a network 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.

Neoplastic Progression in Stomach/Esophageal Cancers

- **multi-decade process**
- **genomic instability**
- **impact of risk factors**

H. Pylori

gastric acid/bile

diet

tobacco

obesity

- **need to identify molecular/cellular mechanisms**

Stomach/Esophageal Cancers Progress Review Group
Priority Recommendations

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.

Gastroesophageal Cancers Represent A Diverse Group of Malignancies

- * up to 25% of gastric cancer patients receive no surgical treatment
- * lack of focus on educating high-risk groups
- * opportunity to develop educational tools for patients, families, the public, advocacy groups and healthcare professionals

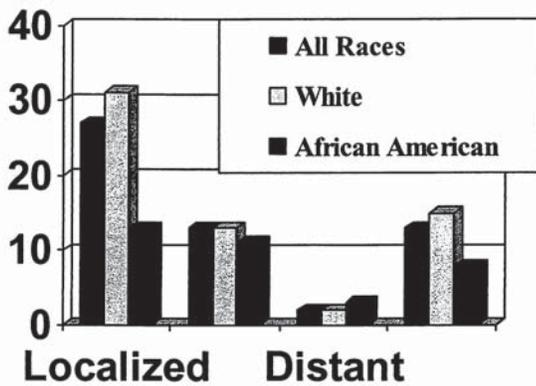
Stomach/Esophageal Cancers Progress Review Group
Priority Recommendations

Patient/Provider Education:

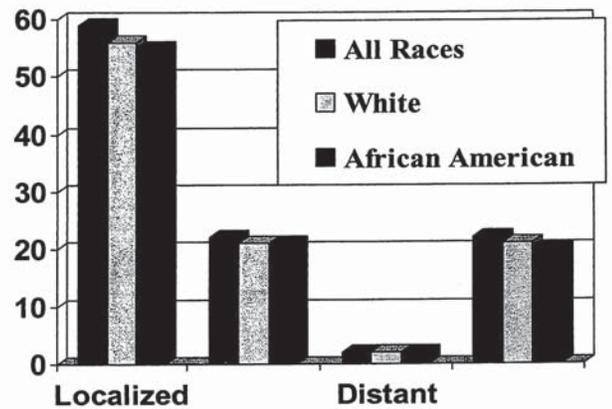
Educate patients and their families, healthcare professionals, and the public regarding risk factors, risk reduction and treatment options and outcomes for gastroesophageal cancers and their precursor states.

5-Year Survival Rates 1992-1998*

Esophagus



Stomach



*Units of measurement

Stomach/Esophageal Cancers Progress Review Group
Priority Recommendations

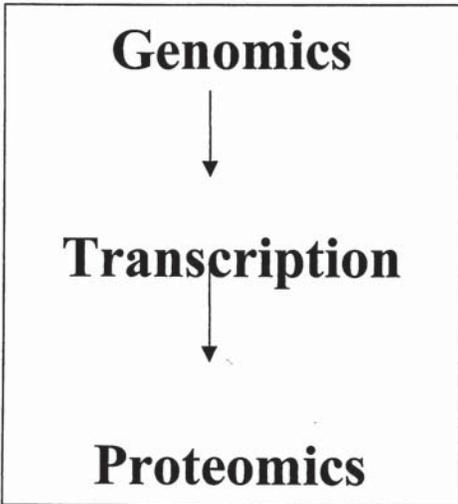
Therapy:

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

C

C

C



+

**Endoscopic
Biopsy**

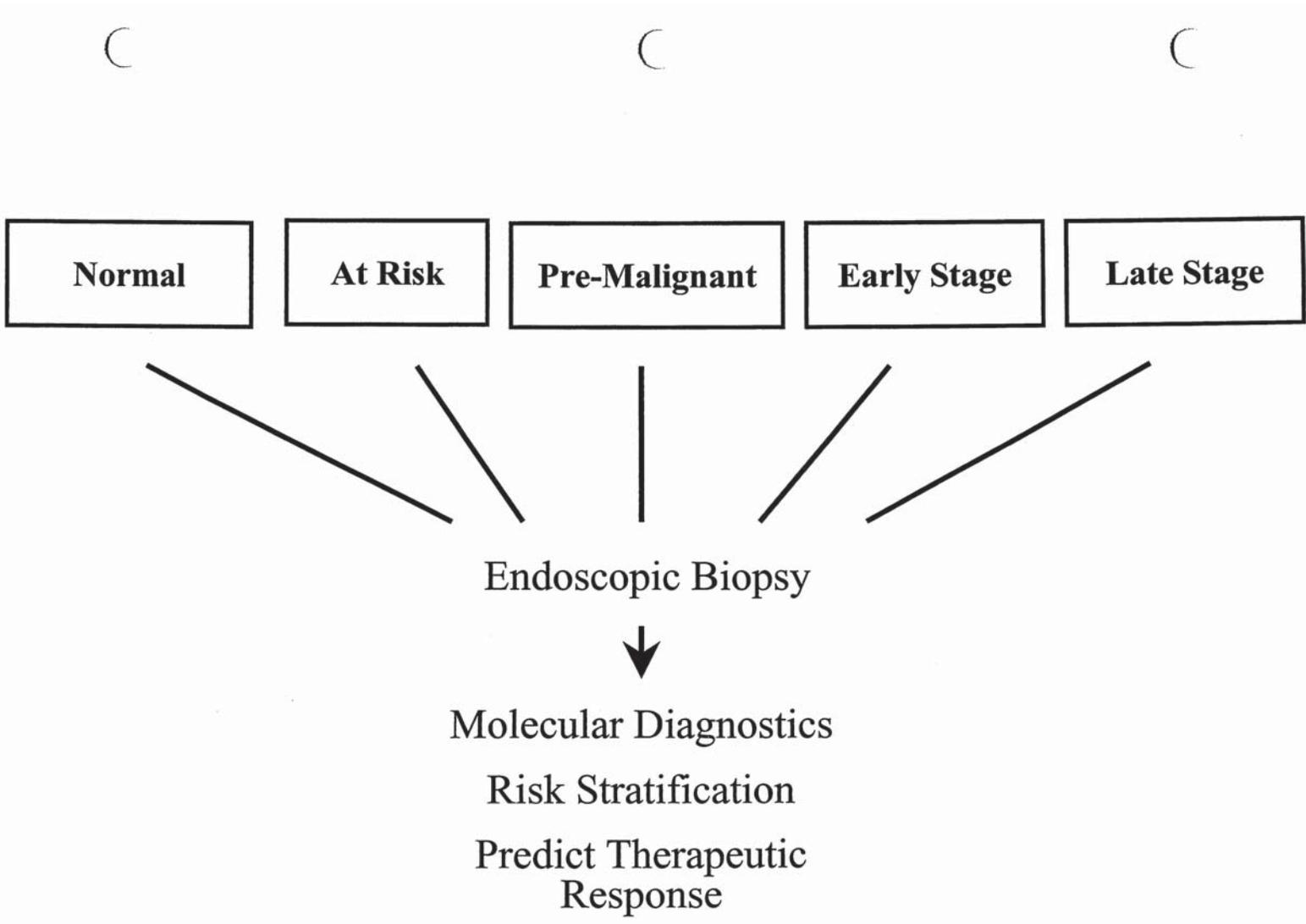
=

**Specific, novel,
less toxic
treatments**

Stomach/Esophageal Cancers Progress Review Group
Priority Recommendations

Therapeutic Targets:

Define host and molecular/biologic tumor characteristics to customize treatment and best predict recurrence/survival for patients with cancer of the esophagus and stomach.



C

C

C

Carcinogenesis

Aneuploidy



Clonal heterogeneity in DNA

Stomach/Esophageal Cancers Progress Review Group
Priority Recommendations

Markers & Molecular Profiling:

Profile the molecular, cellular and epidemiological features of gastroesophageal tumors and their precursor lesions in order to identify diagnostic, prognostic, predictive, preventive and therapeutic targets.

C

C

C

Patients with gastroesophageal cancers

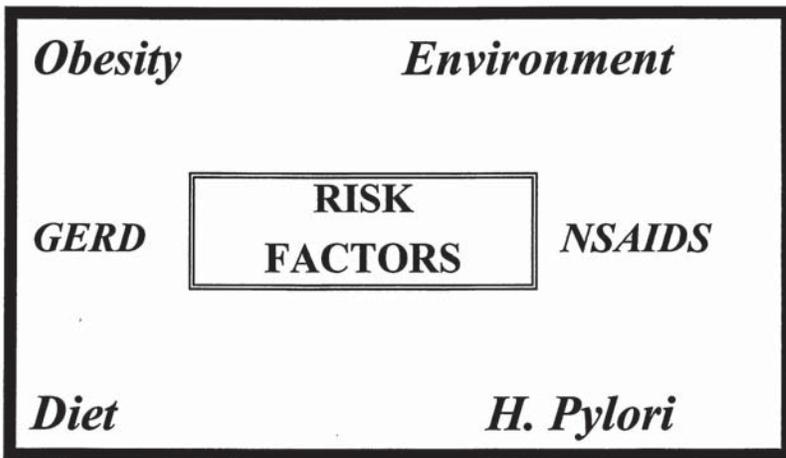
...

**... unique functional problems from
disease and from treatment**

Stomach/Esophageal Cancers Progress Review Group
Priority Recommendations

Outcomes:

Develop and refine disease-specific, patient-oriented methods to assess quality of life, quality of care, and cost-effectiveness of treatments 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.



Biopsy



Molecular Markers



Prevention Strategies

Stratify Patients for Surveillance

Barrett's Esophagus

Molecular Genetics

P16 Clonal Expansion Creates Genetic Field

- > 85% of Barrett's segments are p16 +/- or p16 -/-
- p16 genotype correlated with segment length and 17p LOH, tetraploidy, aneuploidy

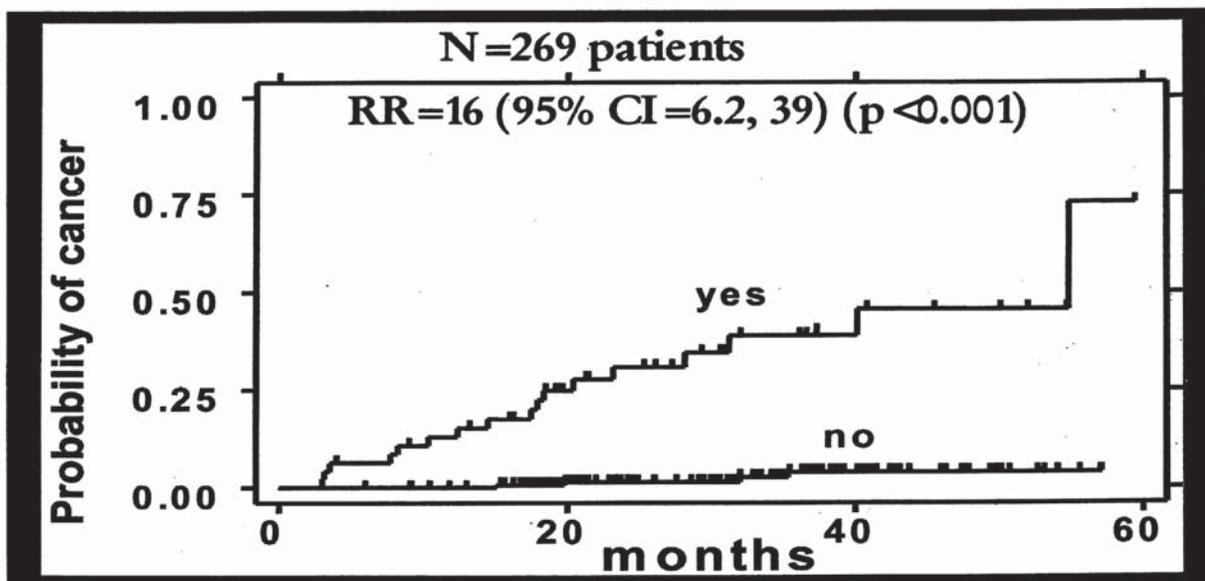
P16 genotype	median segment length	17p LOH, ploidy
p16 +/+	1.5 cm	0%
p16 +/-	6.0 cm	20%
p16 -/-	8.0 cm	44%
	p < 0.001	p < 0.001

Wong, et al., Cancer Research 2001; 61:8284-8289

Barrett's Esophagus

Molecular Risk Stratification

17p (p53) Loss of Heterozygosity Predicts Progression to Cancer

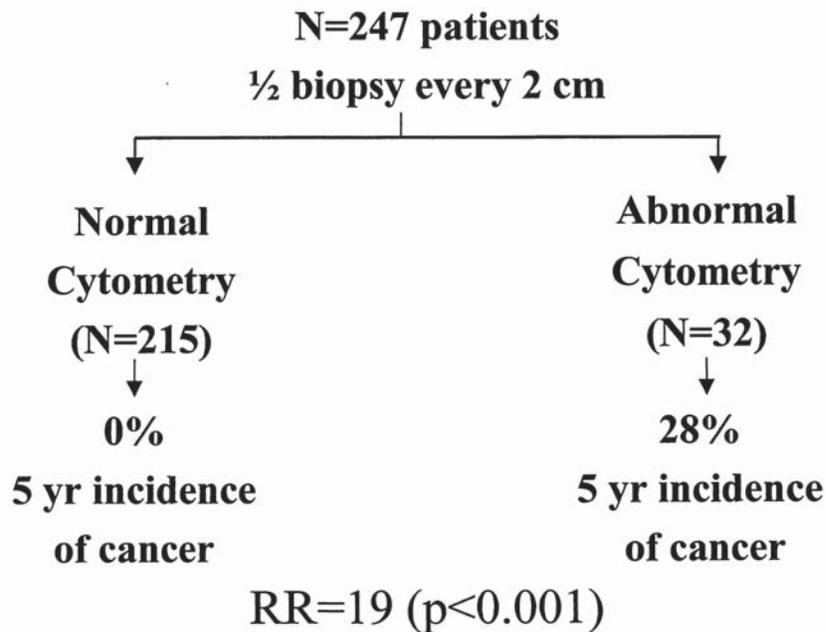


Reid, et al., *Am J. Gastroenterology* 2001; 96:2839-2848

Barrett's Esophagus

Surrogate Endpoints

Flow Cytometry can Identify Low and High Risk Subsets in Patients without *HGD*



Reid, et al., Am J Gastro 2000; 95:1669

Teodori, et al., Cytometry 1998; 34:254

Stomach/Esophageal Cancers Progress Review Group
Priority Recommendations

Host/Environment Interactions:

Identify, develop and validate genetic, biochemical, and biological markers that will help uncover host/environmental interactions in esophageal and gastric carcinogenesis.

Stomach/Esophageal Cancers Progress Review Group
Priority Recommendations

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.



"How disappointing ... they don't appear to have grown at all."

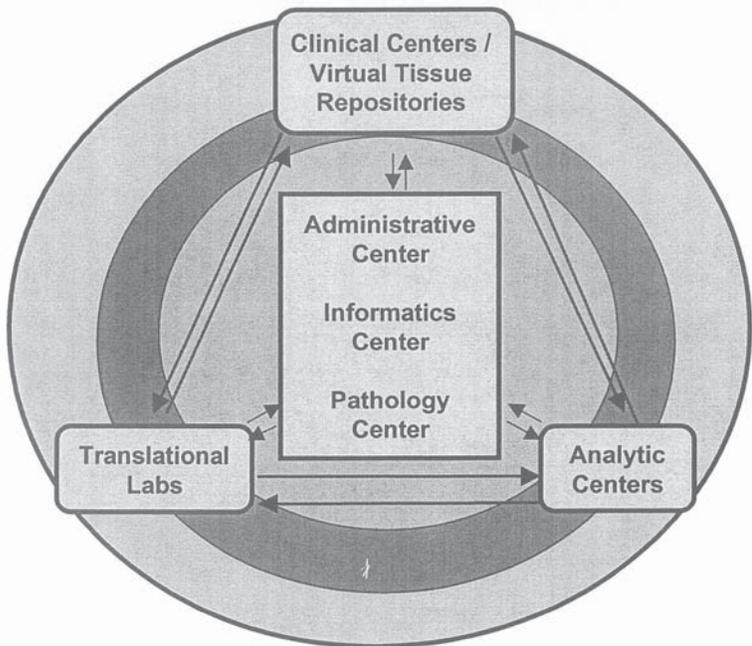
BAKER IN FINANCIAL TIMES, LONDON

Stomach/Esophageal Cancers Progress Review Group
Priority Recommendations

Preclinical Models:

Establish models to understand the biology of gastroesophageal cancers and their precursor lesions, and create prevention, diagnostic and treatment strategies.

Stomach/Esophageal Neoplasia Translational Research Network (SENTRNet) A Peer-Reviewed Partnership Platform

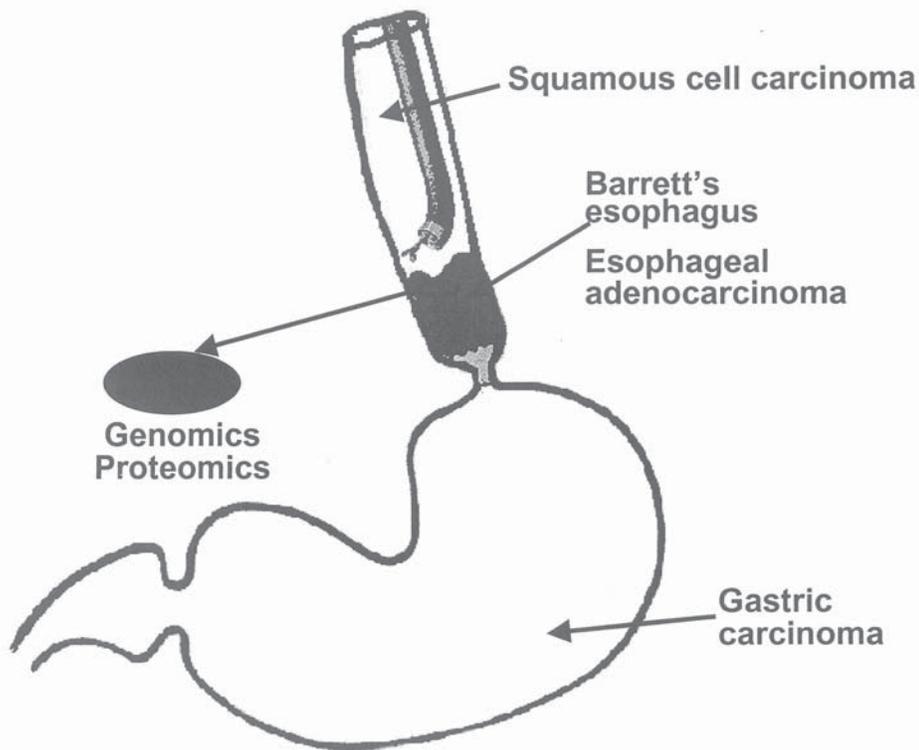


- Patients with cancer
- Persons at risk
- General population

- Extraordinary research opportunity
 - Tissue based approach
 - Population to patient
 - Model for carcinogenesis elsewhere
- Overcome barriers to achieving this opportunity

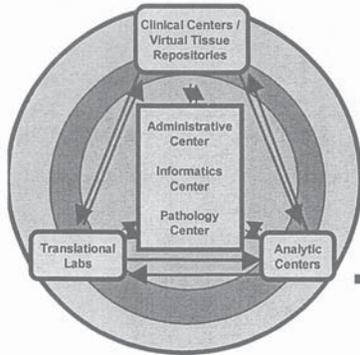
Stomach-Esophageal Cancers

Extraordinary Research Opportunity

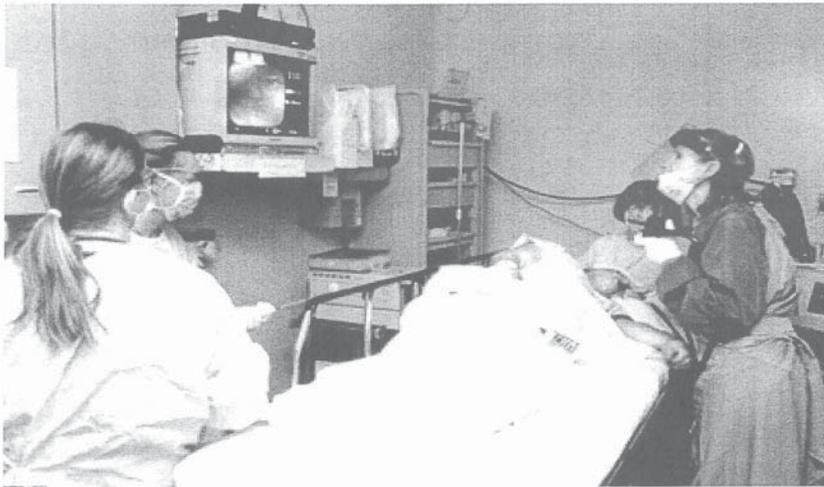


Mechanistic Based Approaches

- Screening
- Early detection
- Prevention
- Therapy



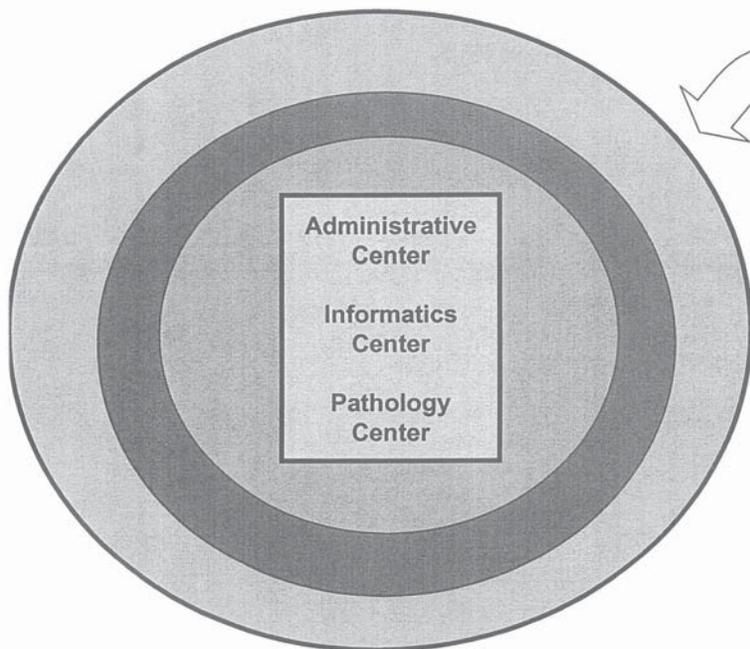
Stomach-Esophageal Cancer Challenges



- Low incidence, high mortality – No single center can make a difference
- Scattered expertise across centers
- Incomplete professional network (Gastroenterologists)

SENTRNet

Multidisciplinary Inter-institutional Partnership Platform



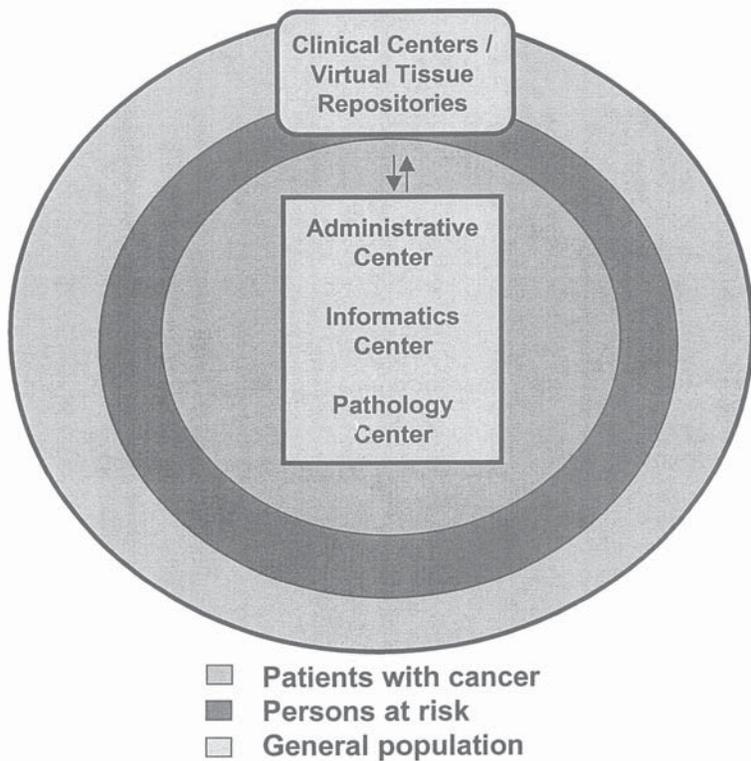
- Patients with cancer
- Persons at risk
- General population

Foundation & Management Principles

- Multi-institutional/agency/disciplinary
- Synergy with existing institutions
- Shared Leadership
- Translational-focused
- Business model
- Mutual Dependence
- Managed Progressive Growth
- Knowledge Management

SENTRNet

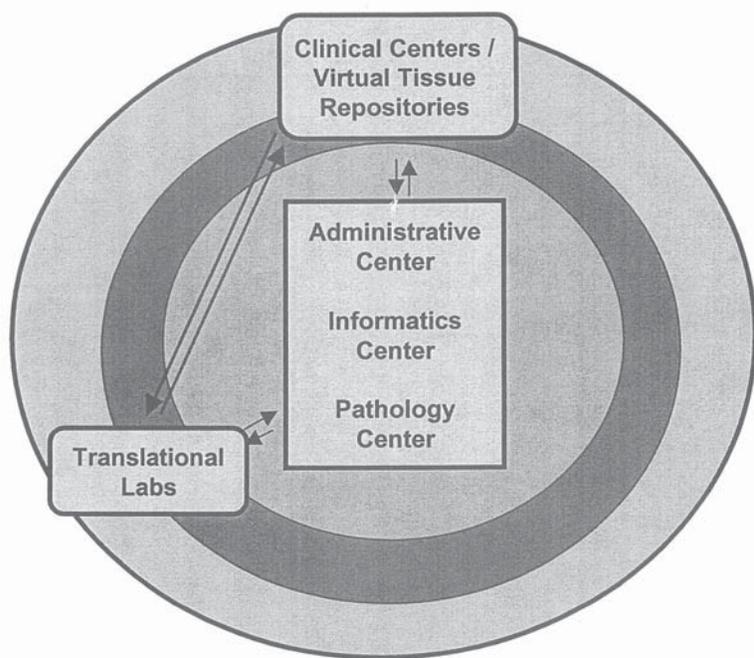
Partnership Platform



- Multi-institutional**
- Gastroenterologists**
- Tissue repository**
- Multi-disciplinary**
 - **Screening**
 - **Early detection**
 - **Prevention**
 - **Treatment**

SENTRNet

Partnership Platform

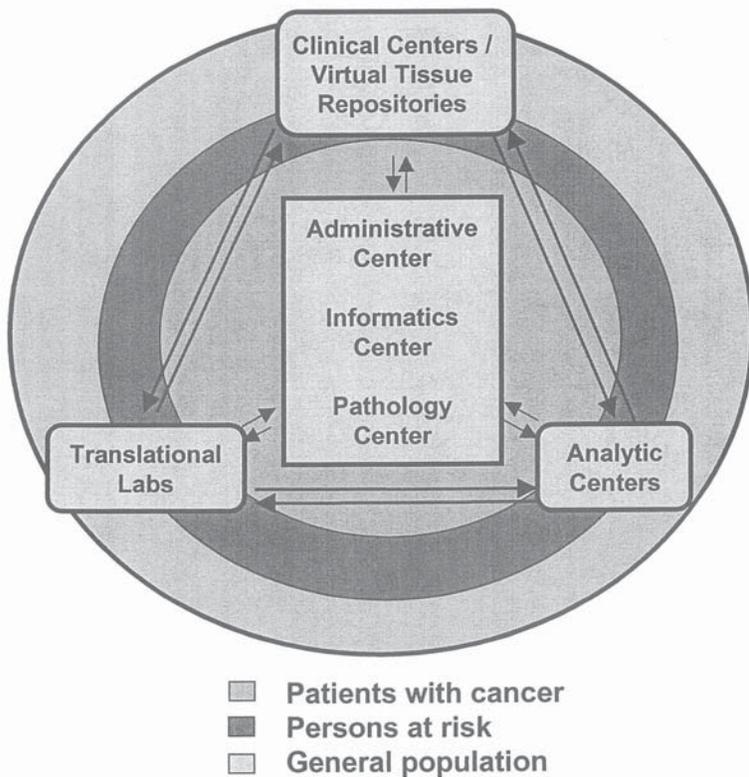


- Patients with cancer
- Persons at risk
- General population

Molecular characterization

- Genesis
- Signatures
- Diagnostics
- Targets
- Response
- Epidemiology

SENTRNet Partnership Platform



Cancer etiology

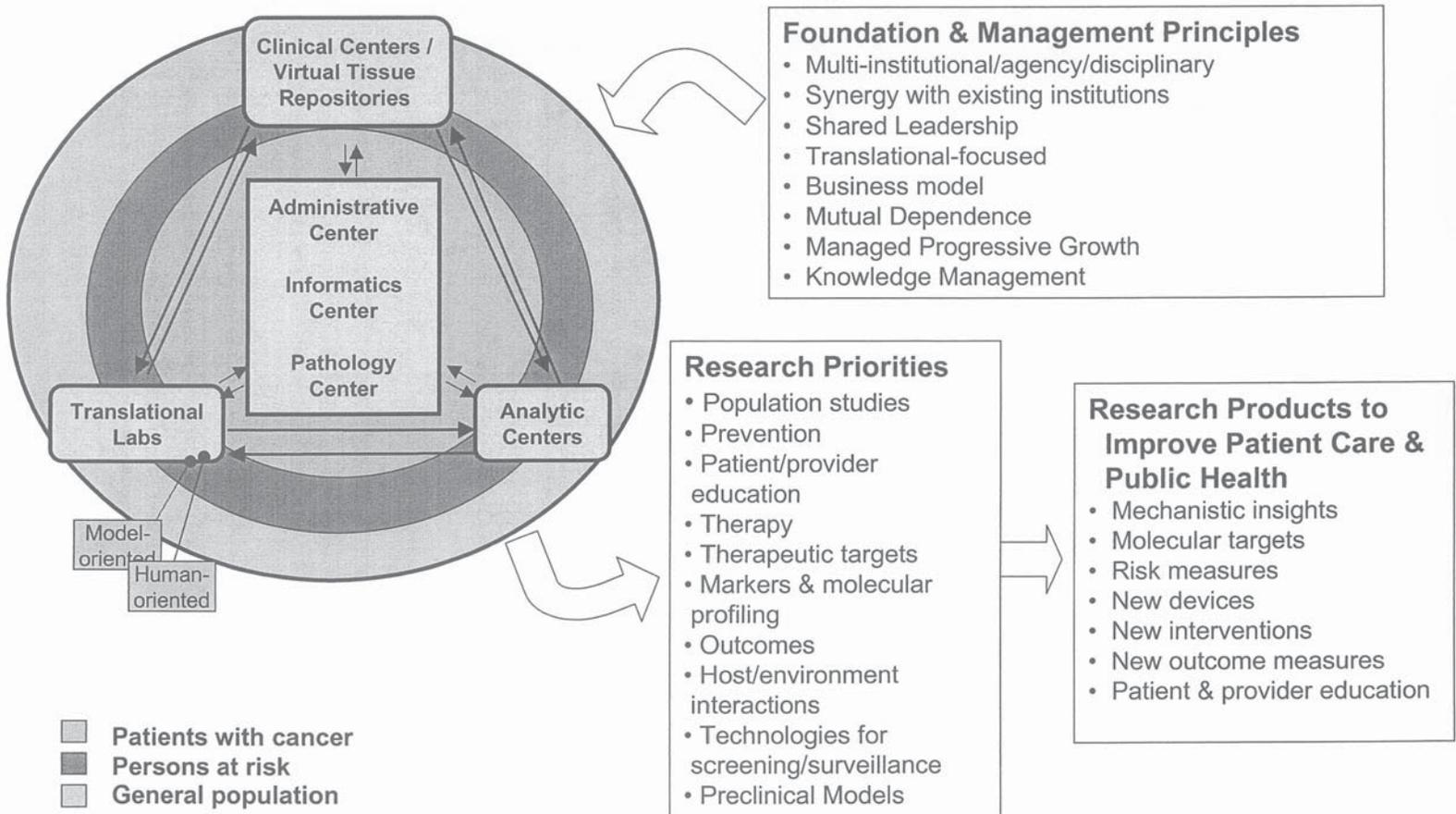
Risk factors

- Obesity
- Reflux
- Tobacco
- *H. pylori*

Protective factors

- NSAIDs
- Fruits and vegetables
- Selenium

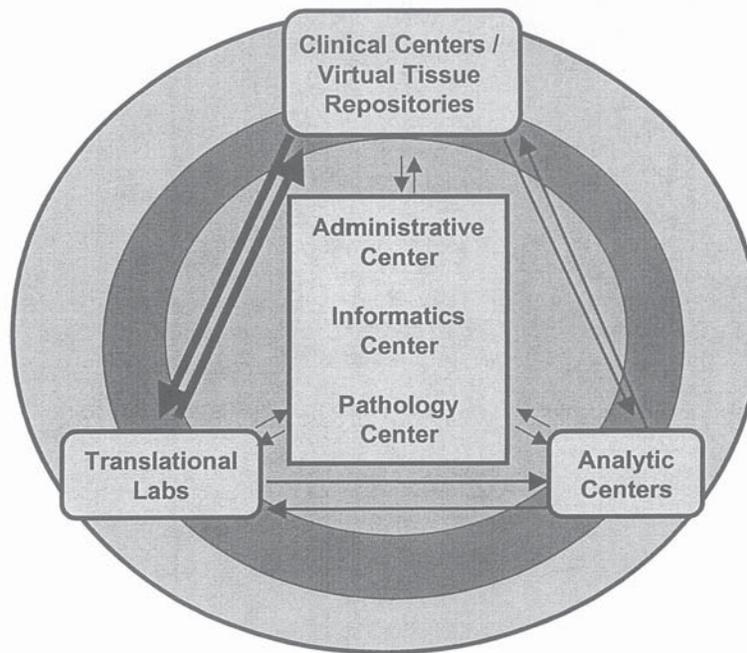
Stomach/Esophageal Neoplasia Translational Research Network (SENTRNet)



SEPRG Priority 1

Endoscopic Population Studies

Molecular Diagnostics
Surrogate Endpoints



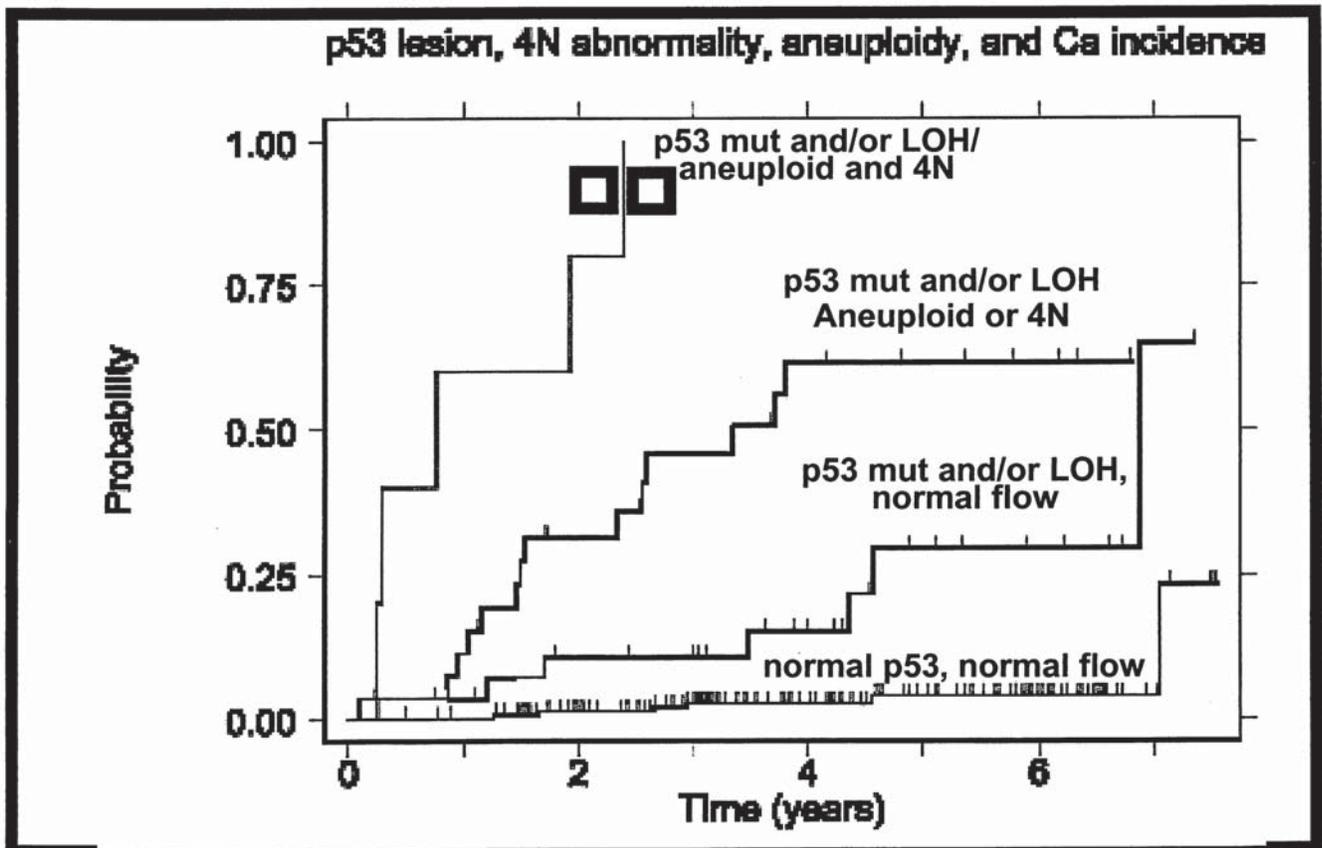
Modulators of Progression
Candidate Interventions

Risk and Protective Factors
Etiologic Mechanisms

- Patients with cancer
- Persons at risk
- General population

Partnership: EDRN (1st generation risk marker standardization & validation)

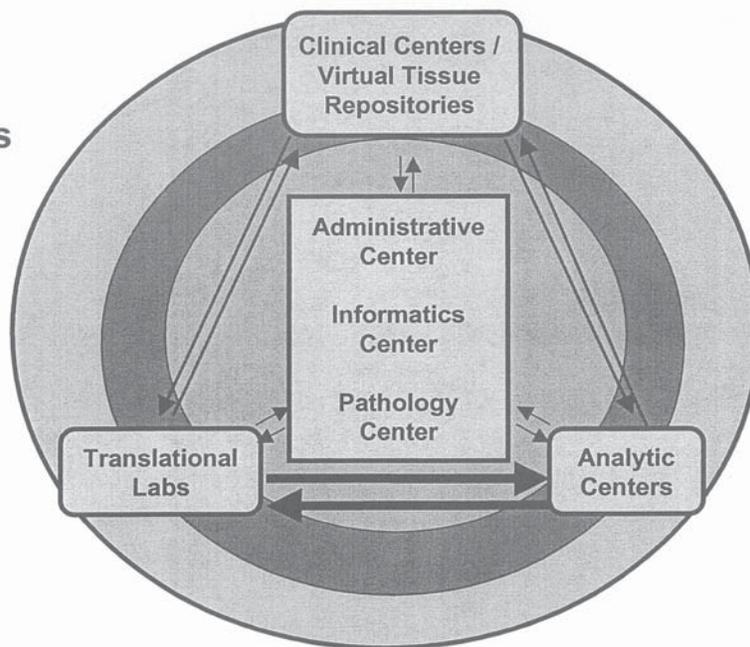
Barrett's Esophagus Molecular Diagnostics Partnership: Gastroenterology, Laboratory Scientists



SEPRG Priority 1

Endoscopic Population Studies

Molecular Diagnostics
Surrogate Endpoints



Modulators of Progression
Candidate Interventions

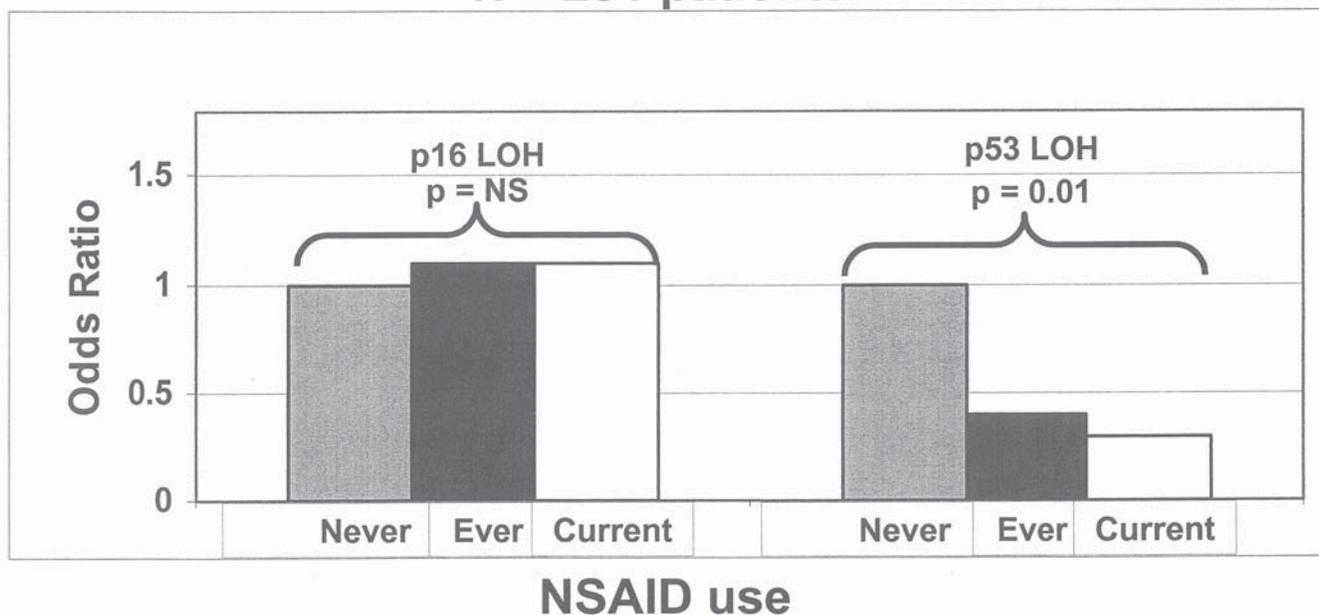
Risk and Protective Factors
Etiologic Mechanisms

- Patients with cancer
- Persons at risk
- General population

Barrett's Esophagus
Molecular Epidemiology & Prevention
Partnership: Analytic, Gastroenterology, Laboratory Scientists

NSAIDs and p53 LOH

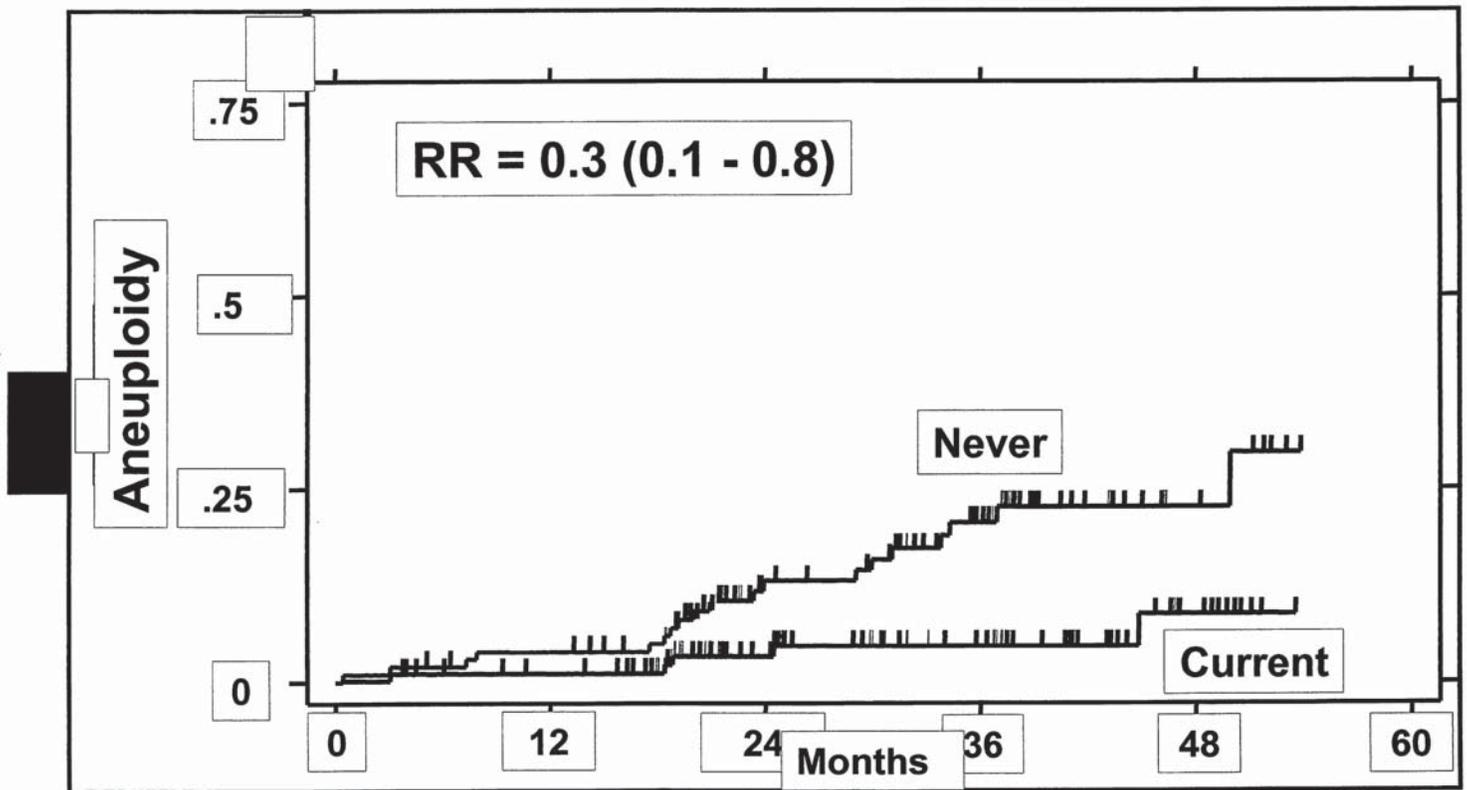
N = 281 patients



Vaughan et al, Cancer Epi Biomarkers & Prevention 2002; 11:745-752

Barrett's Molecular Epidemiology & Prevention Partnership: Analytic, Gastroenterology, Laboratory Scientists

NSAID use and aneuploidy



Vaughan et al, preliminary results

Barrett's Esophagus

Molecular Epidemiology & Prevention

Partnership: Analytic, Gastroenterology, Laboratory Scientists

Serum Selenium and Biomarkers

Markers	Odds Ratio Upper 3 quartiles vs. lowest
9p (p16) LOH	1.0 (0.5-1.7)
17p (p53) LOH	0.5 (0.2-0.9)
Tetraploid	0.6 (0.3-1.2)
Aneuploid	0.4 (0.2-0.8)

Rudolph et al, unpublished

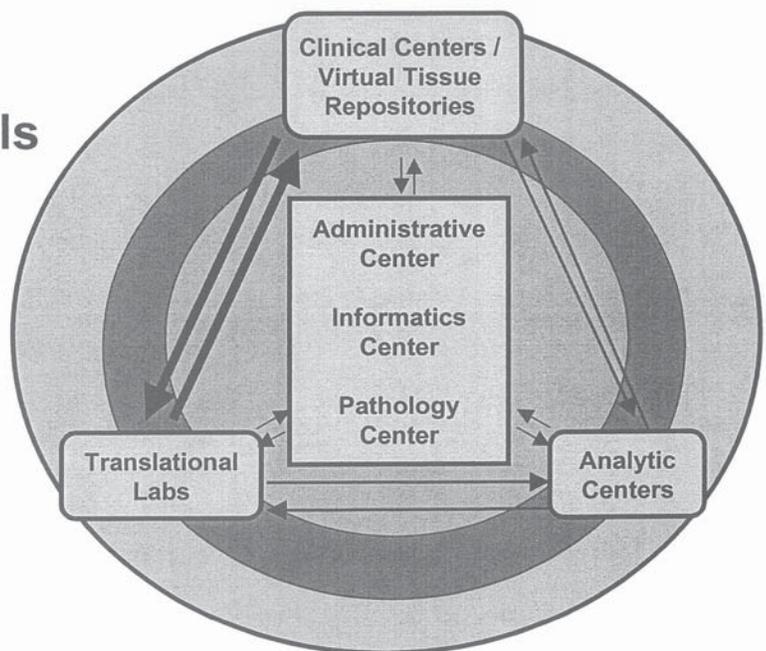
SEPRG Priority 2 Prevention

Randomized prevention trials

- Candidate interventions
- Surrogate endpoints

Partnerships

- Clinical centers
- Translational labs



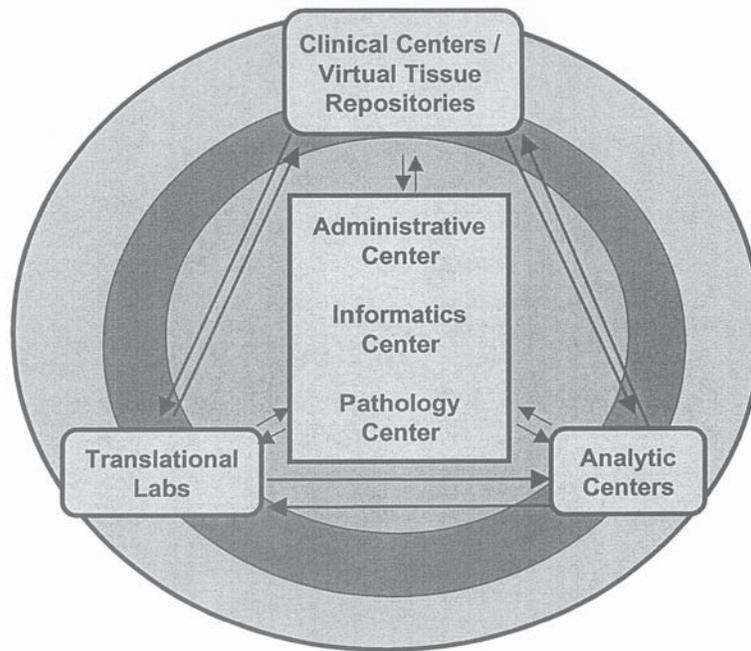
- Patients with cancer
- Persons at risk
- General population

SEPRG Priority 3

Patient Provider Education

Risk Assessment

Chemoprevention
Studies



Risk and Protective Factors

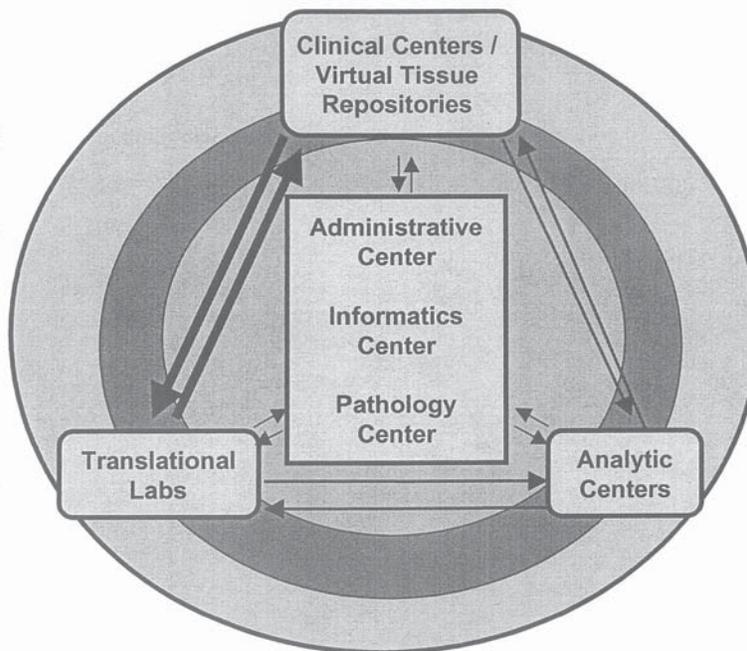
- Patients with cancer
- Persons at risk
- General population

Partnership: Cancer Information Service/PDQ (risk factors)

SEPRG Priorities 4-6

Therapy, Targets and Profiling

Treatment Response
Studies
Surrogate Endpoints



- Patients with cancer
- Persons at risk
- General population

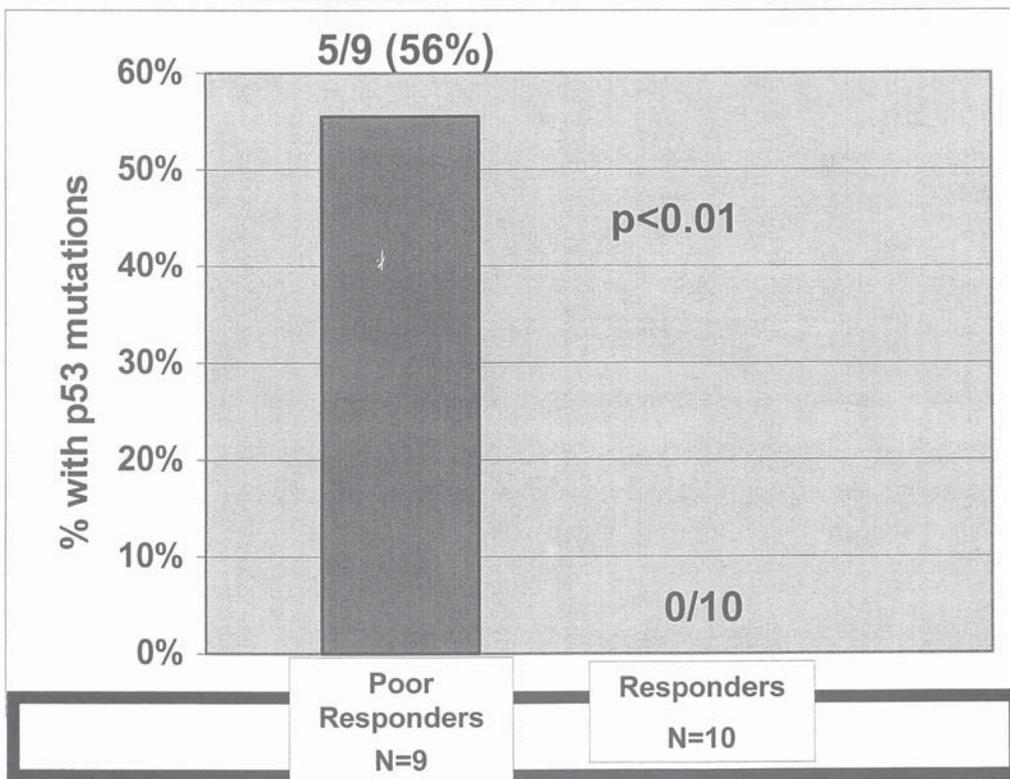
Partnerships:

Cancer Cooperative Groups (GI clinical research center expansion)
EDRN (testing promising risk/response markers)

PDT Treatment Response Study

p53 Mutations Predict Poor Response

Partnership: Gastroenterology, Laboratory Scientists



Responders: Complete Barrett's reversal

Poor Responders: Dysplasia downstaged; Barrett's persists

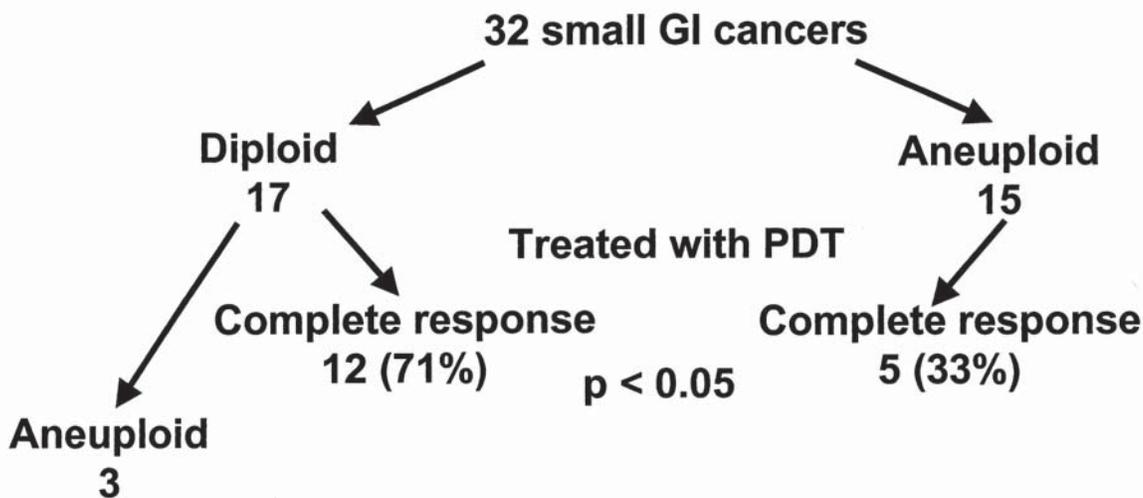
p53 mutations detected in 2 cases of neosquamous epithelium

Krishnadath et al, Gastroenterology 2001; 120:A413

Evolution of Resistant Clones

Photodynamic Therapy (PDT)

Partnership: Gastroenterology, Laboratory Scientists



“The appearance of aneuploid populations after PDT suggests that destruction of sensitive cell populations allows the growth of aneuploid clones that initially are not detectable by flow cytometry.”

Foultier et al, Cancer 1994; 73:1595



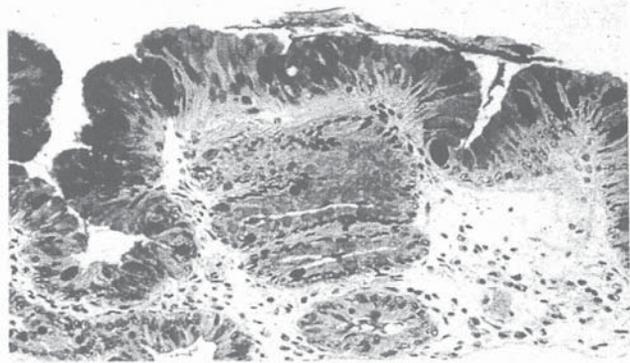
Stomach/Esophagus

Molecular Profiling

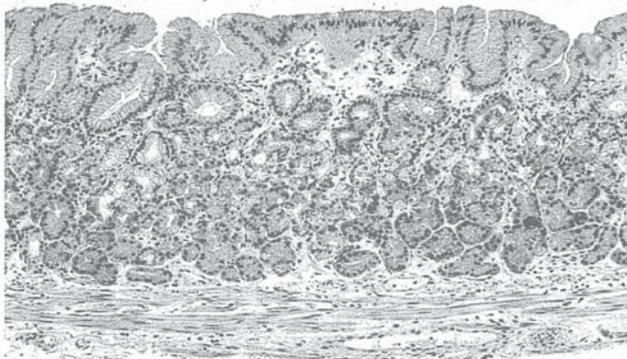
Squamous



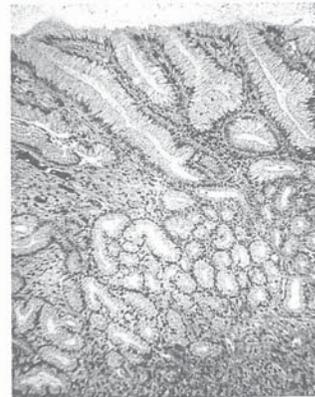
Intestinal Metaplasia



Fundic



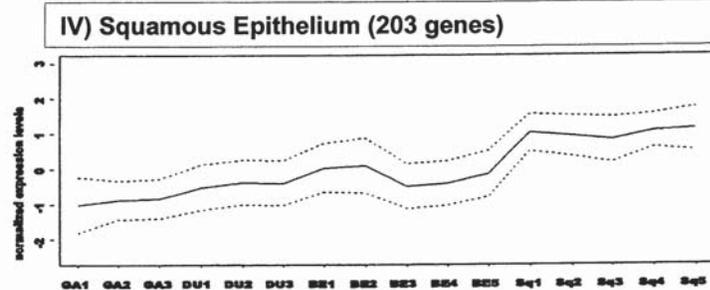
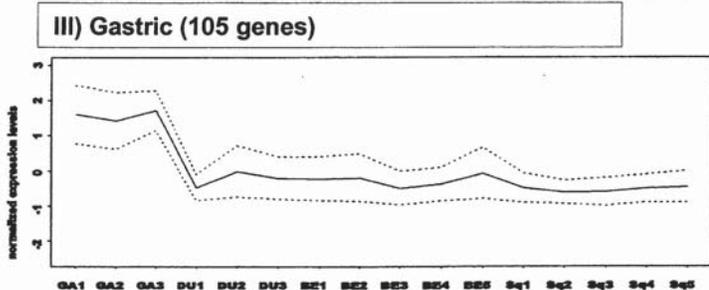
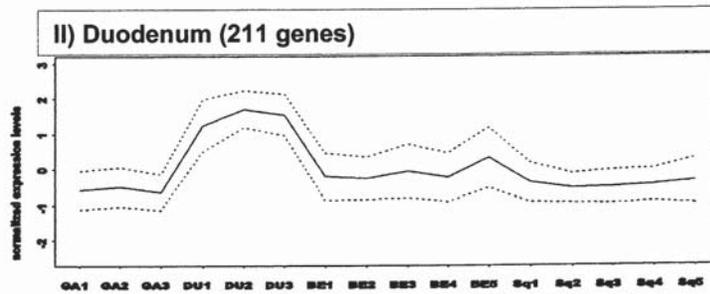
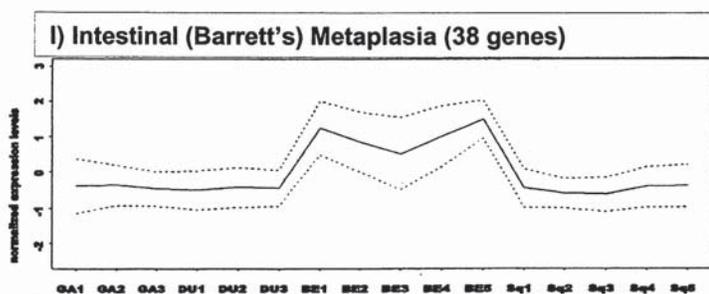
Cardiac



Stomach/Esophagus Molecular Profiling

Partnership: Gastroenterology, Laboratory Scientists

Affymetrix 6800 gene chip



Barrett et al, Neoplasia 2002; 4:2, 121-128

SENTRNet: 5-year Phase-In Strategy to Achieve Stomach/Esophageal PRG Recommendations

Highlighting collaborations with EDRN, CIS, Cancer Cooperative Groups and MMHCC

Potential Funding Partners: Other NIH Institutes, Department of Defense, Centers for Medicare & Medicaid Services, Agency for Healthcare Research and Quality, & Industry

<u>Year</u>	<u>SENTRNet</u>	<u>PRG Priorities</u>	<u>NCI Collaborators/Partners</u>
1-3	Clinical Research Ctrs (tissue repositories)	①	EDRN (1 st generation risk marker standardization & validation)
	Administrative center	②	
	Analytic center	③	Cancer Information Service/PDQ (risk factors)
	Informatics center	④	
	Pathology center	⑤	
4	Translational labs – human	⑥	Cancer Cooperative Groups (GI clinical research center expansion)
		⑦	
		⑧	EDRN (testing promising risk/response markers)
5	Translational labs - animal	⑨	
		⑩	

te: Solely SENTRNet SENTRNet Collaboration with Partners

SENTRNet: Multidisciplinary Inter-institutional Peer-reviewed Partnership Platform

