GOOD SCIENCE
BETTER MEDICINE
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European Society for Medical Oncology

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ESMO Preceptorship

Gastric cancer

Berlin, Germany
11-12 October 2013

Gastric cancer

Multidisciplinary management, standards of care, therapeutic targets and future perspectives

Pathology and carcinogenesis

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&
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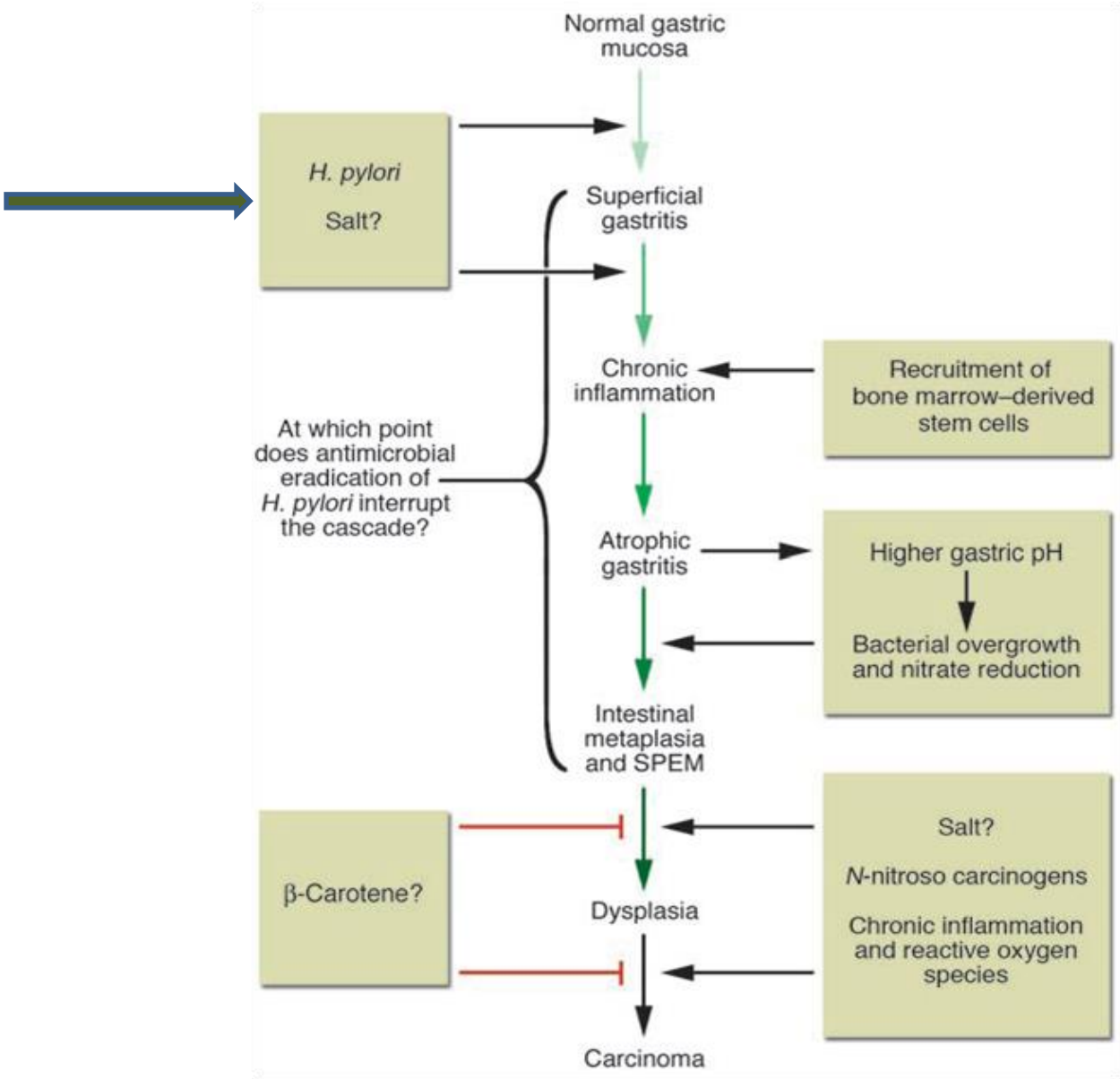

Normal gastric mucosa
H. pylori
Salt?
Superficial gastritis
Chronic inflammation
Recruitment of bone marrow–derived stem cells
At which point does antimicrobial eradication of H. pylori interrupt the cascade?
Atrophic gastritis
Higher gastric pH
Bacterial overgrowth and nitrate reduction
Intestinal metaplasia and SPEM
β-Carotene?
Salt?
N-nitroso carcinogens
Chronic inflammation and reactive oxygen species
Dysplasia
Carcinoma

Helicobacter pylori and gastric carcinogenesis

Normal gastric mucosa

Other host and environmental factors

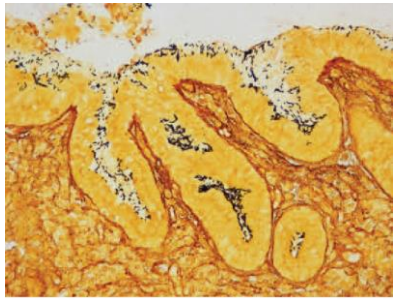
Helicobacter pylori

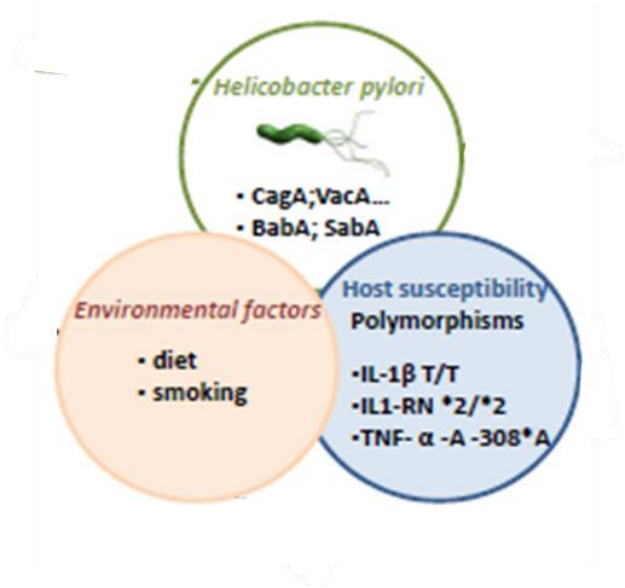
Chronic gastritis

Chronic atrophic gastritis

Intestinal metaplasia

Gastric carcinoma





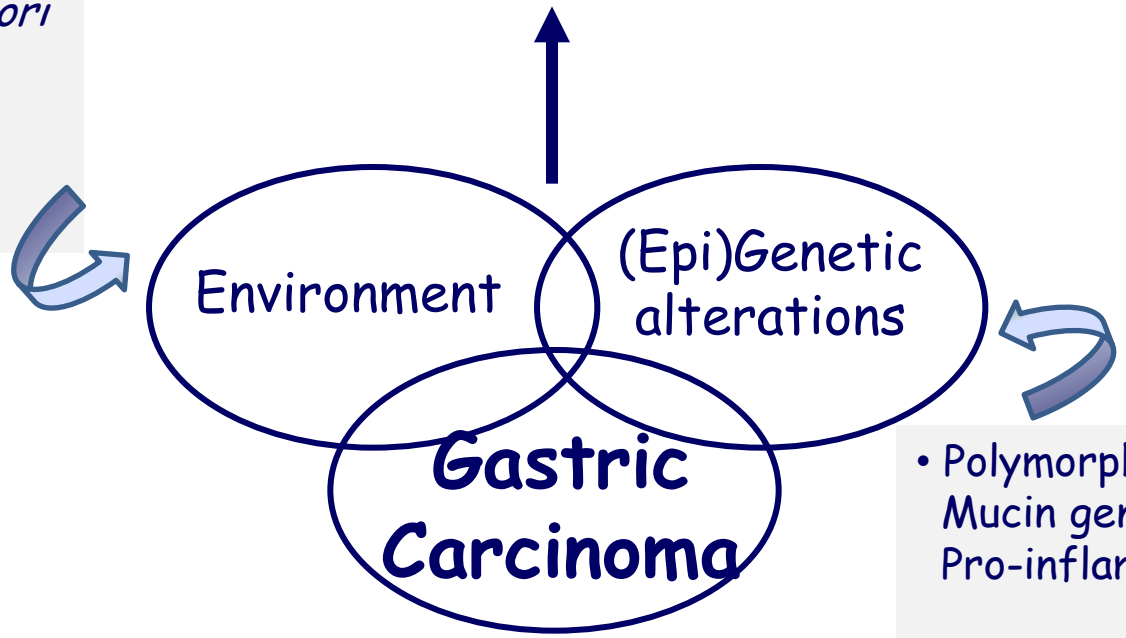
Risk of gastric cancer development

H. pylori virulent genotypes (vacA; CagA)	15 to 17
IL-1 gene polymorphism	3.3
***H. pylori* virulence & *IL-1B* polymorphism**	**87**

Machado *et al.* Gastroenterology 121: 823, 2001
Figueiredo *et al*, JNCI 94: 1680, 2002

Gene-environment interaction

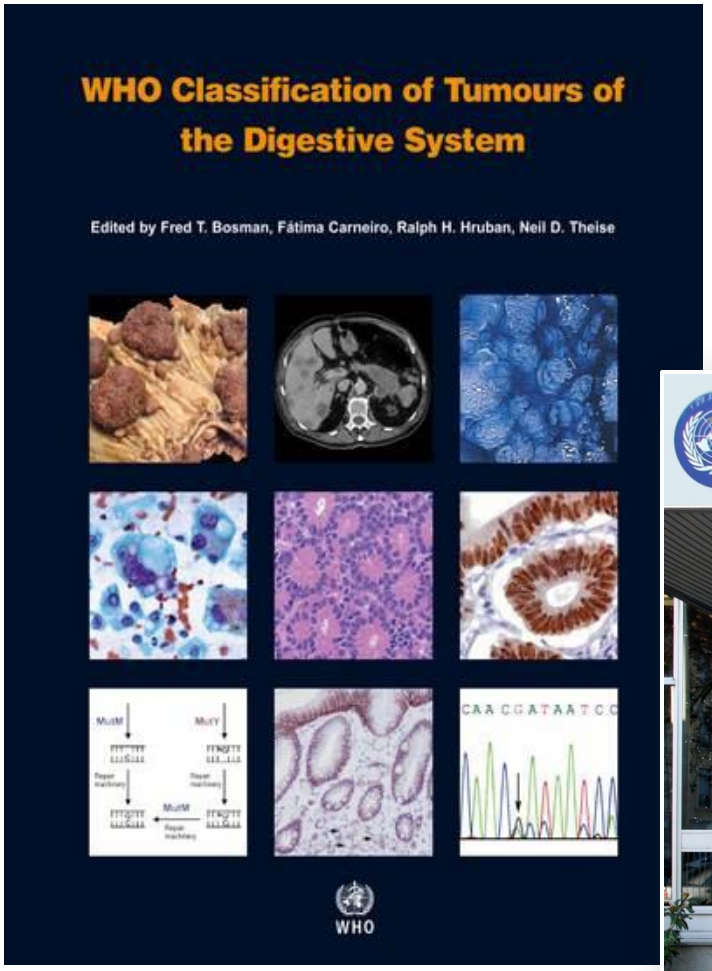
- *Helicobacter pylori* infection
- Epstein Barr
- Diet
- Smoking



- Polymorphisms:
  Mucin genes
  Pro-inflammatory genes
- Mutations in "low" or "high" penetrant genes

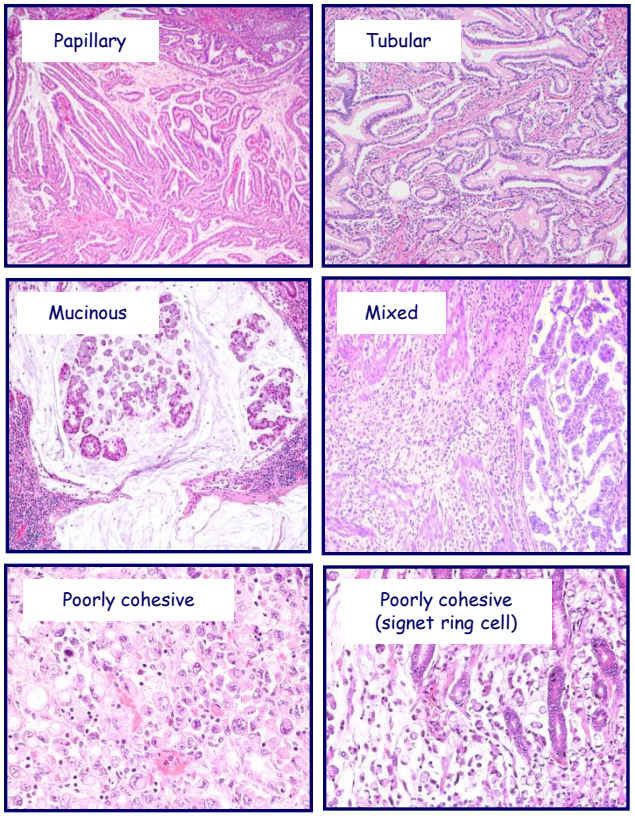
Classification of gastric cancer

WHO – 4th Edition, 2010



4-1 Gastric carcinoma

Gregory Y. Lauwers
Fátima Carneiro
David Y. Graham
Maria-Paula Curado
Silvia Franceschi
Elizabeth Montgomery
Masae Tatematsu
Takenori Hattori

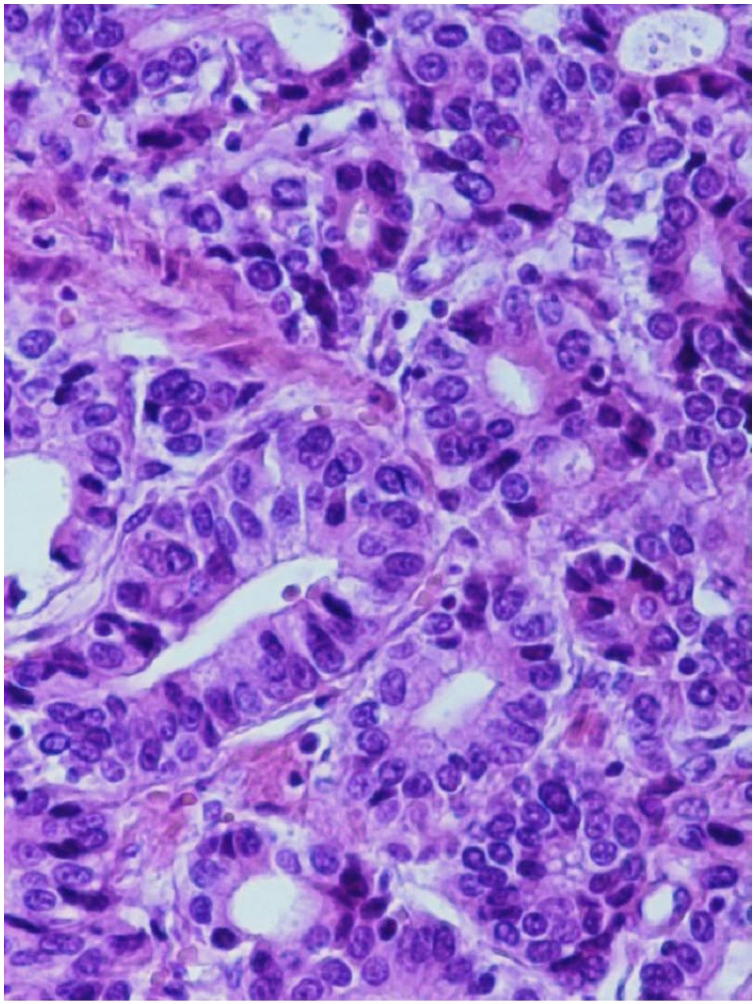


4-1-02 - ICD-O Code

Adenocarcinoma	8140/3
Papillary adenocarcinoma	8260/3
Tubular adenocarcinoma	8211/3
Mucinous adenocarcinoma	8480/3
Poorly cohesive carcinoma (Signet-ring cell carcinoma and variants)	8490/3
Mixed carcinoma	8255/3

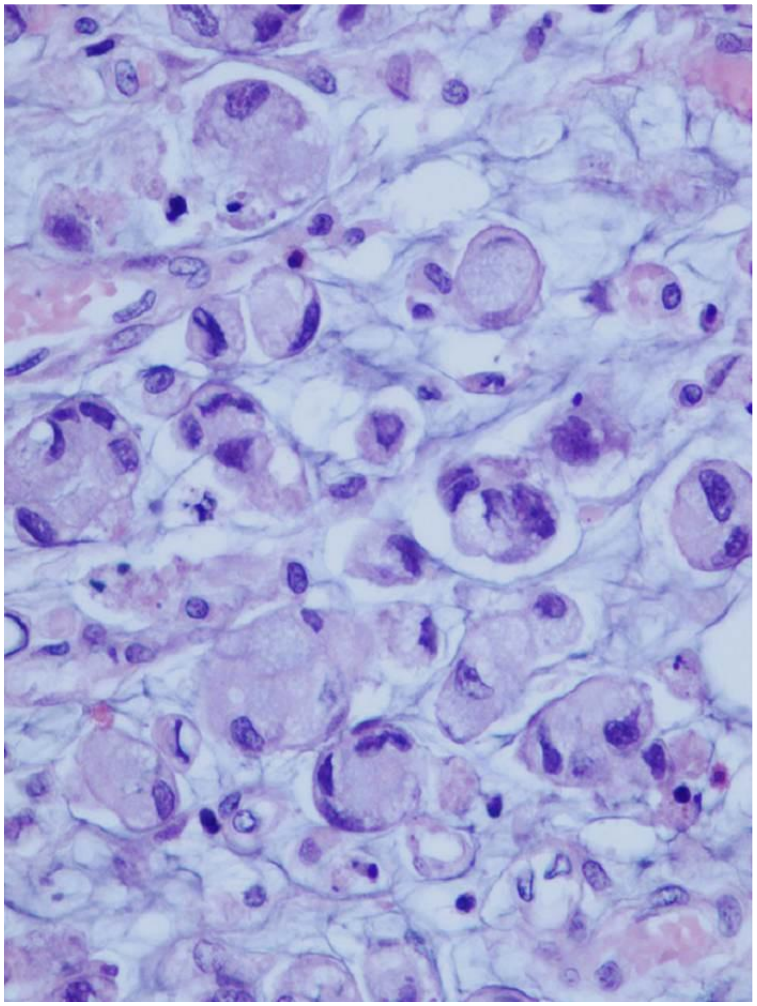
WHO – 4th Edition, 2010

Intestinal carcinoma



- Elderly patients, mainly males
- Decreasing incidence everywher
- Blood-born metastases

Diffuse carcinoma

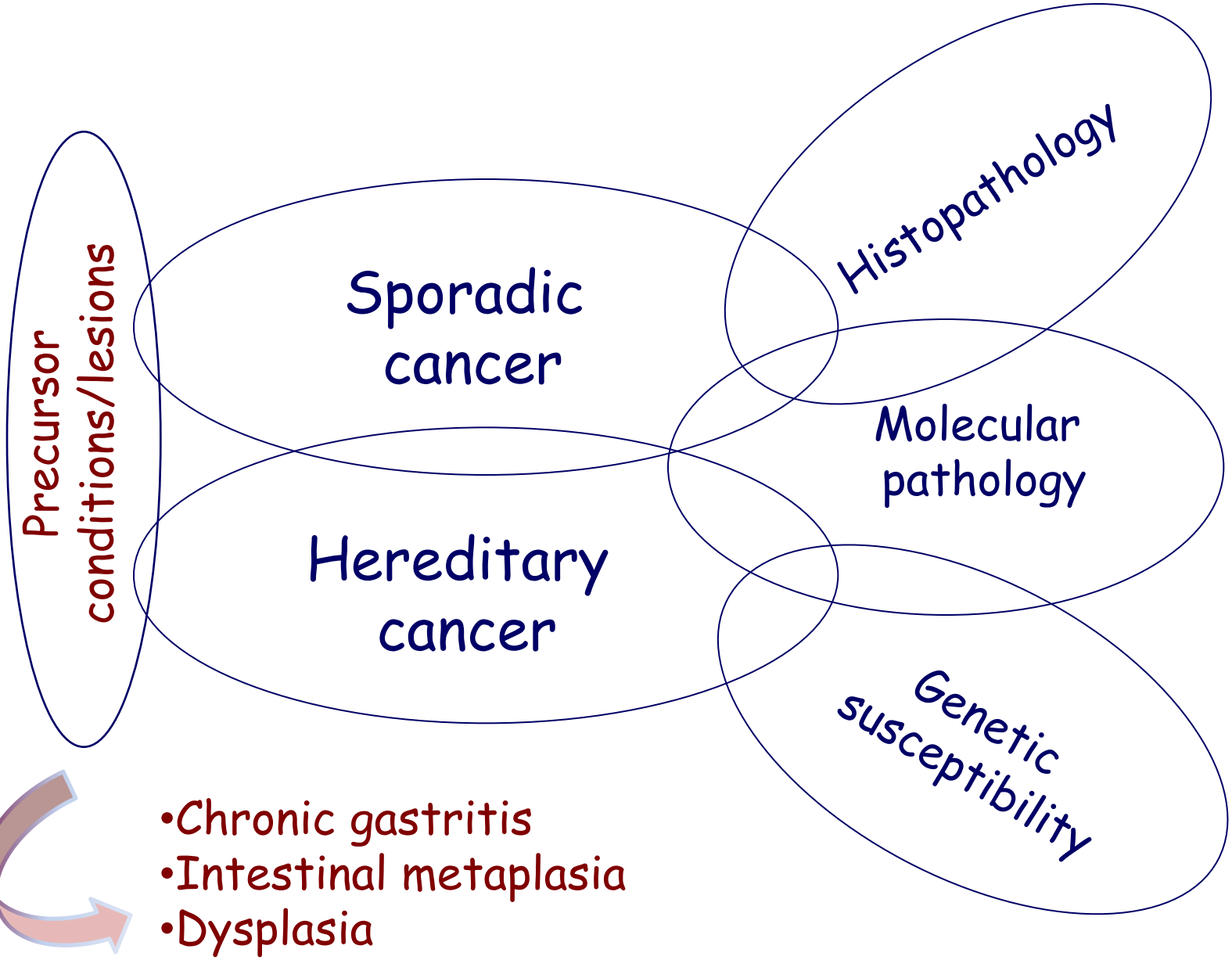


- Young patients, mainly females
- Familial/hereditary conditioning
- Dissemination to the peritoneum

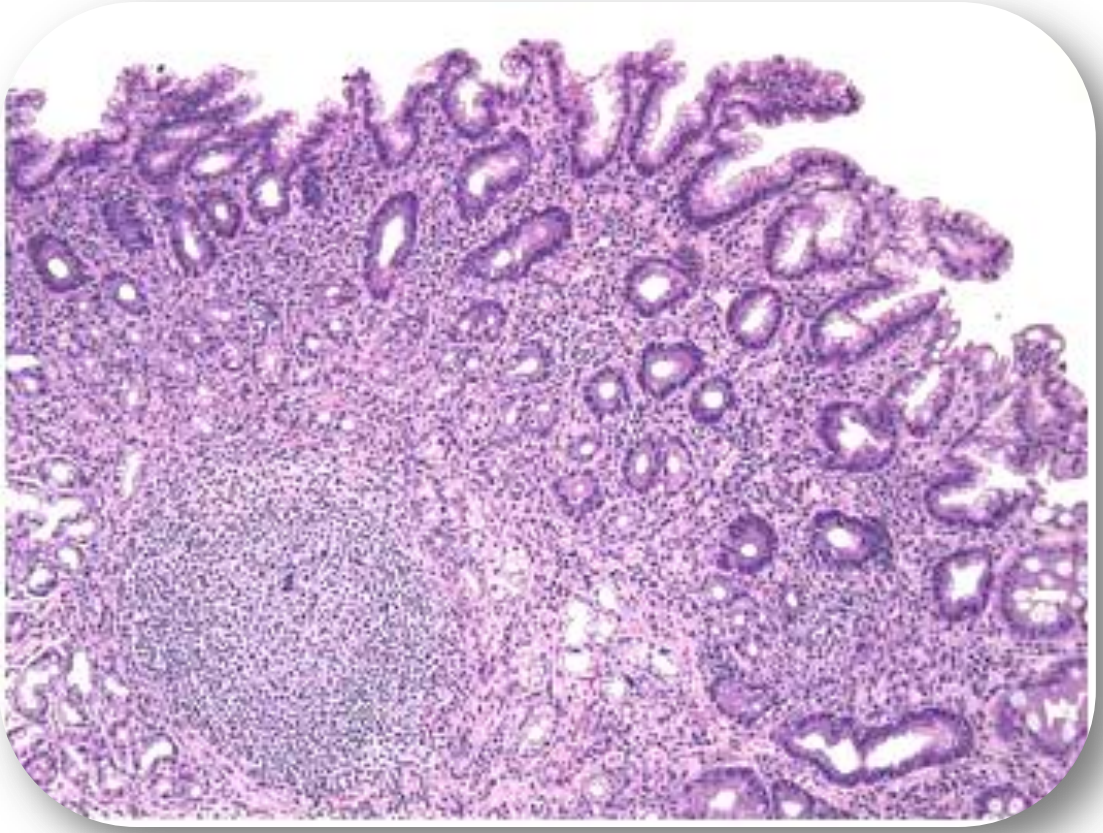
Other classifications with putative prognostic value:

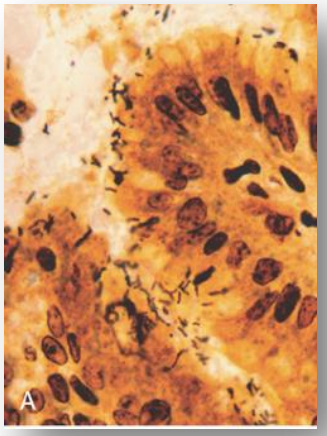
- Goseki
- Kodama
- Carneiro

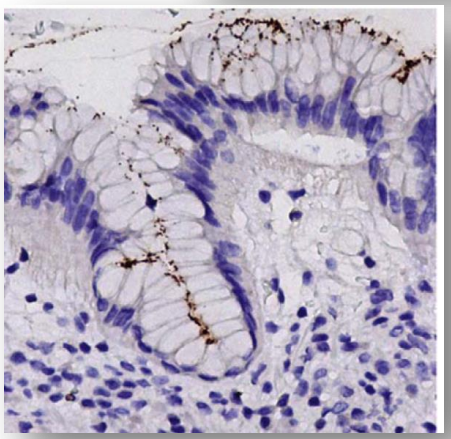
However, one should keep in mind that the most important prognostic factor is staging (in the stomach and other organs)

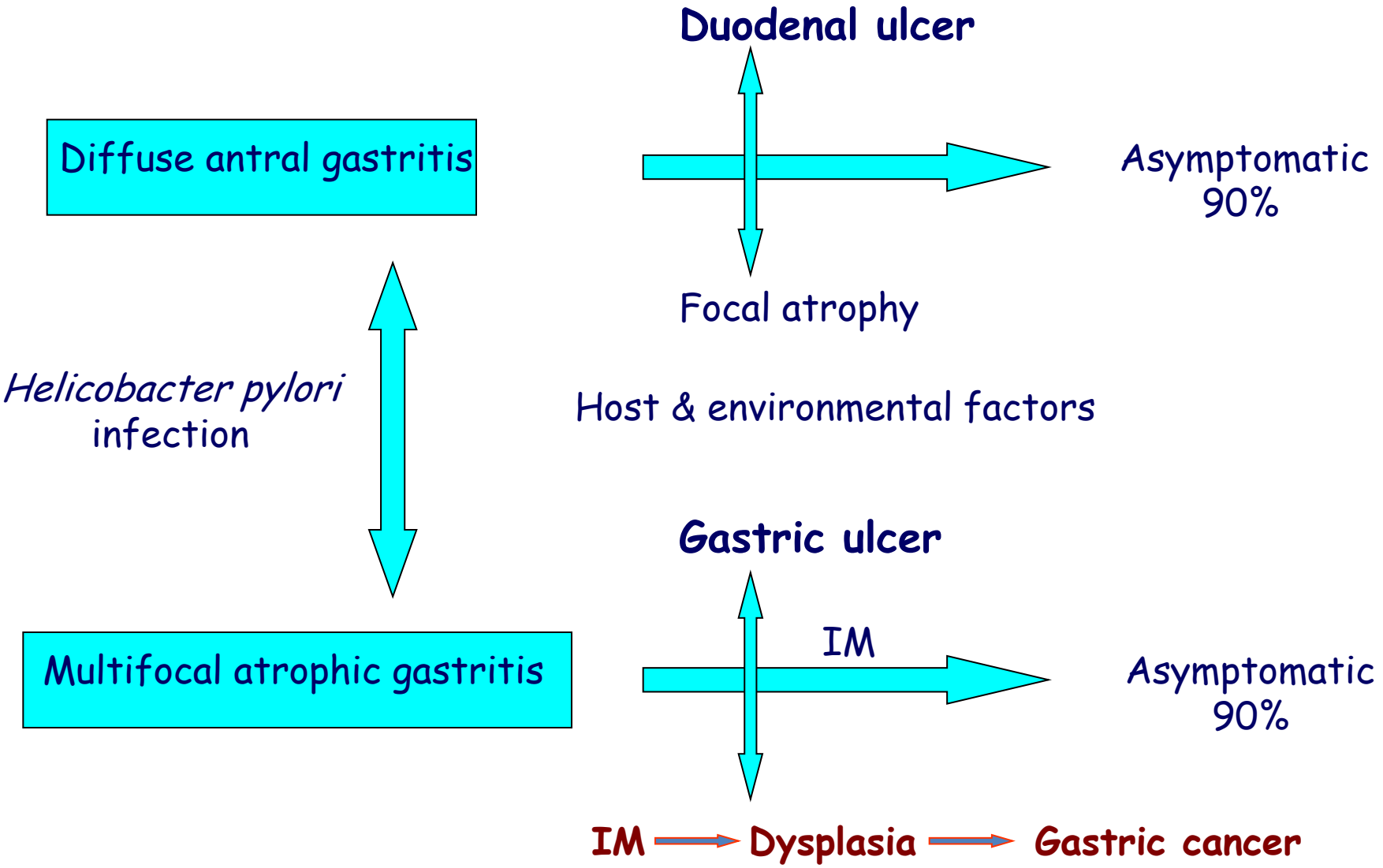

Precursor conditions/lesions
Sporadic cancer
Hereditary cancer
Histopathology
Molecular pathology
Genetic susceptibility
•Chronic gastritis
•Intestinal metaplasia
•Dysplasia

Chronic gastritis

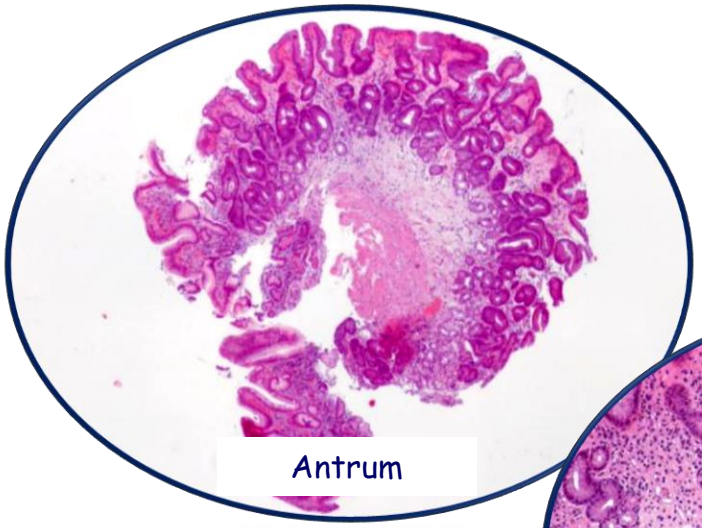


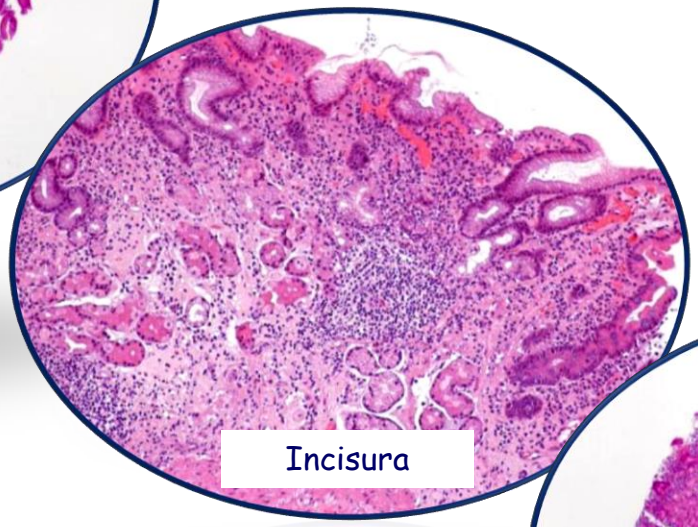


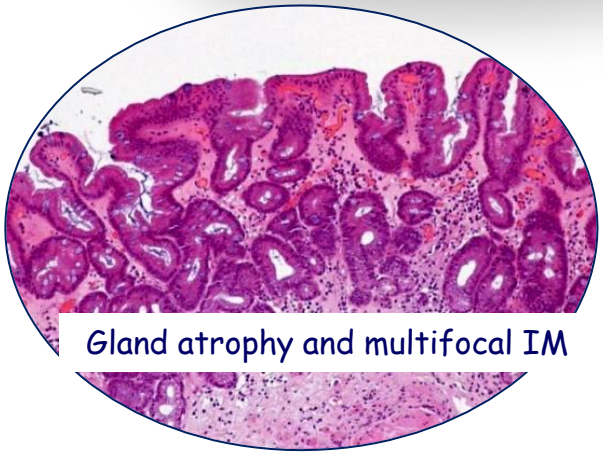


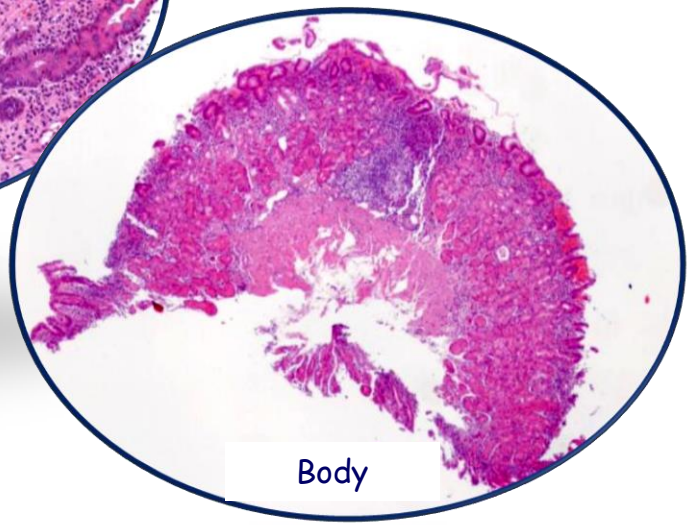

Duodenal ulcer
Diffuse antral gastritis
Asymptomatic
90%
Focal atrophy
Helicobacter pylori
infection
Host & environmental factors
Gastric ulcer
IM
Multifocal atrophic gastritis
Asymptomatic
90%
IM
Dysplasia
Gastric cancer

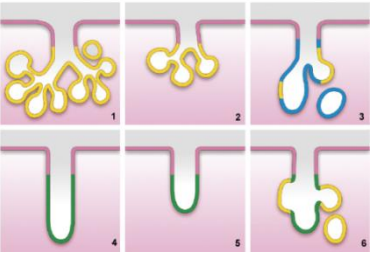
Chronic gastritis


Antrum


Incisura


Gland atrophy and multifocal IM


Body

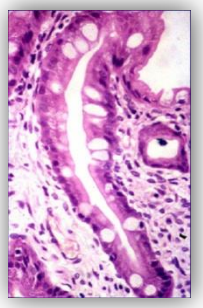


Classification of chronic gastritis OLGA staging

Atrophy Score		Corpus			
		No Atrophy (score 0)	Mild Atrophy (score 1)	Moderate Atrophy (score 2)	Severe Atrophy (score 3)
Antrum	No Atrophy (score 0) (including *incisura angularis*)	STAGE 0	STAGE I	STAGE II	STAGE II
	Mild Atrophy (score 1) (including *incisura angularis*)	STAGE I	STAGE I	STAGE II	STAGE III
	Moderate Atrophy (score 2) (including *incisura angularis*)	STAGE II	STAGE II	STAGE III	STAGE IV
	Severe Atrophy (score 3) (including *incisura angularis*)	STAGE III	STAGE III	STAGE IV	STAGE IV

Fig. 3. The OLGA staging frame.

Rugge M *et al.* Dig Liver Dis 40: 650, 2008



Classification of chronic gastritis OLGIM staging

The staging of gastritis with the OLGA system by using intestinal metaplasia as an accurate alternative for atrophic gastritis

Lisette G. Capelle, MD, Annemarie C. de Vries, MD, PhD, Jelle Haringsma, MD, Frank Ter Borg, MD, PhD, Richard A. de Vries, MD, PhD, Marco J. Bruno, MD, PhD, Herman van Dekken, MD, PhD, Jos Meijer, MD,

TABLE 2. Proposal for the OLGIM staging system

		Corpus			
	IM score	**Not fat: no IM (score 0)**	**Mild IM (score 1)**	**Moderate IM (score 2)**	**Severe IM (score 3)**
Antrum (including incisura angularis)	No IM (score 0)	Stage 0	Stage I	Stage II	Stage II
	Mild IM (score 1)	Stage I	Stage I	Stage II	Stage III
	Moderate IM (score 2)	Stage II	Stage II	Stage III	Stage IV
	Severe IM (score 3)	Stage III	Stage III	Stage IV	Stage IV

IM, Intestinal metaplasia; *OLGIM*, operative link on gastric intestinal metaplasia assessment.

Capelle L *et al.* Gastrointest Endosc 71: 1150, 2010

Progression of chronic atrophic gastritis associated with *Helicobacter pylori* infection increases risk of gastric cancer

(Prospective study – mean follow-up: 7.7 years)

***HP* infection**	–	+	+	–
CAG	–	–	+	+
Gastric cancer				
Cases/incidence rate	0	19/107	24/238	2/871
HR (95% CI)	– (1)	**7.13** (0.95-53.33)	**14.51** (1.96-107.70)	**61.85** (5.60-682.64)

p=0.0007

Ohata H *et al.* Int J Cancer 109:138, 2004

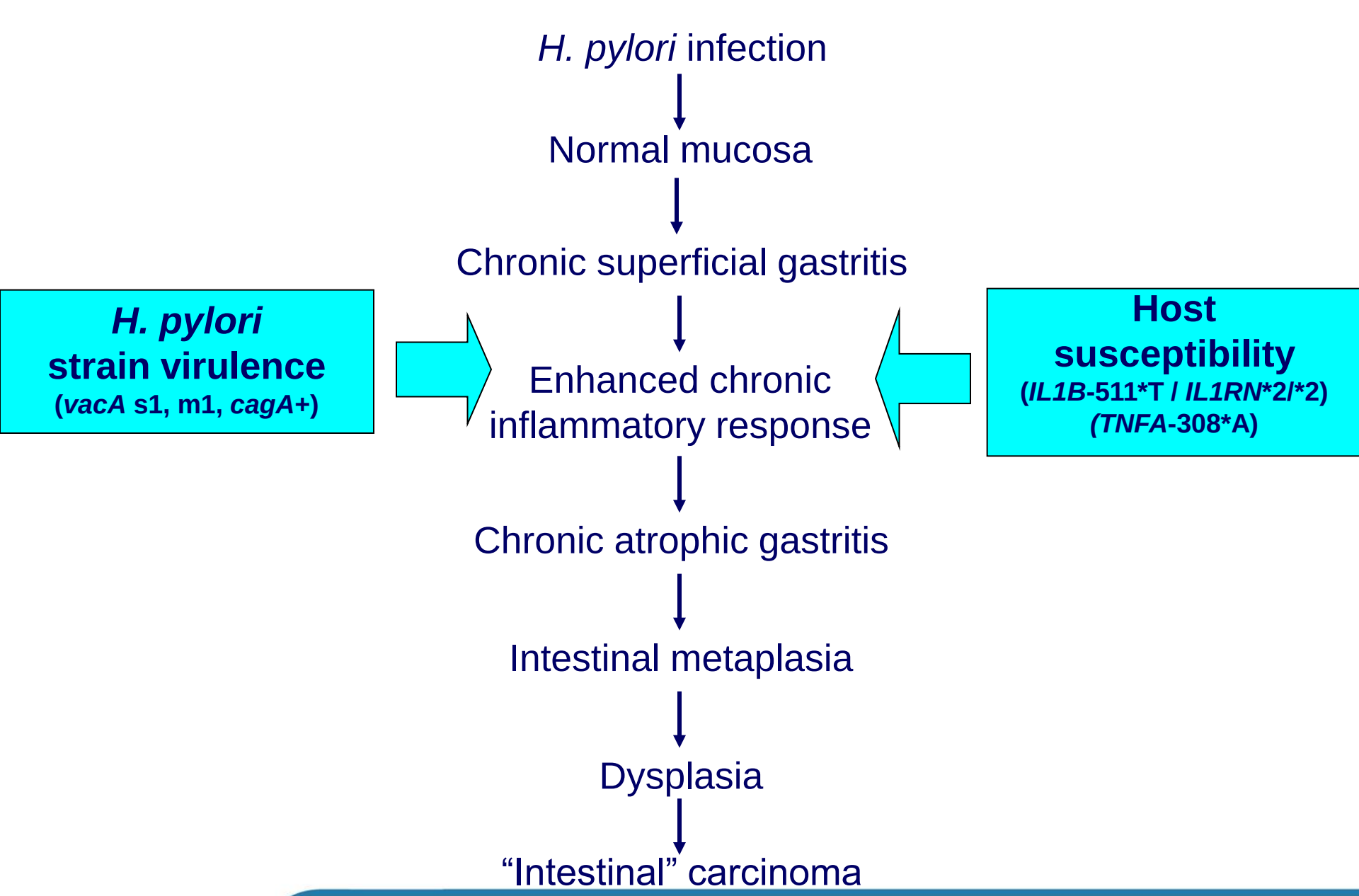
Helicobacter pylori Eradication to Prevent Gastric Cancer in a High-Risk Region of China

A Randomized Controlled Trial

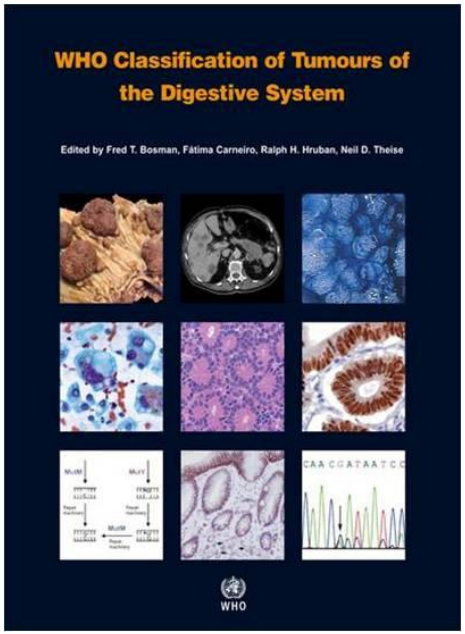
Prospective, randomized, placebo-controlled, population-based primary prevention study of 1630 healthy carriers of *H. pylori* infection

Overall		
H. pylori eradication	7 gastric cancers	
Placebo	11 gastric cancers	***p*=0.33**
Patients without **precancerous lesions** on presentation		
***H. pylori* eradication**	**0 gastric cancers**	
Placebo	6 gastric cancers	***p*=0.02**

Wong BC *et al* JAMA 291: 187, 2004

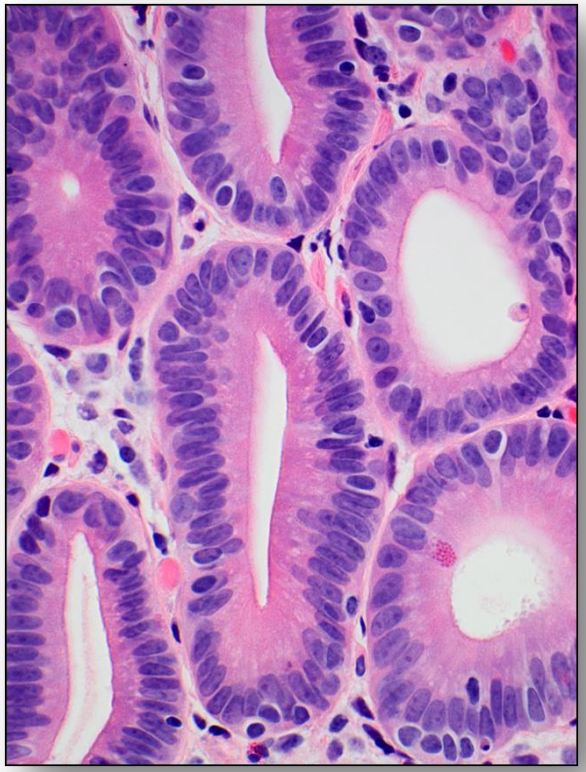

H. pylori infection
Normal mucosa
Chronic superficial gastritis
H. pylori **strain virulence** (***vacA*** **s1, m1, *cagA*+)**
Enhanced chronic inflammatory response
Host susceptibility (***IL1B*-511*T / *IL1RN**2/*2)** (***TNFA*-308*A)**
Chronic atrophic gastritis
Intestinal metaplasia
Dysplasia
"Intestinal" carcinoma

Gastric dysplasia - WHO classification (2010)

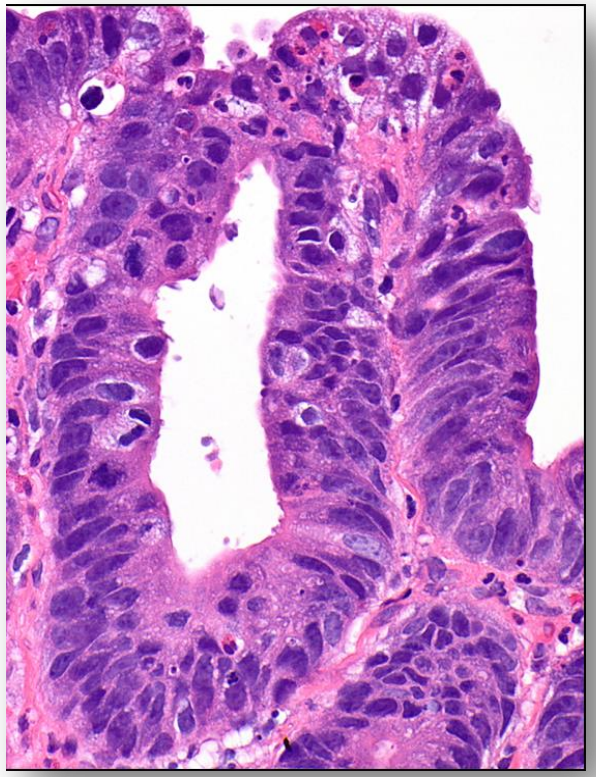


Odze RD *et al*. Premalignant lesions of the digestive system. *In*: WHO Classification of Tumours of the Digestive System, Fouth Edition. Bosman FT, Carneiro F, Hruban RH and Theise ND (eds), IARC Press: Lyon, 2010; Pp 10-12.

LOW- AND HIGH-GRADE DYSPLASIA



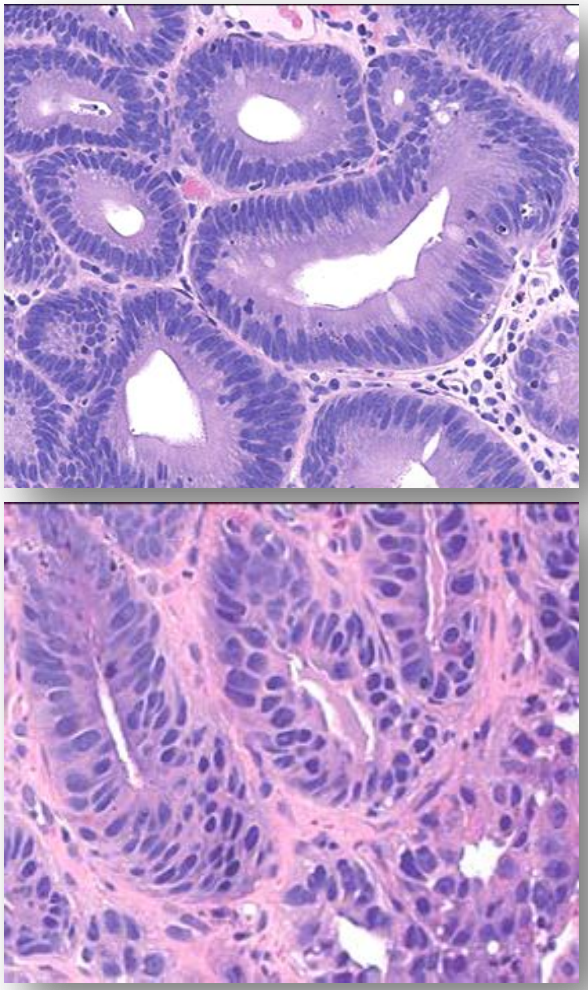
- Minimal architectural disarray
- Mild/moderate cytological atypia
- Nuclei are elongated, polarised, basally located
- Mitotic activity is mild/moderate.



- Pronounced architectural disarray
- High nucleus:cytoplasm ratio
- Numerous mitoses, often atypical
- Nuclei frequently extend towards the luminal half of the gland

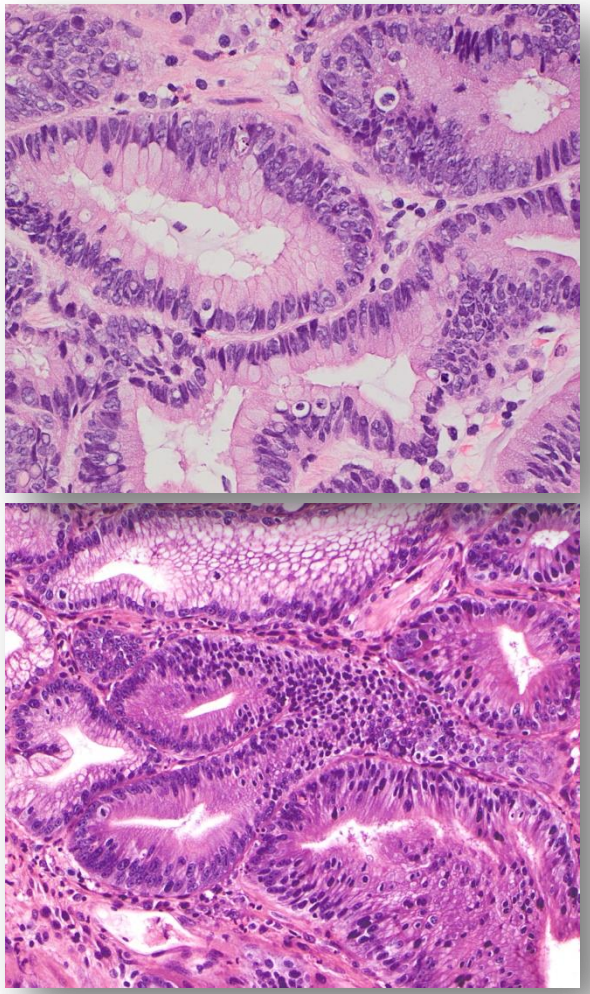
MORPHOLOGIC TYPE

Intestinal type



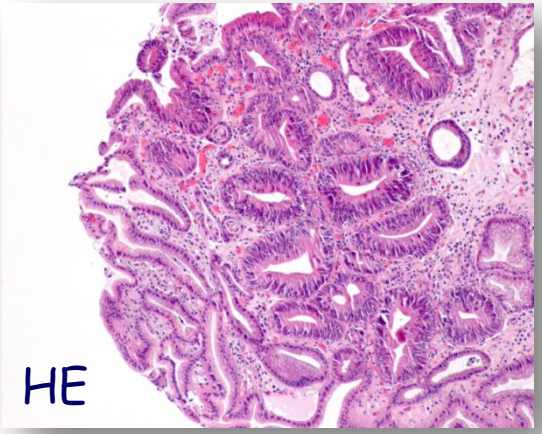
- Columnar cells
- Pencilate nuclei
- Hipercromatic nuclei

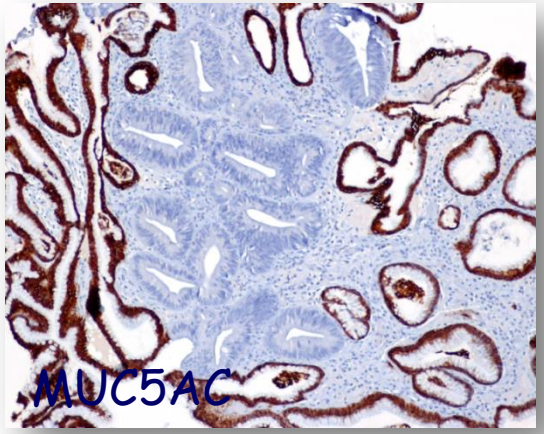
Gastric type

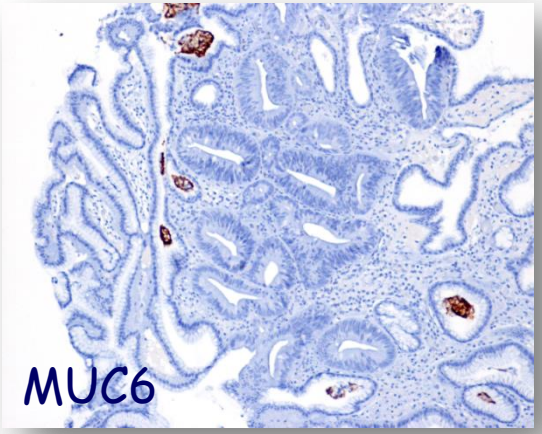


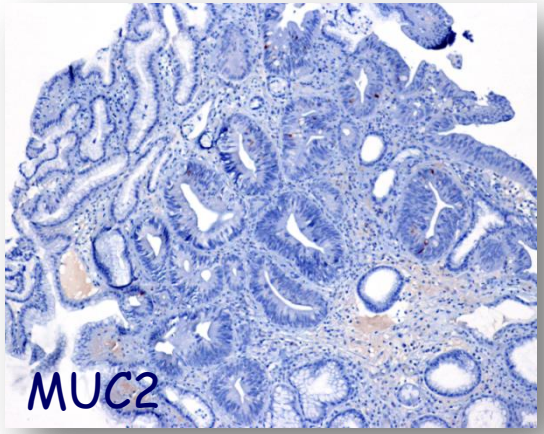
- Cuboidal cells
- Oval, vesicular nuclei
- Clear, eosinophilic cytopasm

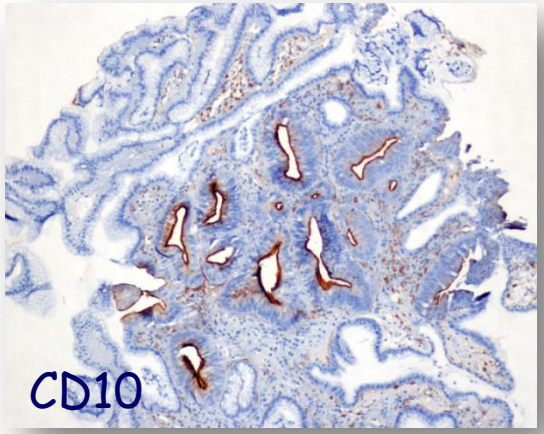
WHO - 4th Edition, 2010

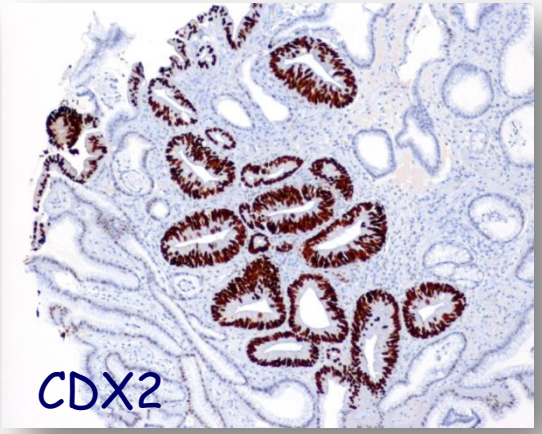




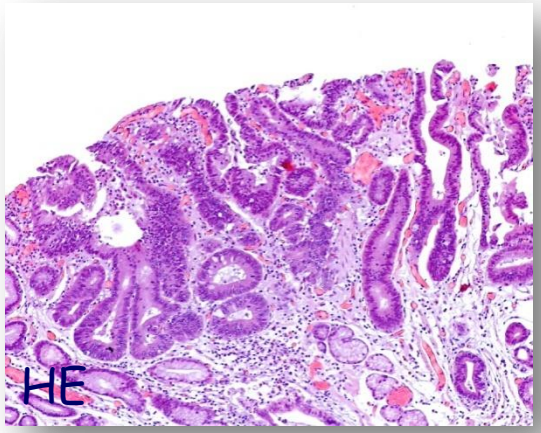


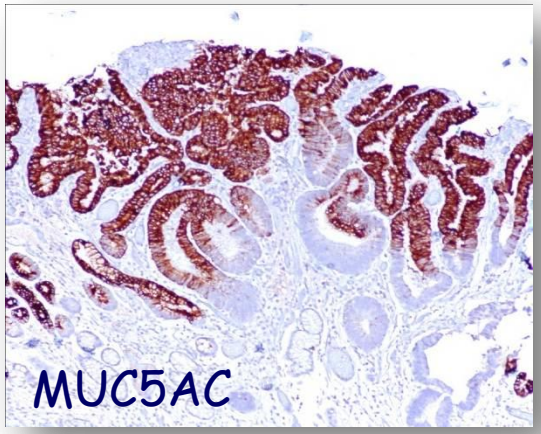


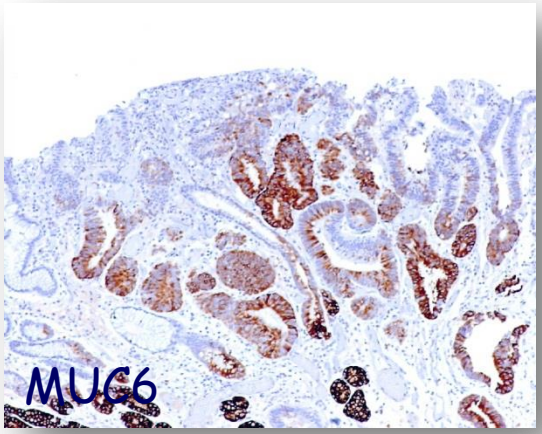


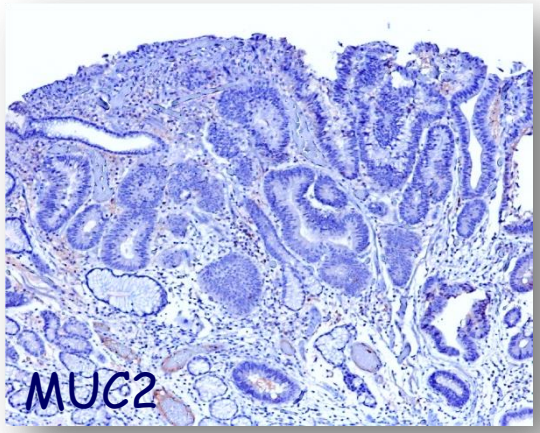


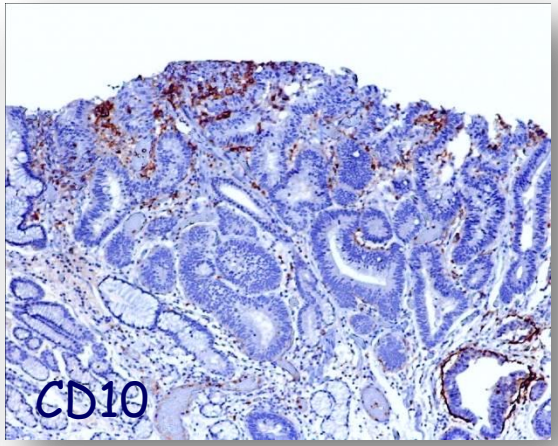
Intestinal phenotype

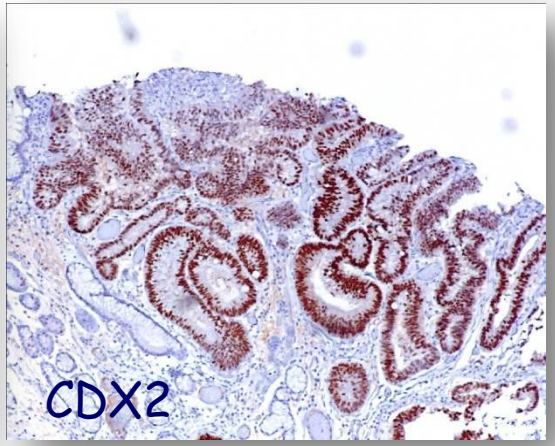












Gastric/foveolar phenotype

Comparison between grade and immunophenotypes

Grade	Immunophenotype			*p value*
	Gastric (n=24)	Intestinal(n=22)	Hybrid(n=14)	
High grade (n=25)	15* 63%	4 18%	6 43%	
Low grade (n=35)	9 37%	18 82%	8 57%	
				0.010

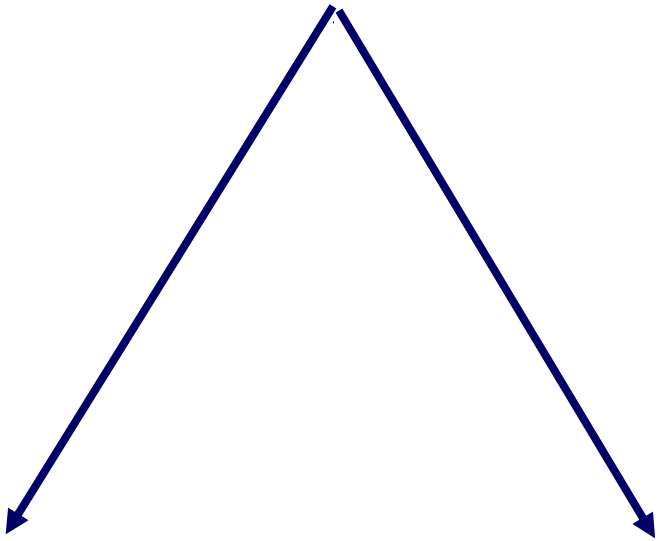
* coexistent intramucosal carcinoma in 8 cases

Gastric differentiation is associated with high-grade dysplasia and coexistence of intramucosal carcinoma.

Baldaia H *et al.* Virchows Archiv 461 (Suppl 1): S7-S8, 2012

What about diffuse gastric cancer

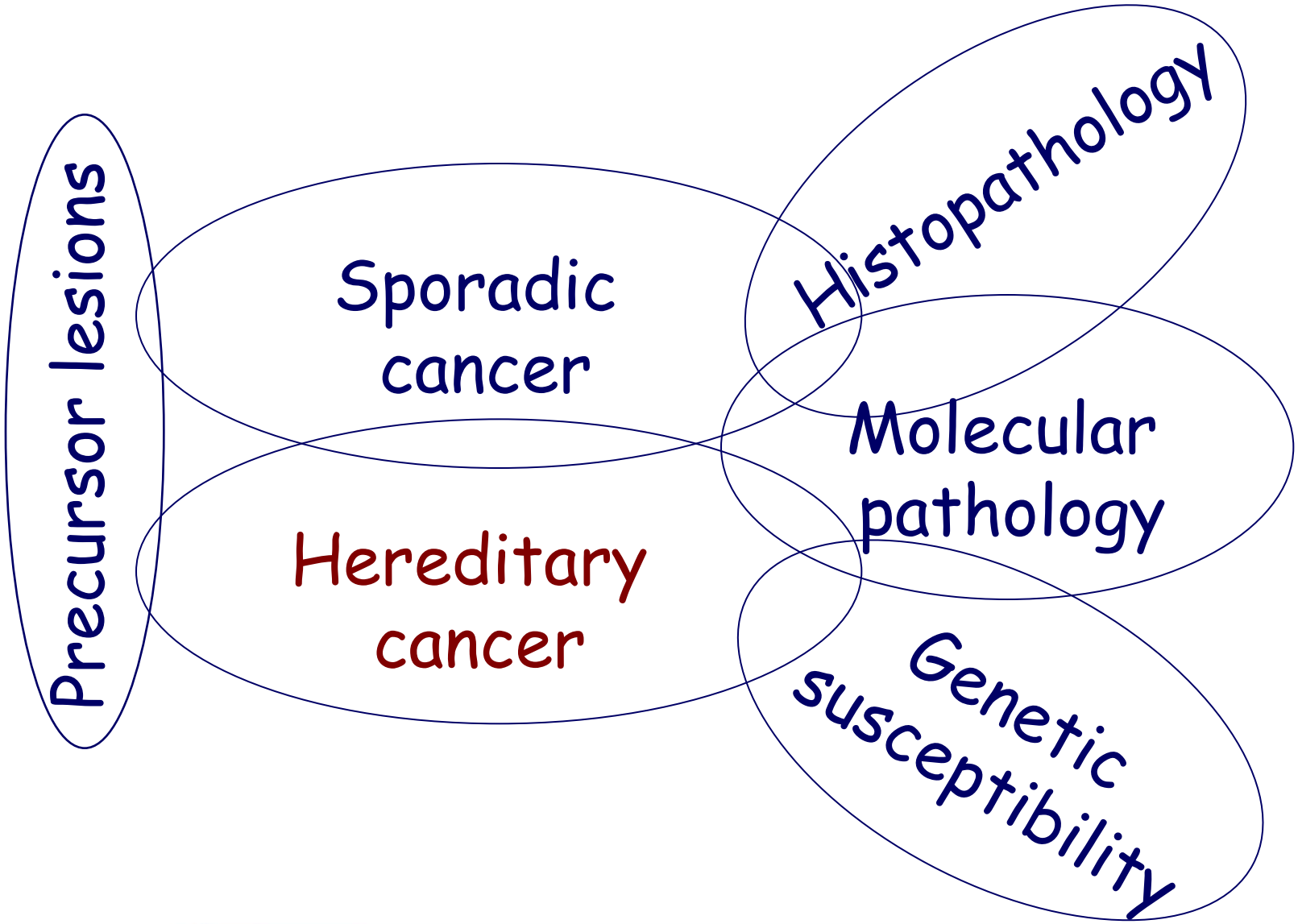
Helicobacter pylori associated gastritis



"Intestinal" carcinoma

Diffuse carcinoma
(lessons from HDCG)

GASTRIC CANCER



New Chapter on:

Hereditary diffuse gastric cancer

F. Carneiro
A. Charlton
D.G. Huntsman

Definition

Hereditary diffuse gastric cancer (HDGC) is an autosomal-dominant cancer-susceptibility syndrome that is characterized by signet-ring cell (diffuse) gastric cancer and lobular breast cancer. The genetic basis for this syndrome was discovered in 1998 by Guilford *et al.* (1081), who identified germline mutations of the E-cadherin (*CDH1*) gene (MIM No. 192090) by linkage analysis and mutation screening in three Maori kindreds with multigenerational, diffuse gastric cancer in New Zealand.

MIM No.: 137215

Diagnostic criteria

In families with an aggregation of gastric cancer, the histopathology of the tumours is often unknown; these cases are designated as familial gastric cancer (FGC). When the histopathological type of one or more gastric cancers is known, discrete syndromes/diseases can be diagnosed; these include HDGC, familial diffuse gastric cancer (FDGC) and familial intestinal gastric cancer (FIGC) (397).

On the basis of clinical criteria, the International Gastric Cancer Linkage Consortium (IGCLC) in 1999 defined families with the HDGC syndrome as those fulfilling one of the following features: (1) two or more documented cases of diffuse gastric cancer in first- or second-degree relatives, with at least one being diagnosed before the age of 50 years; or (2) three or more cases of documented diffuse gastric cancer in first- or second-degree relatives, independent of age of diagnosis (397). Women in these families also have an elevated risk of lobular breast cancer (341, 1501, 1513, 2855, 3136). IGCLC criteria for genetic testing, updated in 2009 (871) are shown in Table 4.2.01. An alternative genetically-based nomenclature, proposed by the New Zealand group, in which the term "HDGC" is restricted to families with germline mutations in the *CDH1* gene (1081, 1082). The IGCLC definition for HDGC will be used for the remainder of this section (871).

Epidemiology

The vast majority of gastric cancers are sporadic, but approximately 1–3% result from an inherited predisposition (870, 2396, 2439).

The prevalence of HDGC is uncertain, partly due to the recent identification of this syndrome. In a review of 439 families with aggregation of gastric cancer (2395), *CDH1* mutations were preferentially observed in families fulfilling the clinical criteria for HDGC (36.4%). In FDGC, the frequency of germline mutations in *CDH1* was much lower (12.5%) (2395). *CDH1* mutations have not been found in families with weaker histories of gastric cancer; however, mutation rates of up to 10% have been described in individuals with no family history but DGC diagnosed at less than age 35 years, from populations with a low incidence of gastric cancer (1501, 3136). There are striking population-specific differences regarding the fraction of families with aggregation of gastric cancer and frequency of *CDH1* germline mutations. In countries with a low incidence of gastric cancer, the frequency of germline alterations in the *CDH1* gene is > 40%, while in countries with a moderate or high incidence of gastric cancer, the frequency of alterations in *CDH1* is about 20% (2396). These observations in moderate- or high-incidence countries are probably related to clustering of gastric cancer attributable to environmental risk factors (lifestyle, diet) and/or variation in genes conferring a weak susceptibility (2396).

Localization

Most index cases with HDGC present with cancers that are indistinguishable from sporadic diffuse gastric cancer, often with linitis plastica, which can involve all topographic regions within the stomach. Systematic complete mapping of total gastrectomies from asymptomatic carriers

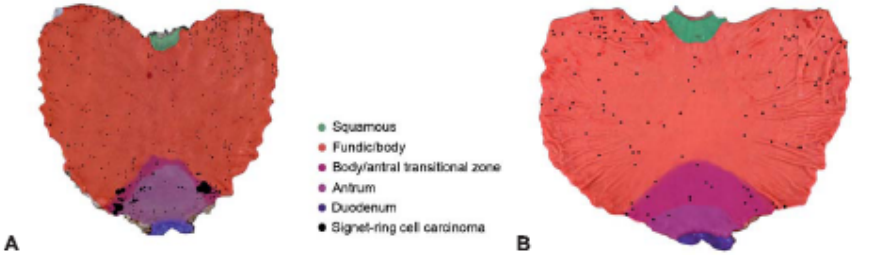


Fig. 4.2.01 Mapping of gastric mucosal zones (semi-opaque colours) and location of foci of stage T1a signet-ring cell (diffuse) carcinoma (black circles) on photos of two stomachs. Adapted from Charlton *et al.* (493). A Asymptomatic *CDH1*-mutation carrier, aged 15 years; the map indicates the location of 318 foci and mucosal zones. B Asymptomatic *CDH1*-mutation carrier, aged 19 years, from the same family; the map indicates the location of 115 foci and mucosal zones.

GASTRIC CARCINOMA

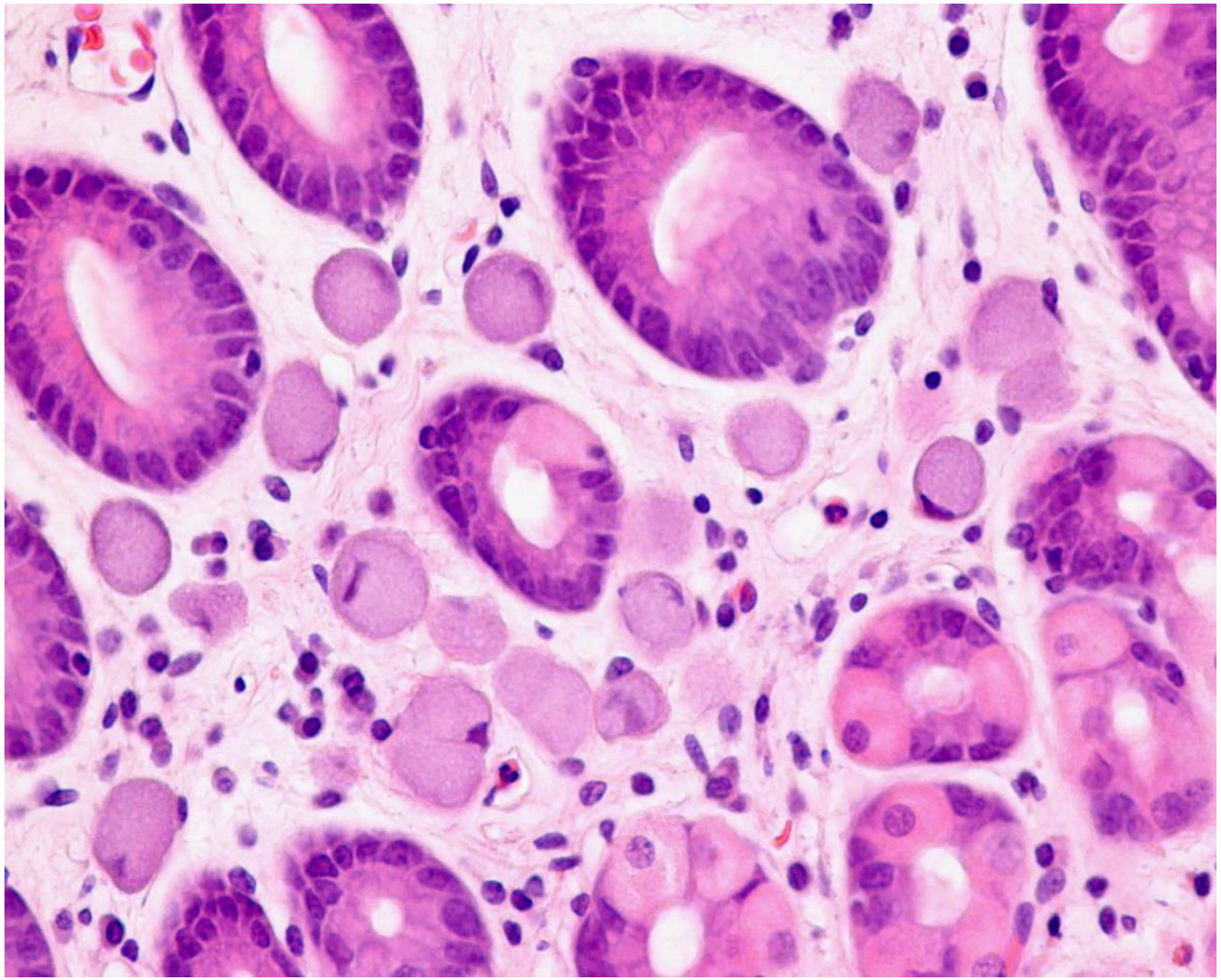
- Sporadic (90%)
- Familial Aggregation (10%)

  Familial Gastric Cancer (FGC)
  Familial Intestinal Gastric Cancer (FIGC)
  Familial Diffuse Gastric Cancer (FDGC)

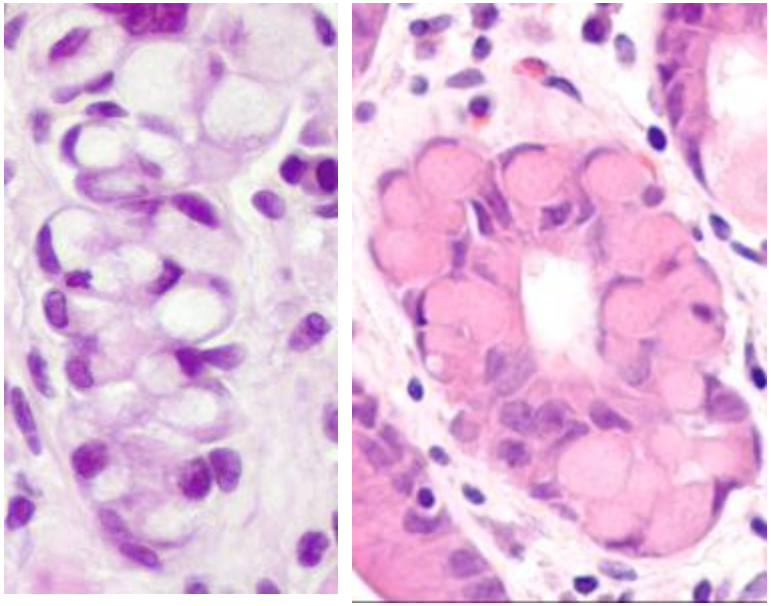
- Hereditary (1%)*

  Hereditary Diffuse Gastric Cancer (HDGC)

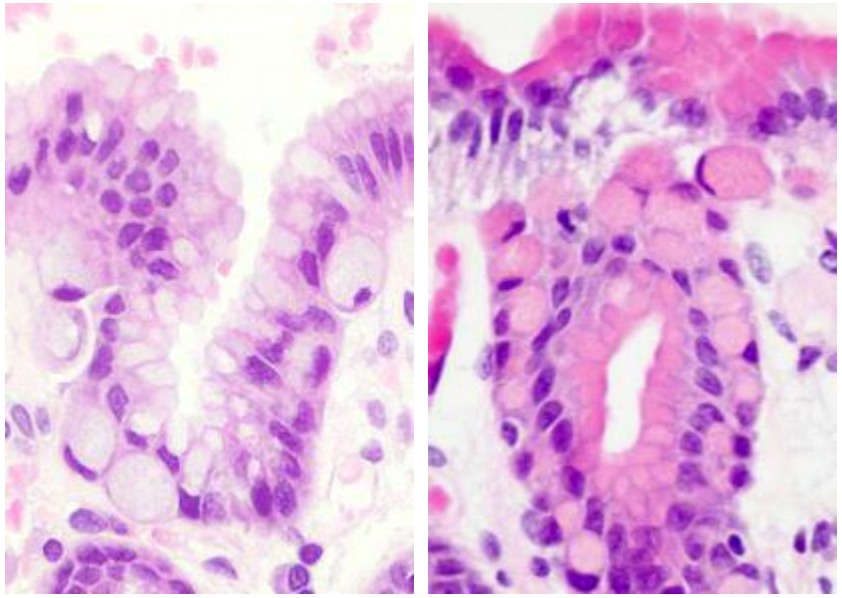
* Most caused by E-cadherin alterations



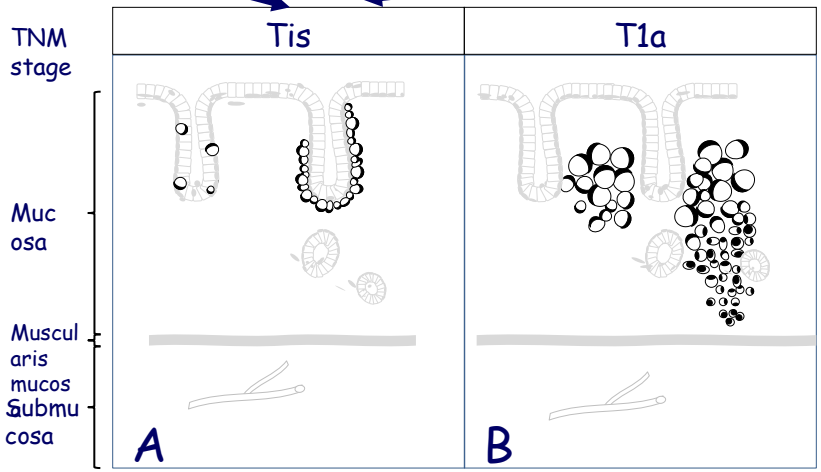
Intramucosal signet ring cell (diffuse) carcinoma



In situ (signet ring cell) carcinoma



Pagetoid spread of signet ring cells:
Two-layer structure: an inner layer composed of benign mucous cells and an outer layer of signet ring cells.



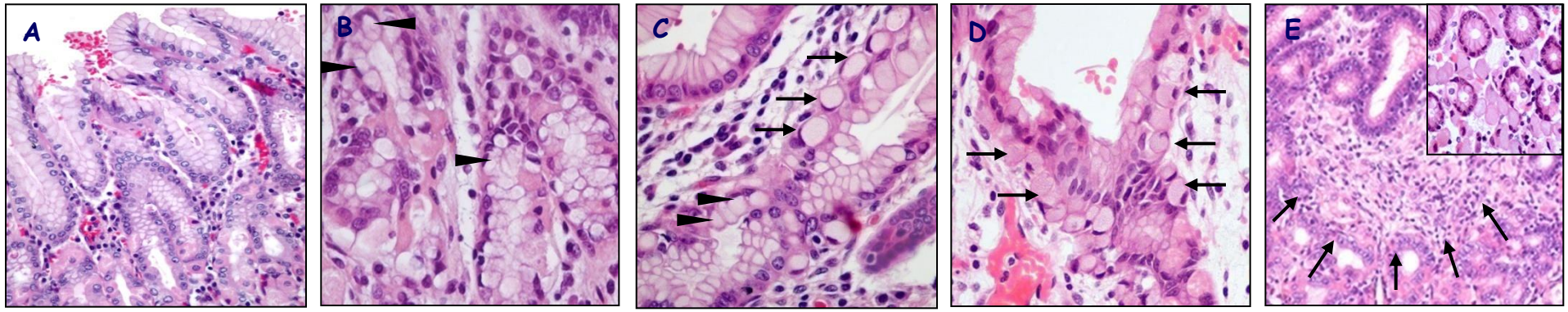
Carneiro F, Charlton A, Huntsman D
4th Edition of WHO book , 2010

Development model of HDGC

?

Inactivation of second allele of *CDH1*

CDH1 germline mutation



Non-neoplastic mucosa with foveolar hyperplasia

In situ signet ring cell carcinoma

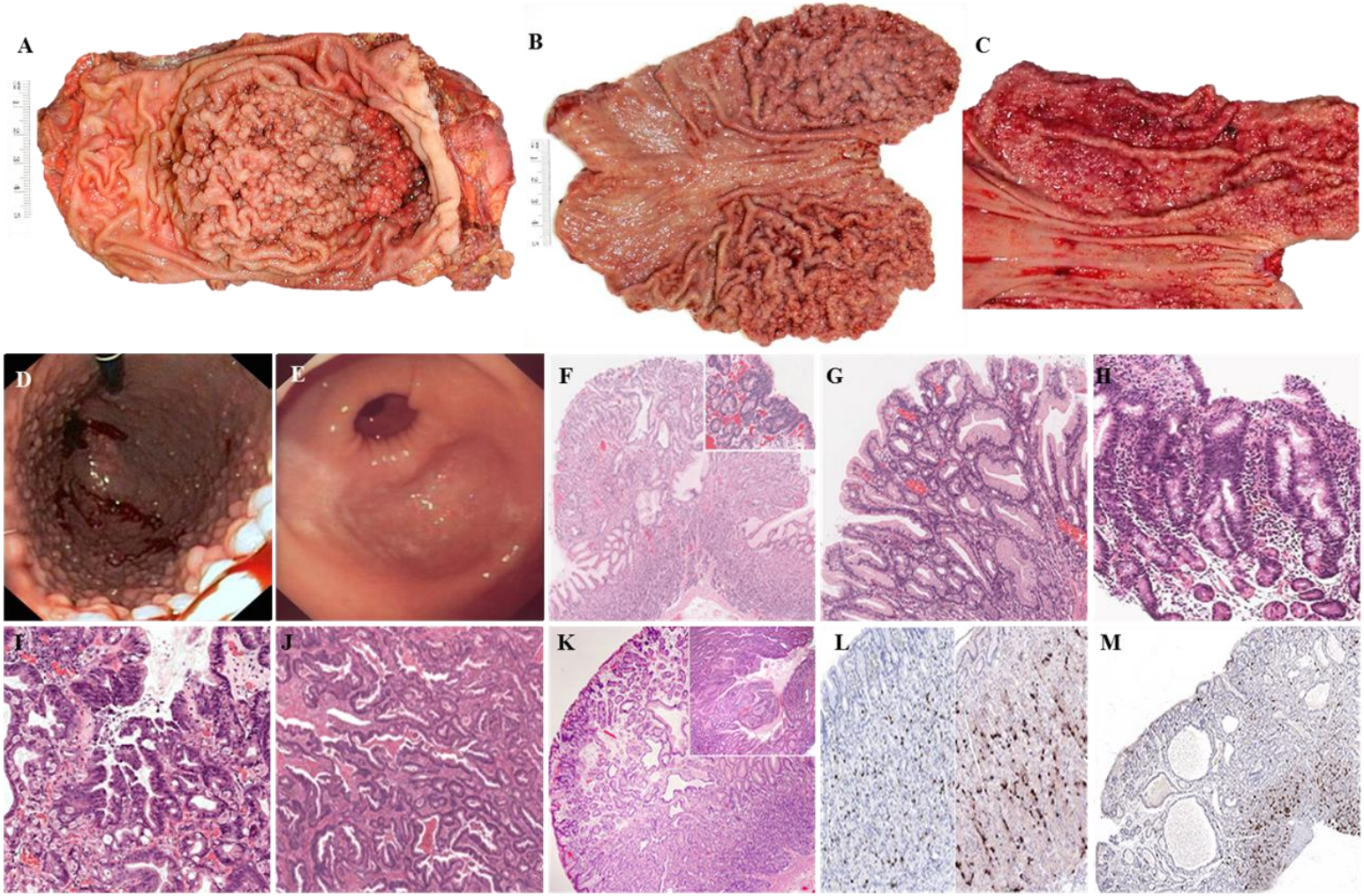
In situ signet ring cell carcinoma and pagetoid spread

Pagetoid spread of signet ring cell carcinoma

Early invasive (intramucosal) signet ring cell carcinoma

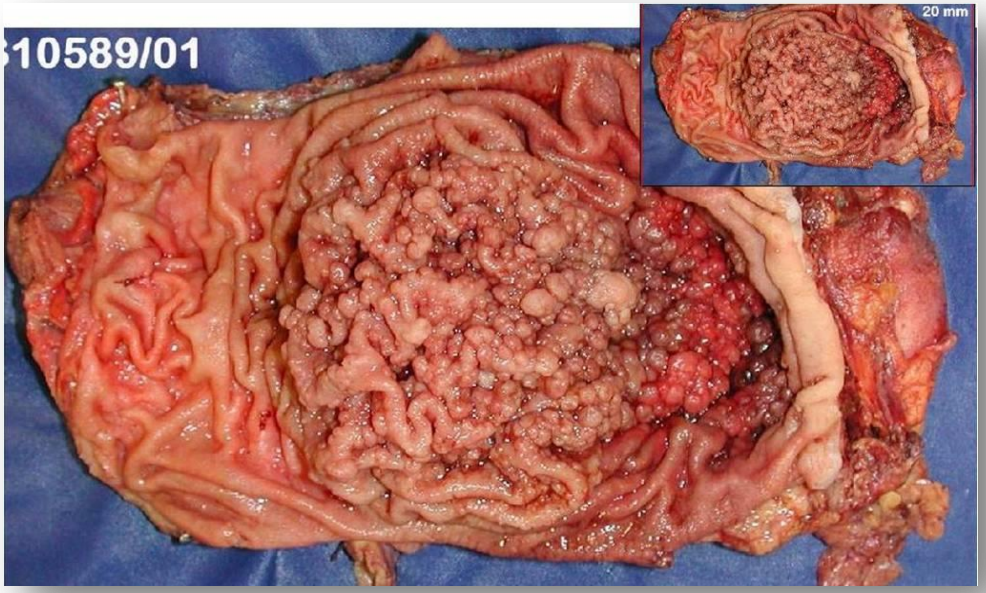
Carneiro F *et al*. J Clin Pathol 61:25, 2008

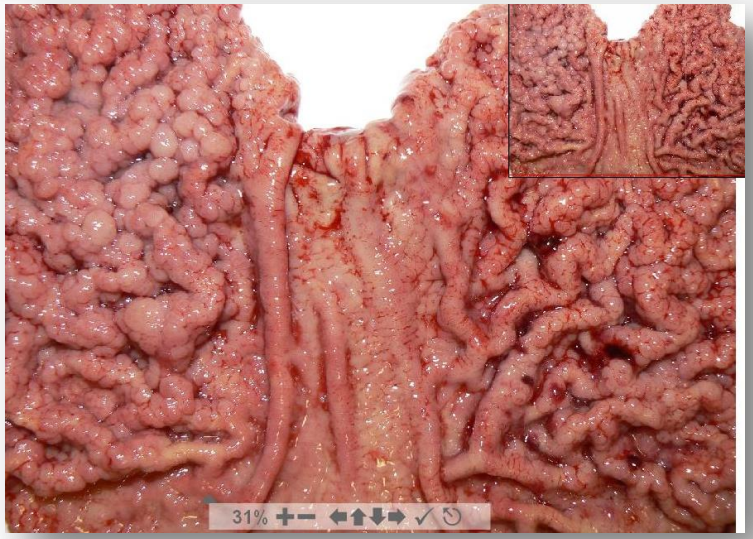
Gastric Adenocarcinoma and Proximal Polyposis of the Stomach (GAPPS): a new autosomal dominant syndrome.

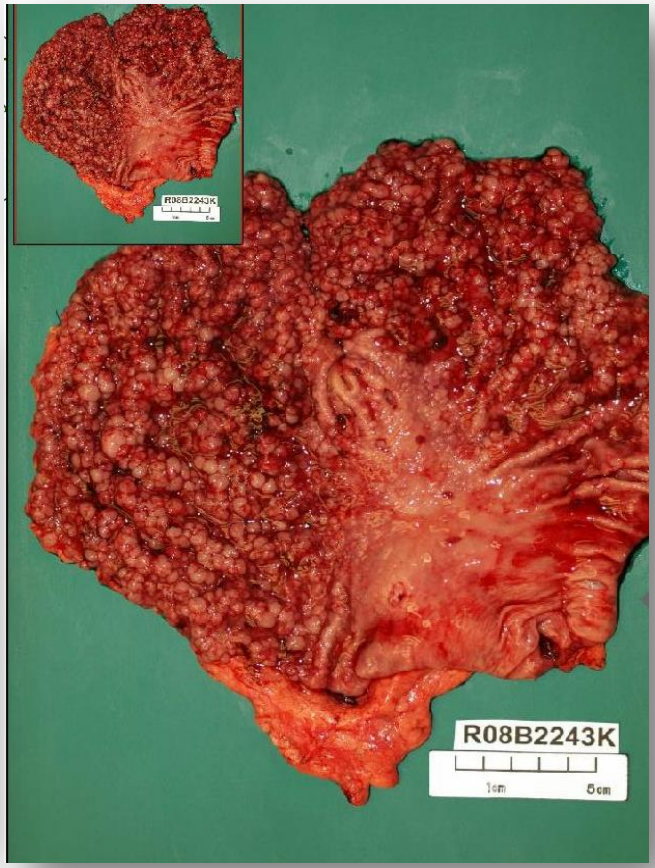


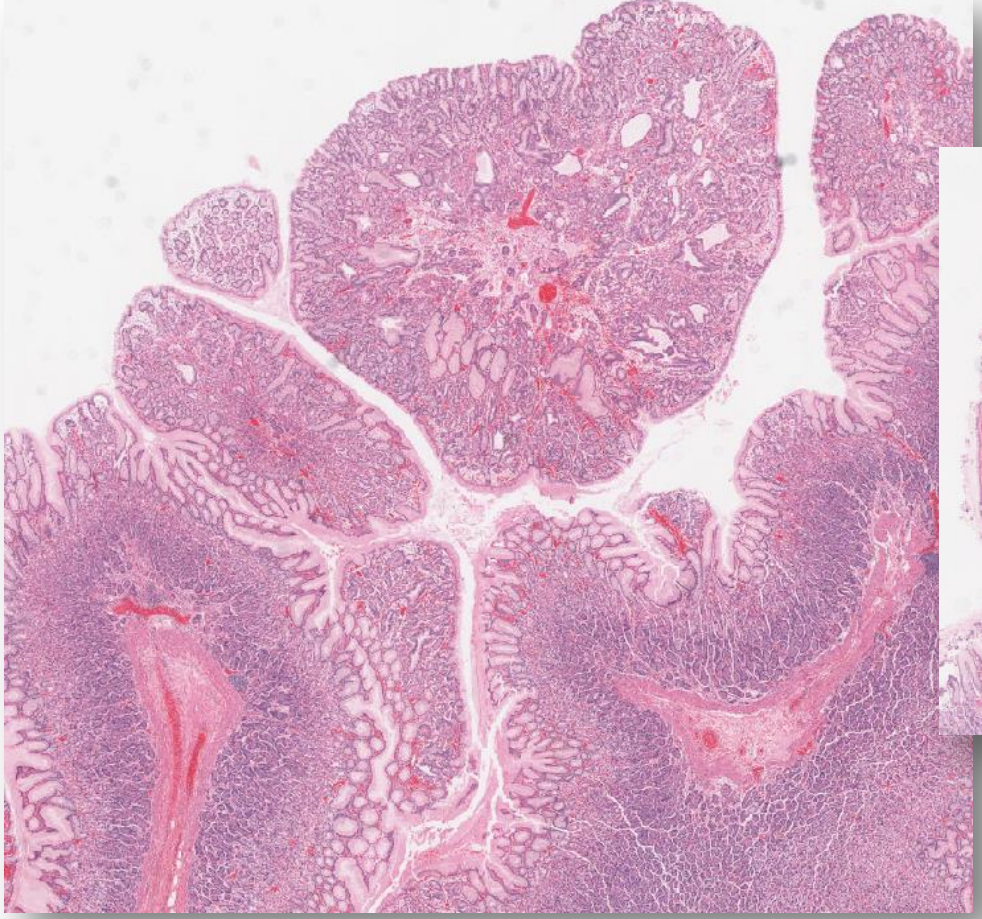
Worthley et al; Gut 61:774-779, 2012

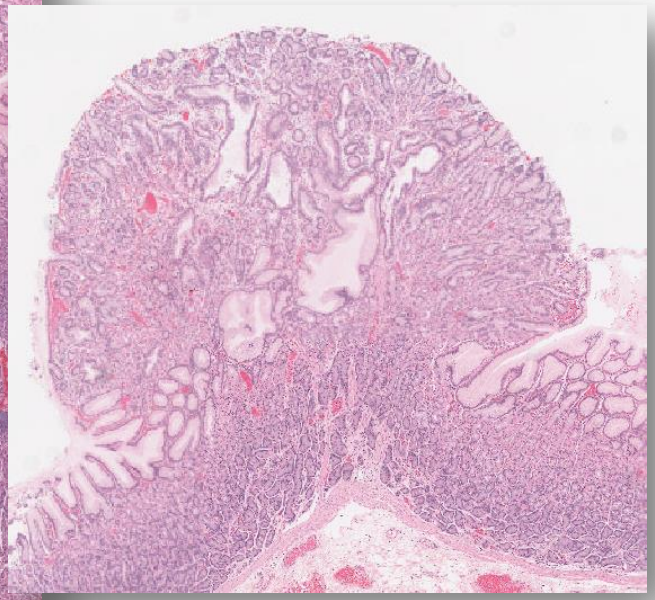
Proximal polyposis of the stomach

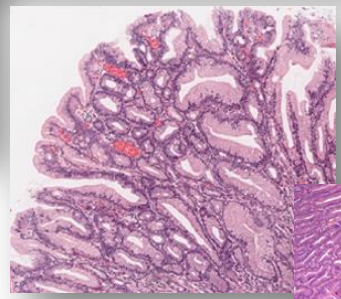


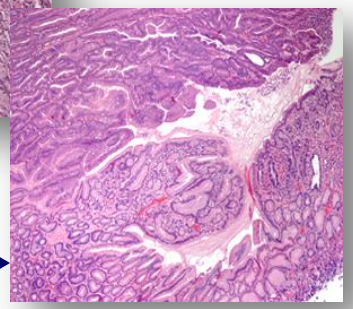






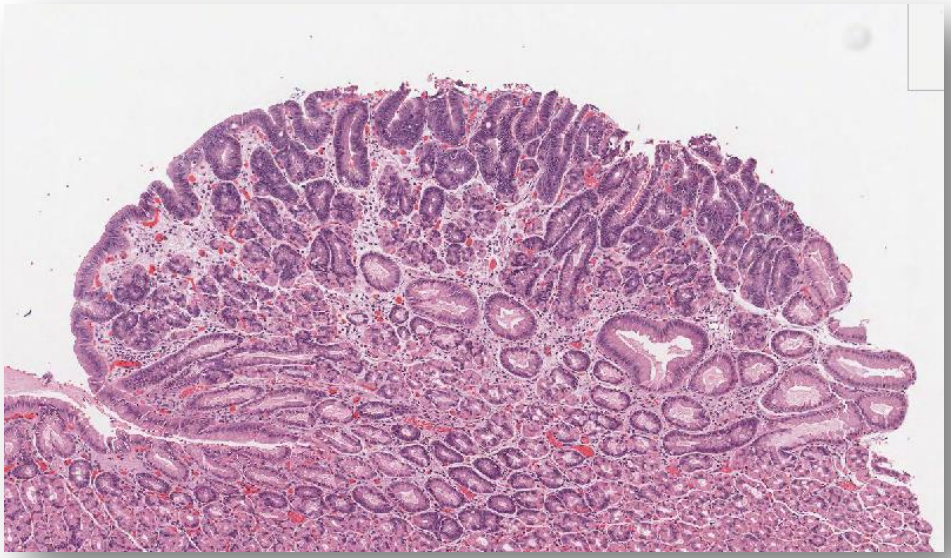


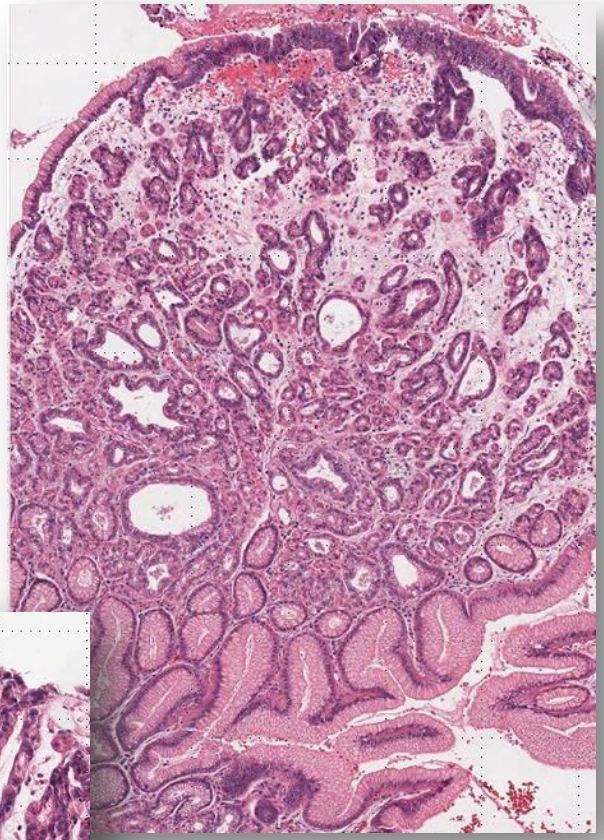


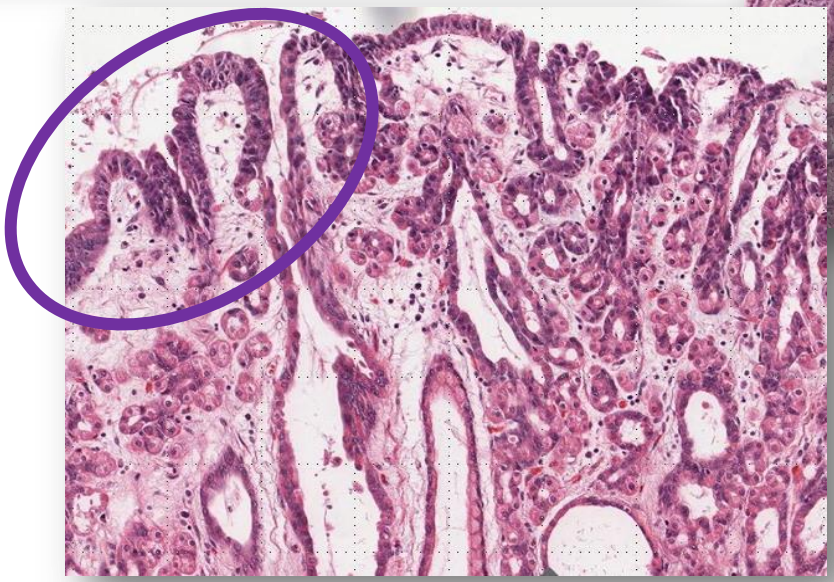


Proximal polyposis of the stomach:

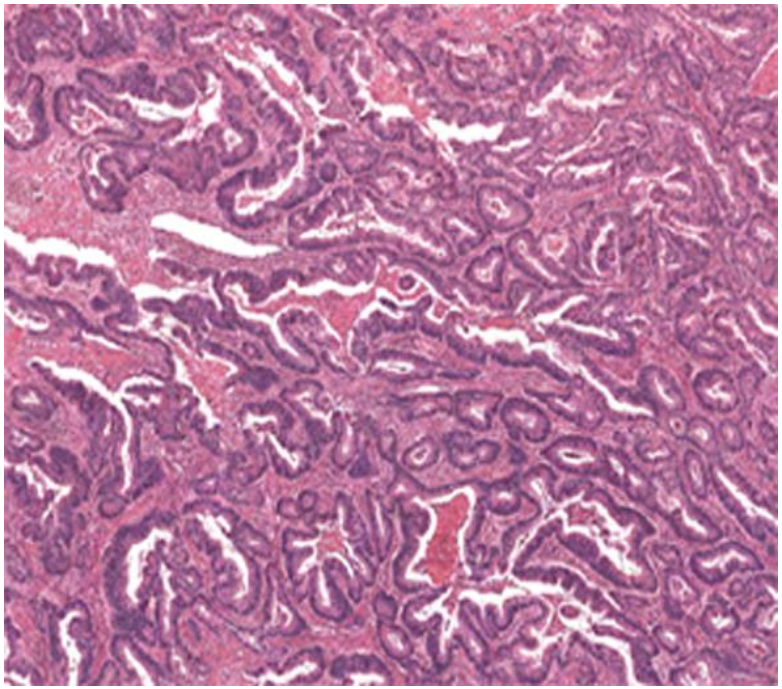
- Fundic gland polyps (predominant)
- Hyperplastic (rare)
- Adenomatous (rare)

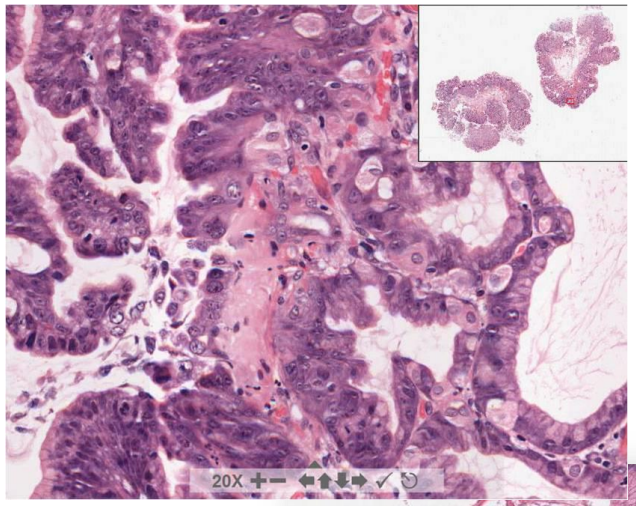


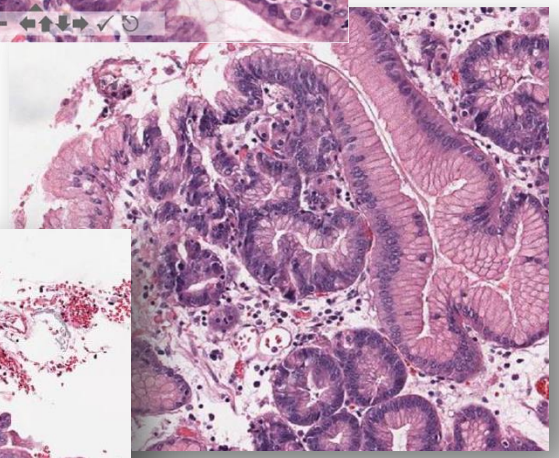


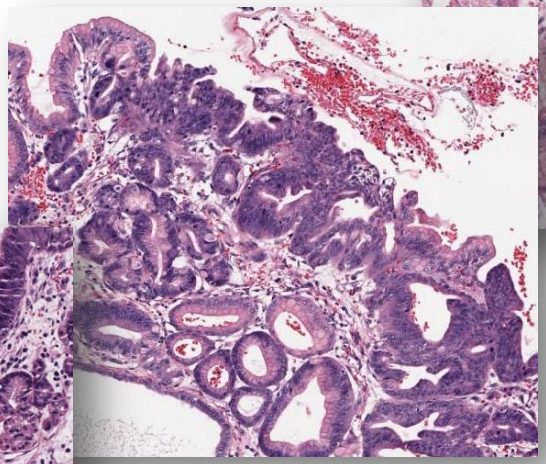


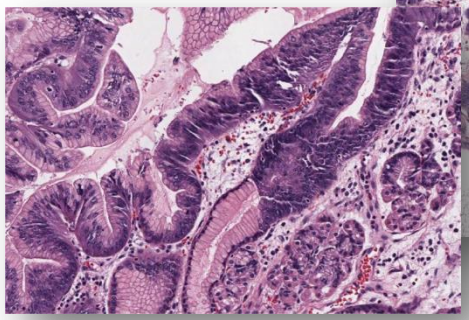
Dysplasia in fundic gland polyps





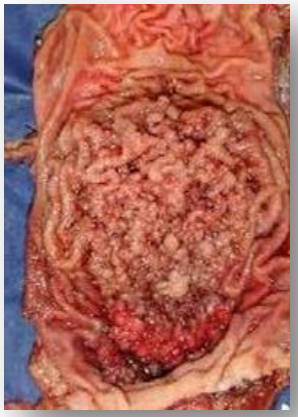




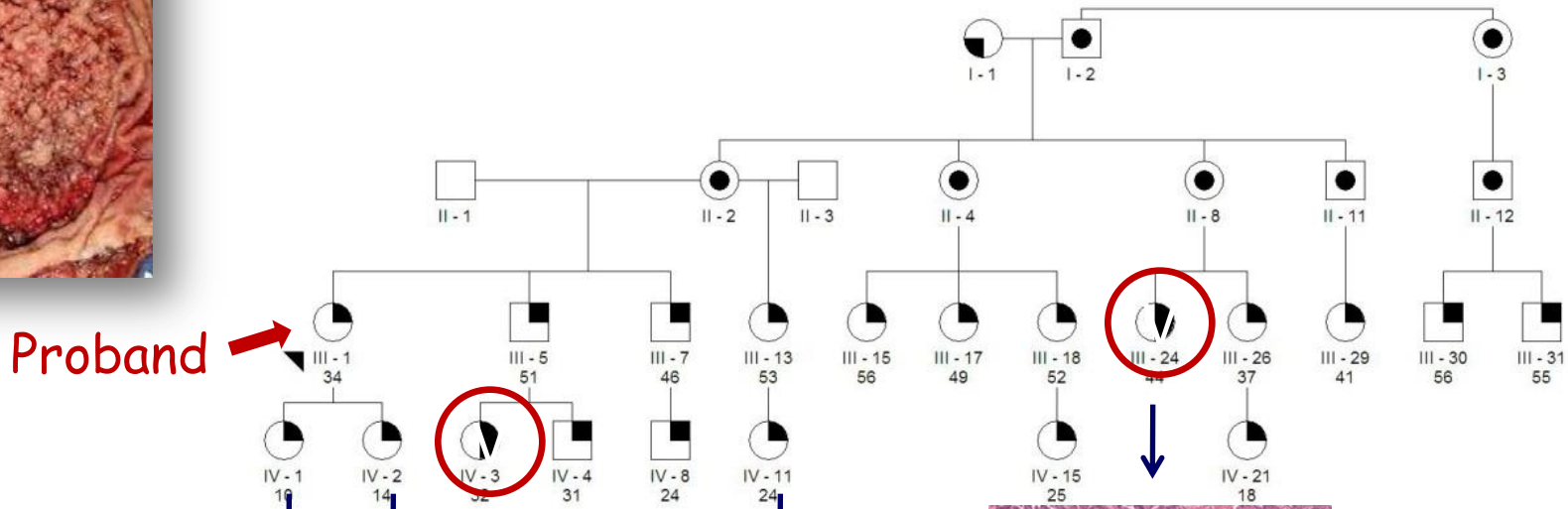


Gastric Adenocarcinoma and Proximal Polyposis of the Stomach

Family 1

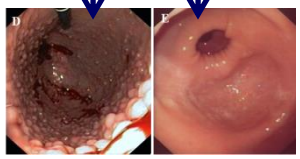


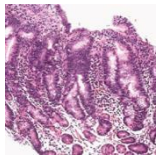
FGP



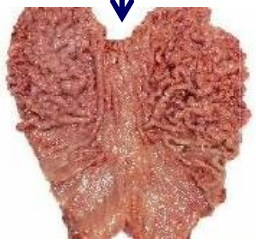
Proband

FGP

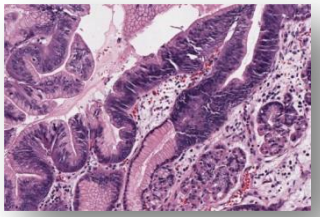




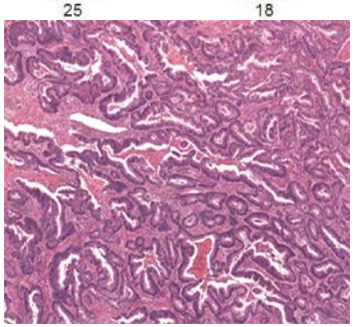
Dysplasia



FGP



Dysplasia



Gastric Adenocarcinoma

FGPs in 20 family members

Gastric adenocarcinoma and proximal polyposis of the stomach (GAPPS): a new autosomal dominant syndrome

D L Worthley,[1] K D Phillips,[2] N Wayte,[3] K A Schrader,[4] S Healey,[5] P Kaurah,[4] A Shulkes,[6] F Grimpen,[7] A Clouston,[7] D Moore,[8] D Cullen,[9] D Ormonde,[9] D Mounkley,[10] X Wen,[11] N Lindor,[11] F Carneiro,[11] D G Huntsman,[4] G Chenevix-Trench,[5] G K Suthers[2,12]

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[3]School of Medicine, University of Queensland, Queensland, Australia
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[7]Royal Brisbane and Women's Hospital, Queensland, Australia
[8]Women's and Children's Hospital, South Australia, Australia
[9]St John of God Hospital, Western Australia, Australia
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ABSTRACT

Objective The purpose of this study was the clinical and pathological characterisation of a new autosomal dominant gastric polyposis syndrome, gastric adenocarcinoma and proximal polyposis of the stomach (GAPPS).

Methods Case series were examined, documenting GAPPS in three families from Australia, the USA and Canada. The affected families were identified through referral to centralised clinical genetics centres.

Results The report identifies the clinical and pathological features of this syndrome, including the predominant dysplastic fundic gland polyp histology, the exclusive involvement of the gastric body and fundus, the apparent inverse association with current *Helicobacter pylori* infection and the autosomal dominant mode of inheritance.

Conclusions GAPPS is a unique gastric polyposis syndrome with a significant risk of gastric adenocarcinoma. It is characterised by the autosomal dominant transmission of fundic gland polyposis, including areas of dysplasia or intestinal-type gastric adenocarcinoma, restricted to the proximal stomach, and with no evidence of colorectal or duodenal polyposis or other heritable gastrointestinal cancer syndromes.

include *MUTYH*-associated polyposis (MAP), generalised juvenile polyposis syndrome (GJPS), Peutz Jeghers syndrome (PJS) and Cowden syndrome.[5 6] However, FGPs are relatively rare in MAP, an autosomal recessive disorder, and GJPS and PJS are often characterised by the presence of specific hamartomatous (rather than purely dysplastic fundic gland) polyps.[5 6]

Sporadic FGPs are usually innocuous, but syndromic FGPs can progress to dysplasia and gastric adenocarcinoma.[7 9] Therefore, clinicians must distinguish patients with sporadic versus syndromic fundic gland polyposis so that additional scrutiny is provided for the latter without subjecting the majority of patients to needless investigation.

Here we describe a new autosomal dominant syndrome characterised by fundic gland polyposis and gastric cancer. We refer to the syndrome as gastric adenocarcinoma and proximal polyposis of the stomach (GAPPS). This report documents the detailed clinical and pathological features of GAPPS in a large Australian family and in two smaller North American families. We propose diagnostic criteria and management strategies for GAPPS and examine potential factors that may contribute to the pathogenesis.

Gut Online First, published on October 25, 2011 as 10.1136/gutjnl-2011-301384

LETTER

Familial fundic gland polyposis with gastric cancer

We read with interest the article by Worthley *et al*[1] regarding a new autosomal dominant syndrome characterised by fundic gland polyposis (FGP) and gastric cancer, which was not associated with familial adenomatous polyposis (FAP). We have experienced two similar cases of gastric adenocarcinoma occurring in pedigrees with familial FGP without FAP.

CASE 1

A 56-year-old woman was referred to our institution for further investigation of her multiple gastric polyps. On admission, serology and ^{13}C urea breath test yielded negative results for *Helicobacter pylori*. Upper gastrointestinal endoscopy revealed numerous fundic gland polyps covering the gastric fundus and corpus (figure 1A). In the fundus, there was also a flat and discoloured area circumscribed by polyps (figure 1B). A biopsy from the area revealed well-differentiated adenocarcinoma. No other polyps or adenomas were found in the duodenum. The colonoscopy did not show any colorectal lesions and the CT scan of the chest and abdomen was normal. A total gastrectomy was performed. Macroscopically, there were numerous small polypoid lesions. There was also a discoloured area measuring 6×5.5 cm in the gastric fundus (figure 1C). Histologically, numerous small fundic gland polyps were diffusely distributed (figure 1D). The tumour was a well-differentiated adenocarcinoma focally invading the superficial portion of the submucosa (figure 1E). Since hereditary hamartomatous polyposis was suspected, we performed an upper endoscopy on seven other family members: two sisters, one brother, two daughters, one son and one nephew. As a result, five of the seven subjects had similar gastric FGP (figure 2).

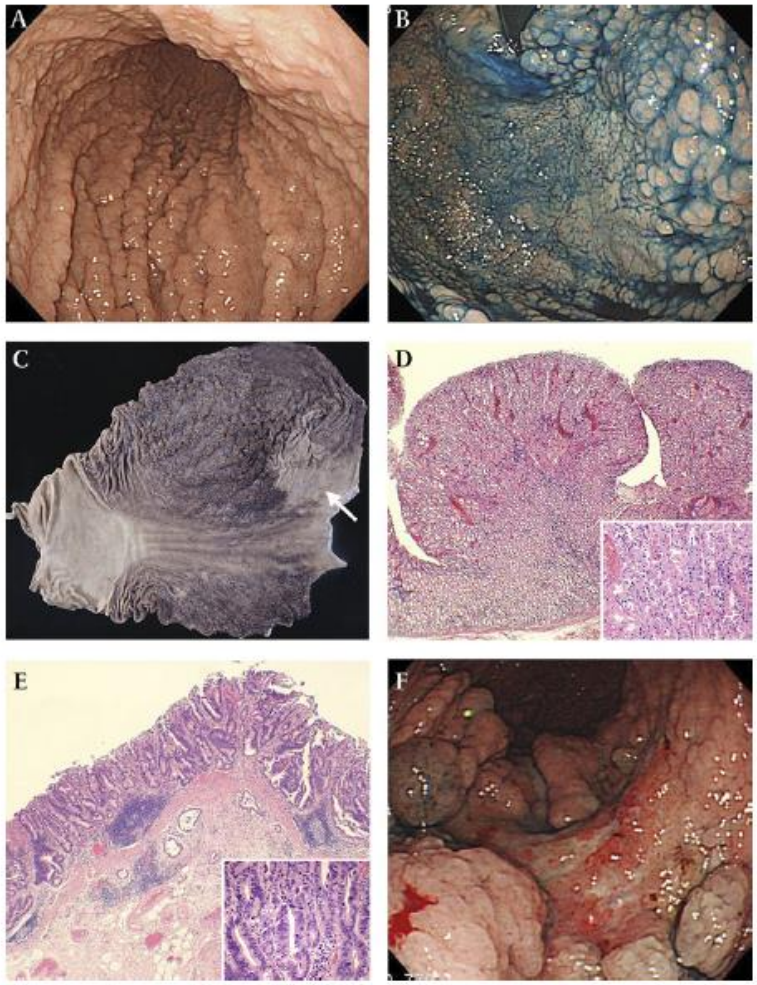

Figure 1 Endoscopic and pathological findings. (A and B) Case 1. Endoscopic images reveal numerous fundic gland polyps in the corpus (A), while a flat area circumscribed by polyps can be seen in the fundus (B). (C) Macroscopic finding of the gastrectomy specimen showing numerous

Autosomal dominant pattern of inheritance for FGP.

Diagnostic criteria for GAPPS

i) gastric polyps restricted to the body and fundus with no evidence of colorectal or duodenal polyposis;

ii) >100 polyps carpeting the proximal stomach in the index case or >30 polyps in a first degree relative of another case;

iii) predominantly FGPs, some having regions of dysplasia (or a family member with either dysplastic FGPs or gastric adenocarcinoma);

iv) an autosomal dominant pattern of inheritance.

Exclusions include other heritable gastric polyposis syndromes and use of PPIs. In patients on PPIs it is recommended to repeat the endoscopy off therapy.

Familial gastric cancer

- Sporadic (90%)
- Familial Aggregation (10%)

  Familial Gastric Cancer (FGC)
  Familial Intestinal Gastric Cancer (FIGC)
  Familial Diffuse Gastric Cancer (FDGC)

- Hereditary (1%?)
  - Hereditary Diffuse Gastric Cancer (HDGC)
  - Gastric Adenocarcinoma and Proximal Polyposis of the Stomach – GAPPS (HIGC)

Thanks for your attention

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