XXIV CONGRESO SOCIEDAD CHILENA DE ANATOMIA PATOLOGICA 2020

Hereditary diffuse gastric cancer: updated clinical practice guidelines

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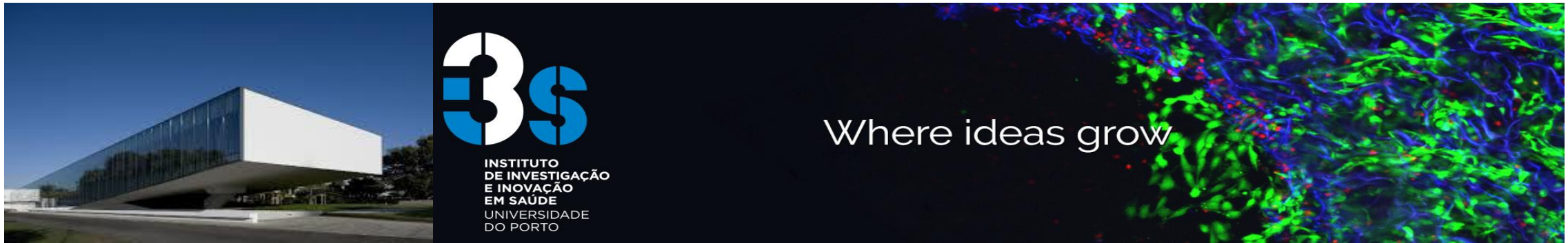
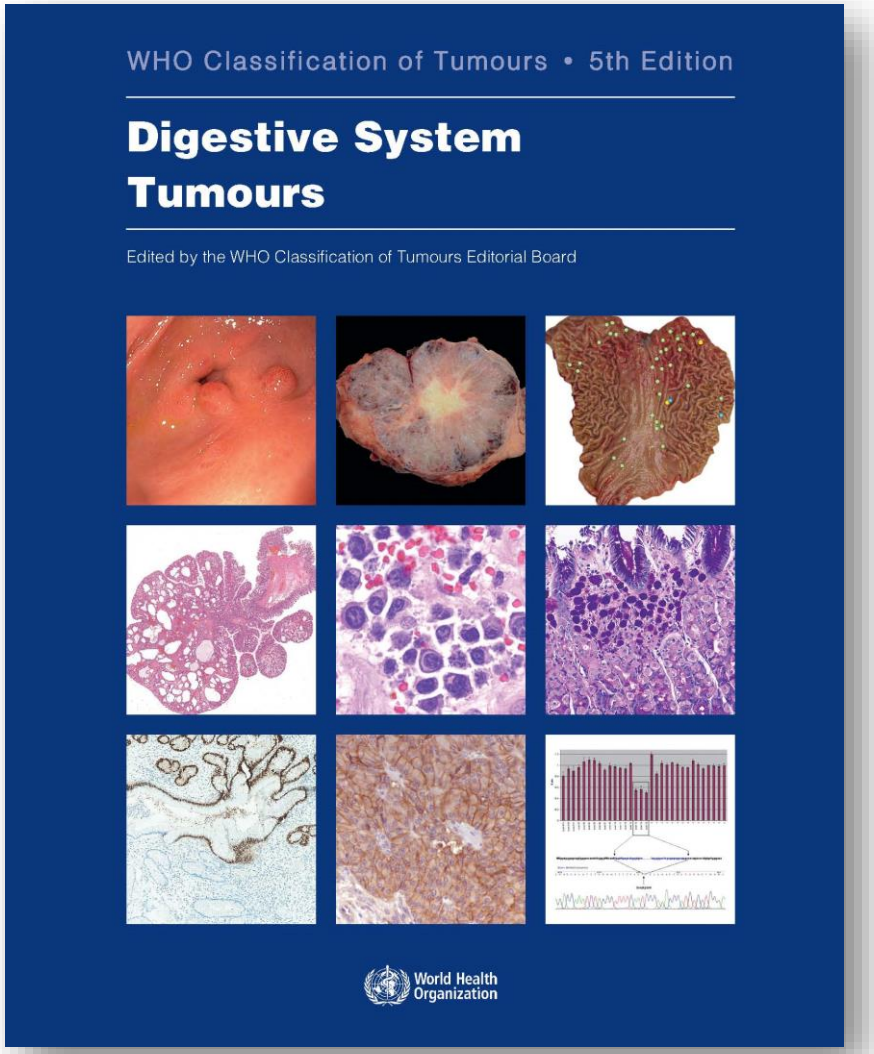


WHO Classification of Tumours of the Digestive System, 5th edition, 2019



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Review article

Hereditary gastrointestinal carcinomas and their precursors: An algorithm for genetic testing

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Emerging Concepts in Gastric Neoplasia

Heritable Gastric Cancers and Polyposis Disorders

Rachel S. van der Post, MD[a,*],
Fátima Carneiro, MD, PhD[b,c,d,e]

Fam Cancer. 2019 Apr 15. doi: 10.1007/s10689-019-00127-7. [Epub ahead of print]

Hereditary gastric cancer: what's new? Update 2013-2018.

van der Post RS[1], Oliveira C[2,3,4], Guilford P[5], Carneiro F[6,7,8].

Author information

Abstract

Around 10-20% of gastric cancer patients have relatives with a diagnosis of GC and in 1-3% of patients a genetic cause can be confirmed. Histopathologically, GC is classified into intestinal-type, with glandular growth, and diffuse-type with poorly cohesive growth pattern often with signet ring cells. Familial or hereditary GC is classified into hereditary diffuse GC (HDGC), familial intestinal GC (FIGC) and polyposis forms. This review focuses on recent research findings and new concepts of hereditary GC.

KEYWORDS: E-Cadherin; Hereditary diffuse gastric cancer; Stomach

WHO Classification of Tumours of the Digestive System, 5th edition, 2019

Genetic tumour syndromes of the digestive system

- Genetic tumour syndromes of the digestive system: Introduction
- Genetics
- Genetic tumour syndromes of the digestive system
  - Lynch syndrome
  - Familial adenomatous polyposis 1
  - GAPPS and other fundic gland polyposes
  - Other adenomatous polyposes
  - Serrated polyposis
  - Hereditary diffuse gastric cancer
  - Familial pancreatic cancer
  - Juvenile polyposis syndrome
  - Peutz-Jeghers syndrome
  - Cowden syndrome
  - Other genetic tumour syndromes

Genetic tumour syndromes of the digestive system

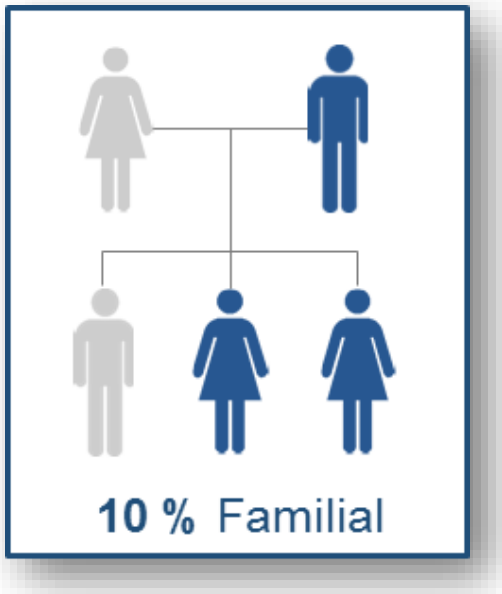
#1567 -Table

Disease/phenotype	Syndrome MIM number	Inheritance	Locus	Gene(s)	Gene MIM number	Encoded protein(s)	Normal protein function
Lynch syndrome	609310	AD	3p22.2	*MLH1*	120436	MLH1	DNA mismatch repair
	120435	AD	2p21-p16.3	*MSH2*	609309	MSH2	
	614350	AD	2p16.3	*MSH6*	600678	MSH6	
	614337	AD	7p22.1	*PMS2*	600259	PMS2	
	613244	AD	2p21	*EPCAM*	185535	EpCAM	Calcium-independent cell–cell adhesion; mutation results in epigenetic silencing of *MSH2*

Mark Arends
Ian Frayling
Alexander Lazar

- lists each of the syndromes discussed in this chapter
- summarizes key information about the disease/phenotype, pattern of inheritance, causative gene(s), and normal function of the encoded protein(s).

Some of the syndromes included in the table are not discussed in detail in this chapter because of space limitations.



Familial/hereditary Gastric Cancer
– three main syndromes –

- *Hereditary Diffuse Gastric Cancer*
  HDGC - CDH1 *germline mutations mainly*

  Guilford P et al, Nat Genetics 1998

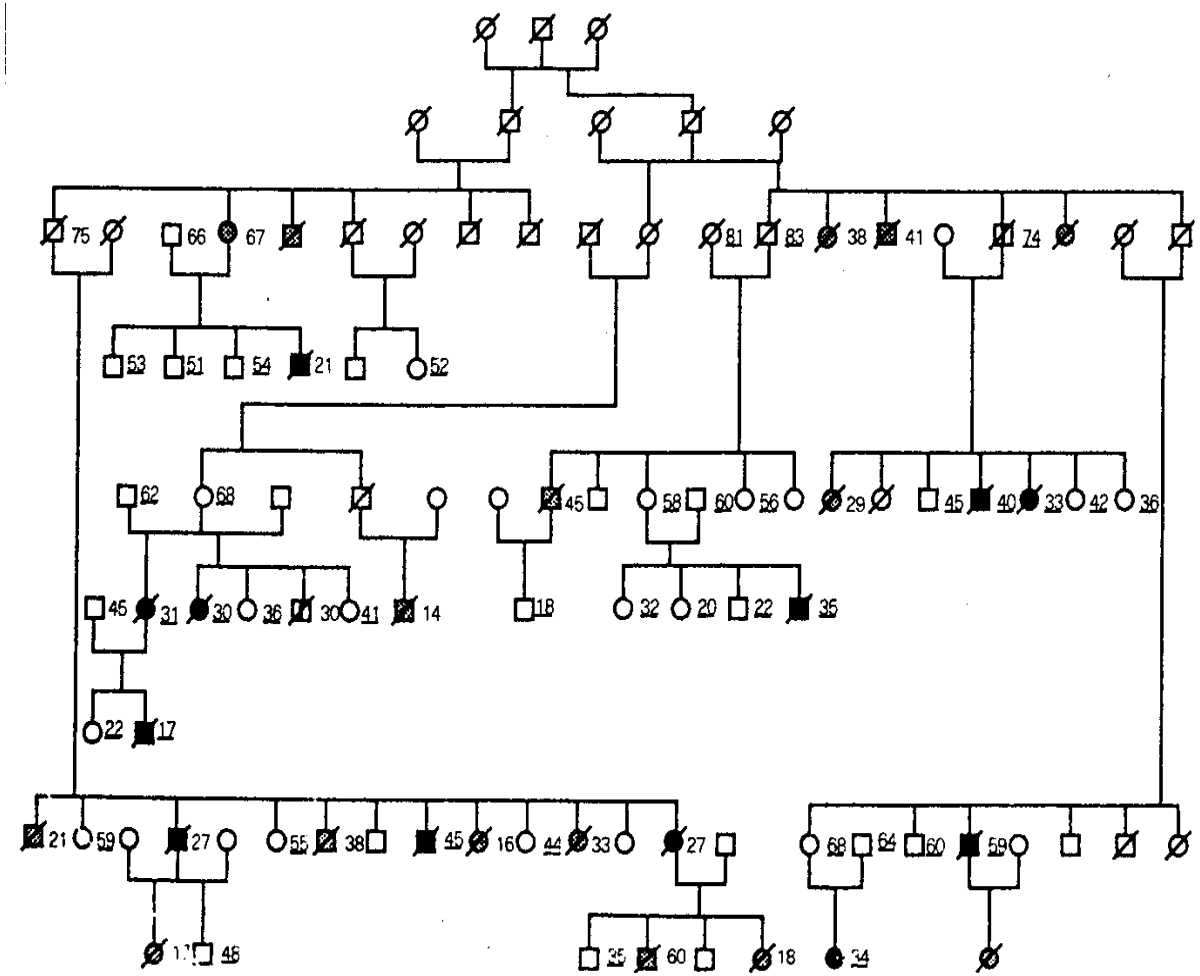
- *Gastric Adenocarcinoma and Proximal Polyposis of the Stomach*
  GAPPS - APC *promoter germline mutations*

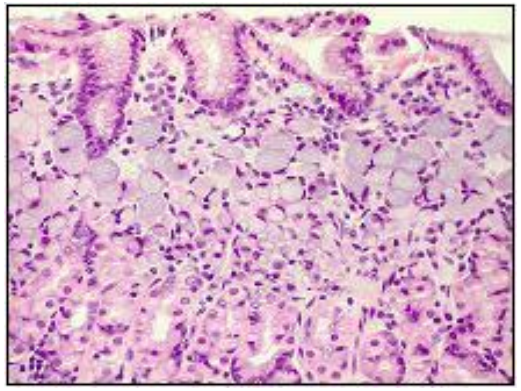
  Worthley et al, Gut 2012

- *Familial Intestinal Gastric Cancer*
  FIGC - No cause *identified to date*

  Caldas and the IGCLC, JMG 1999 *Oliveira C et al, Lancet Oncol 2015*

Maori kindred





E-cadherin gene *(CDH1)* *germline mutations

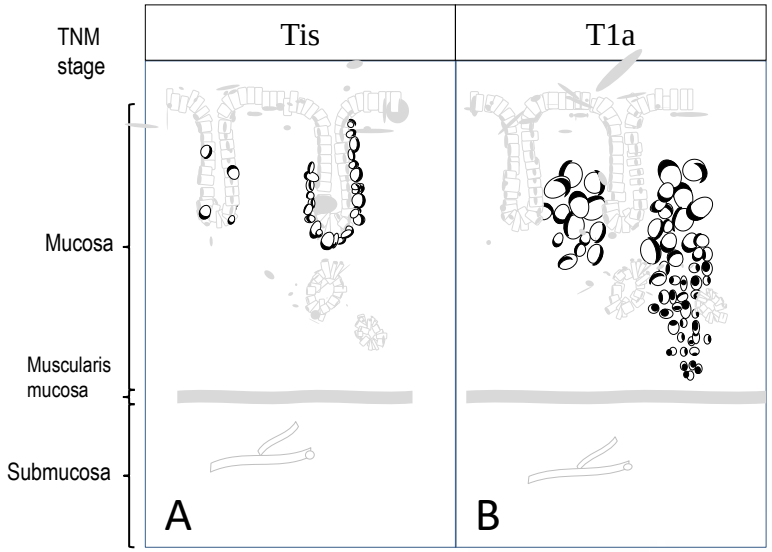
Hereditary Diffuse Gastric Cancer (HDGC)

Guilford P *et al.* Nature 392:402,1998

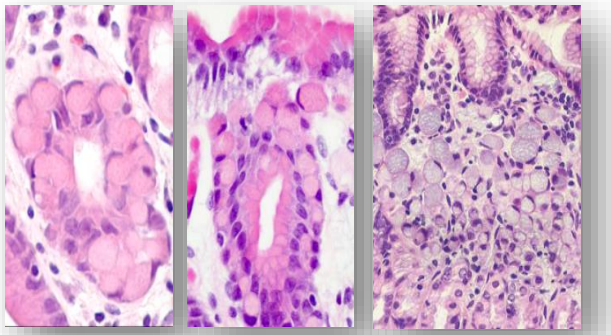
*Gene map locus: 16q22.1 (MIM ID +192090)

4-3 Hereditary Diffuse Gastric Cancer

Fátima Carneiro
Amanda Charlton
David Huntsman



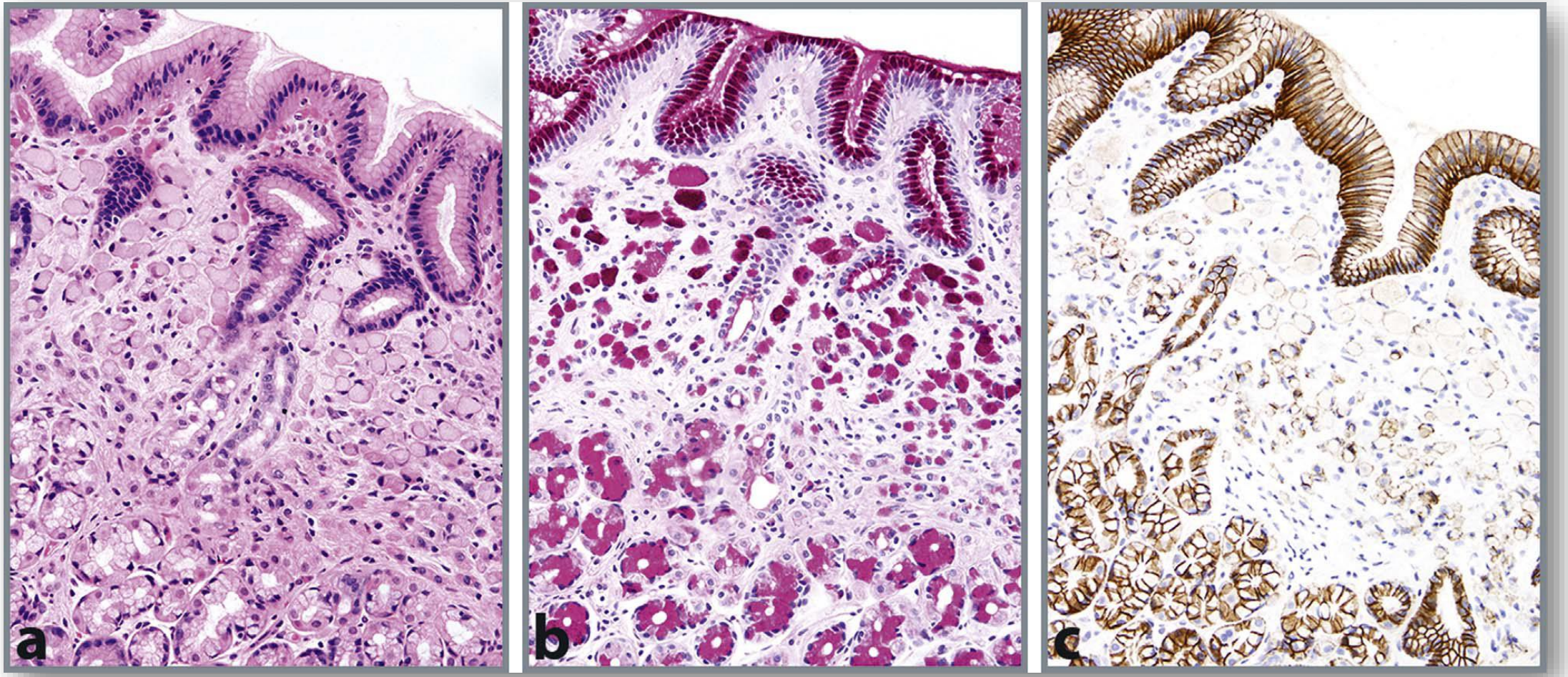
WHO – 4th Edition, 2010



In situ carcinoma | Pagetoid spread | T1a intramucosal signet-ring cell

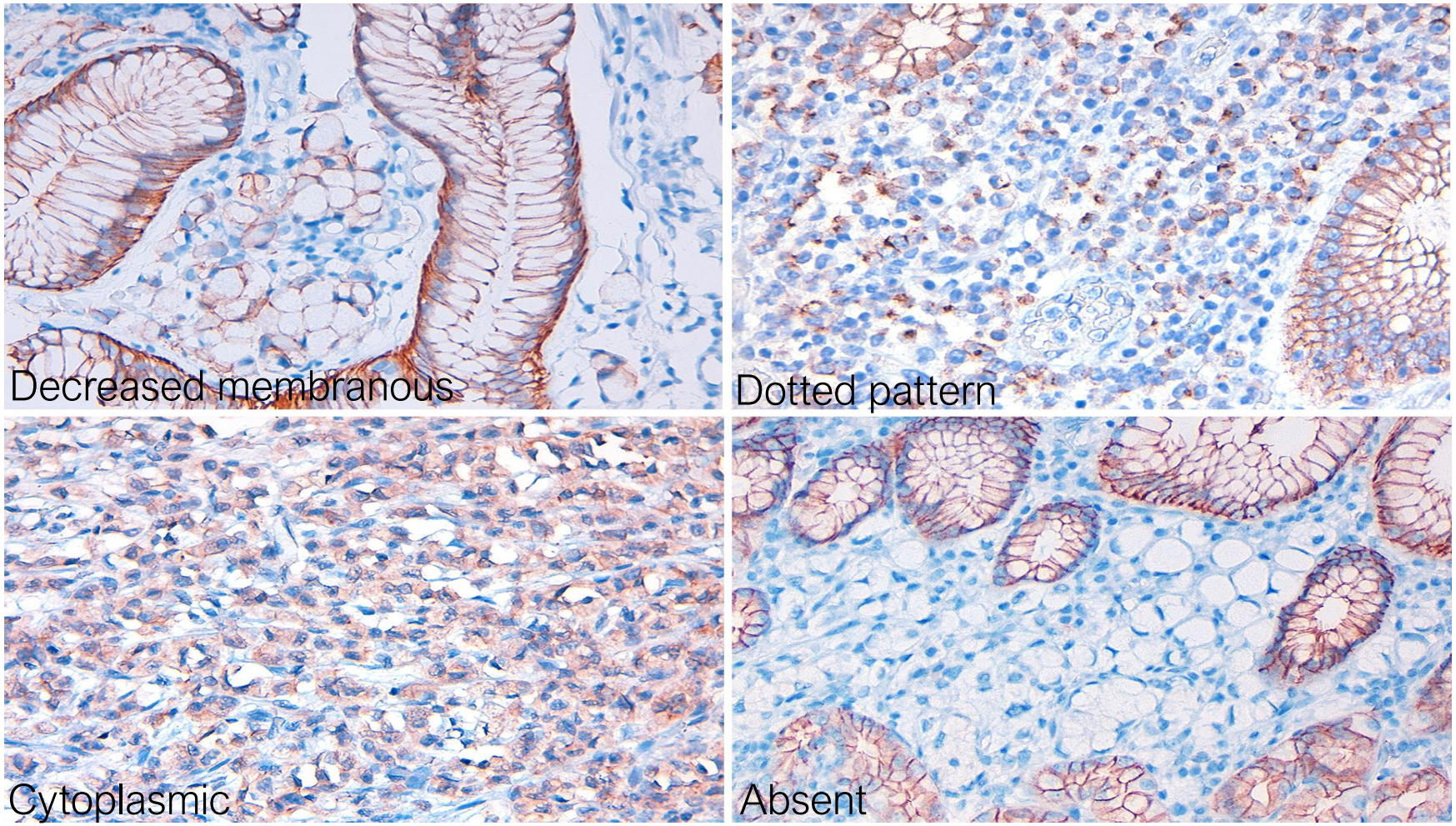
- Genetic susceptibility (germline alterations)
- Molecular Pathology (somatic alterations)
- Clinical features
- Pathology

Hereditary Diffuse Gastric Cancer (HDGC)



Hereditary Diffuse Gastric Cancer

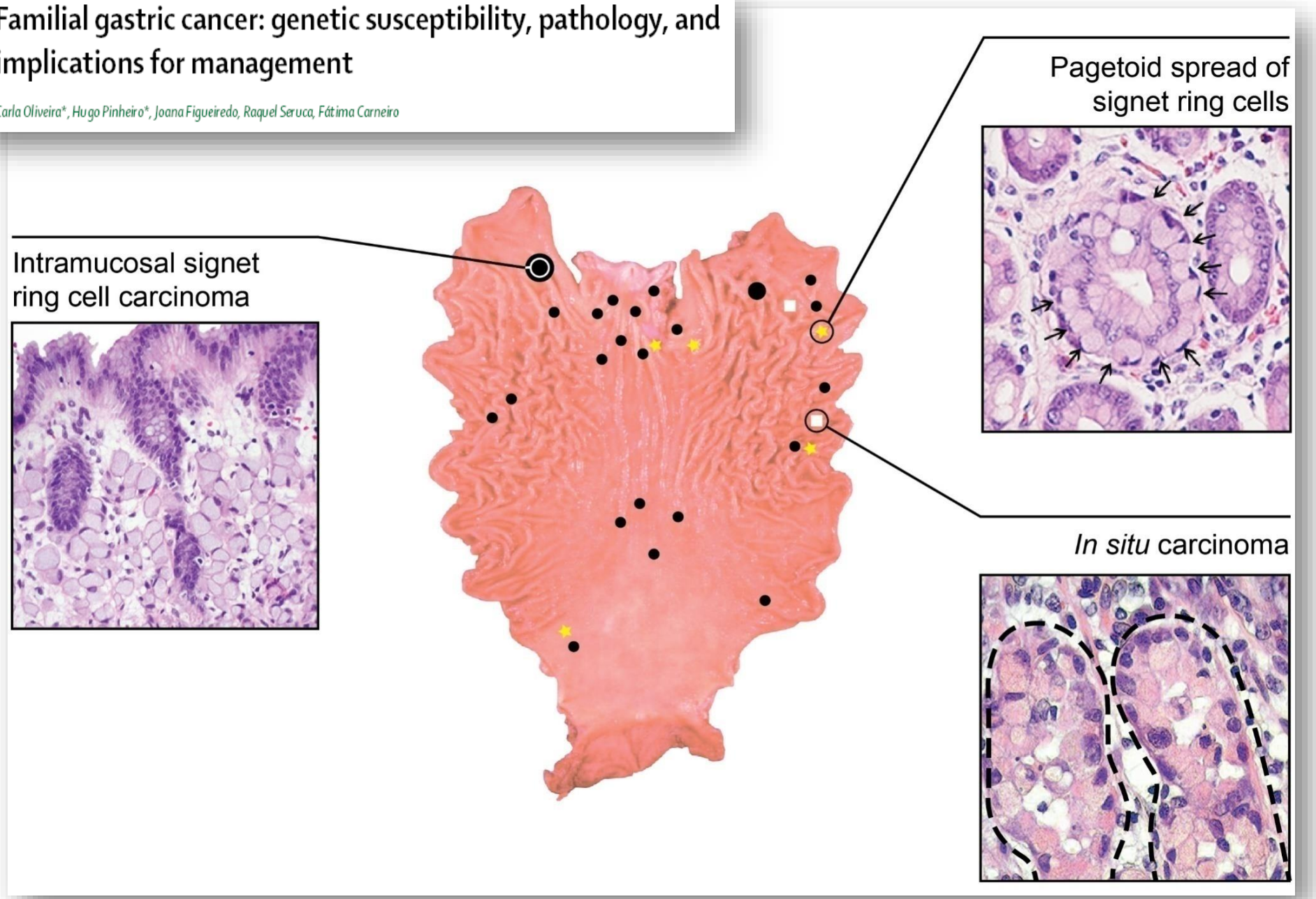
E-CADHERIN EXPRESSION



Van Der Post, Gullo I et al. Adv Exp Med Biol 2016

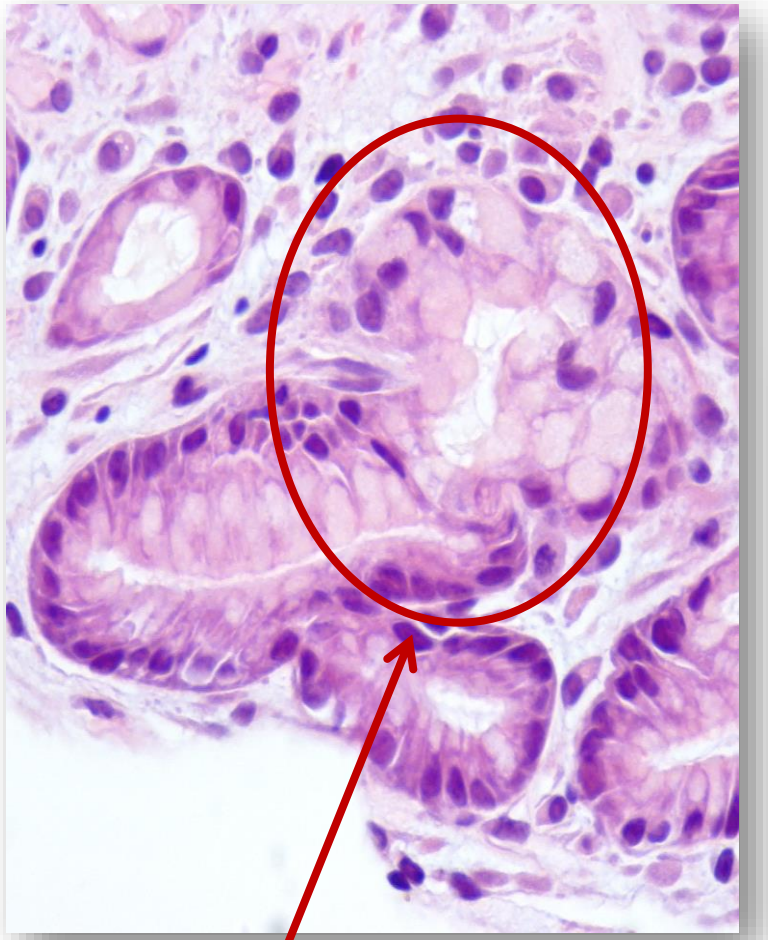
Familial gastric cancer: genetic susceptibility, pathology, and implications for management

Carla Oliveira*, Hugo Pinheiro*, Joana Figueiredo, Raquel Seruca, Fátima Carneiro

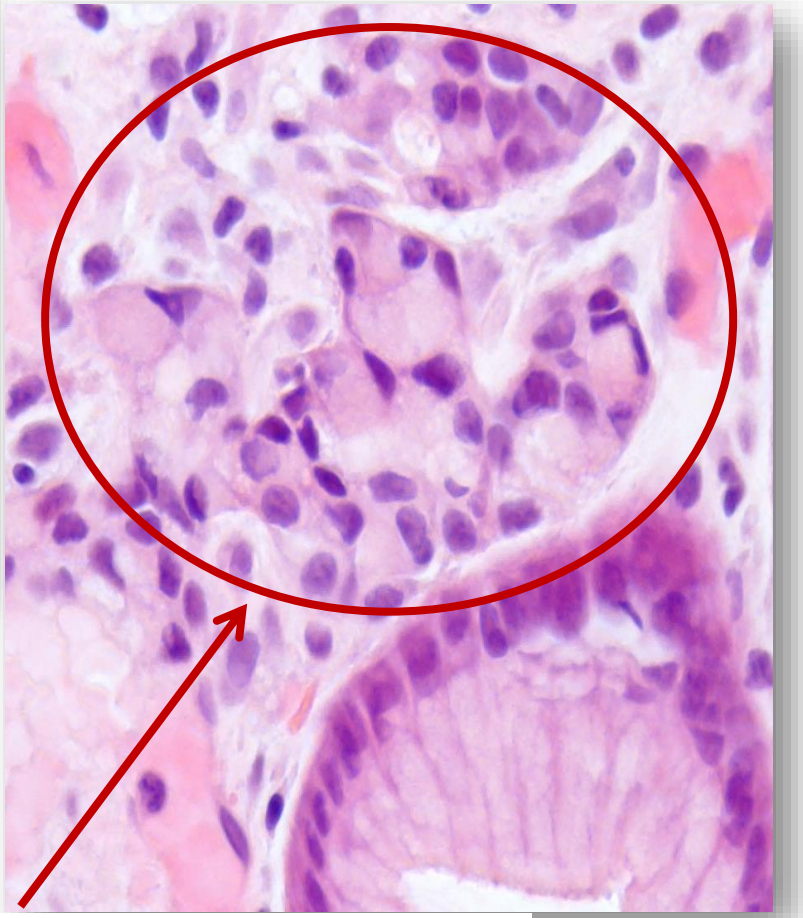


Oliveira *et al*; Lancet Oncology 16(2):e60-70, 2015

Consultation case



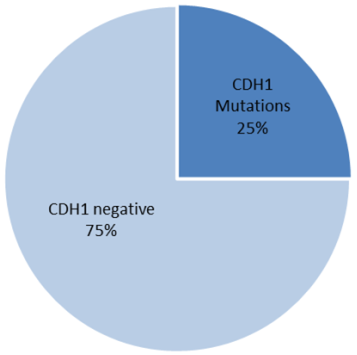
In situ SRCC



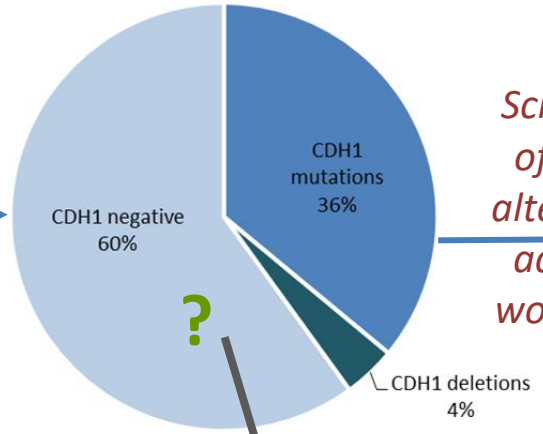
Intramucosal carcinoma (T1a)

CDH1 inactivation mechanism in HDGC families with clinical utility

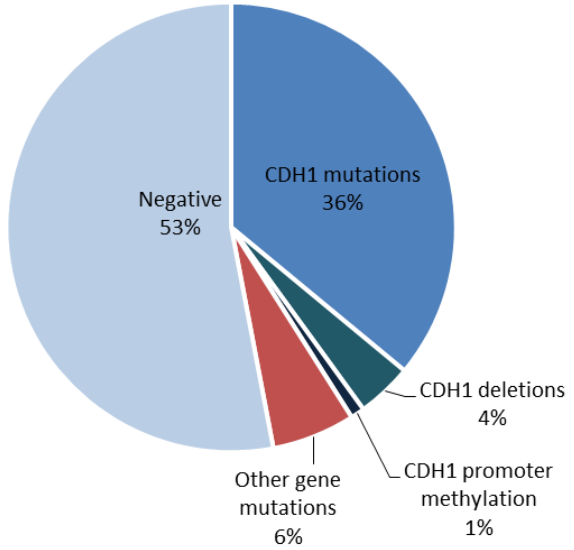
1998/2002 → 2018



IGCLC criteria validation



Screening of CDH1 alterations adopted worldwide

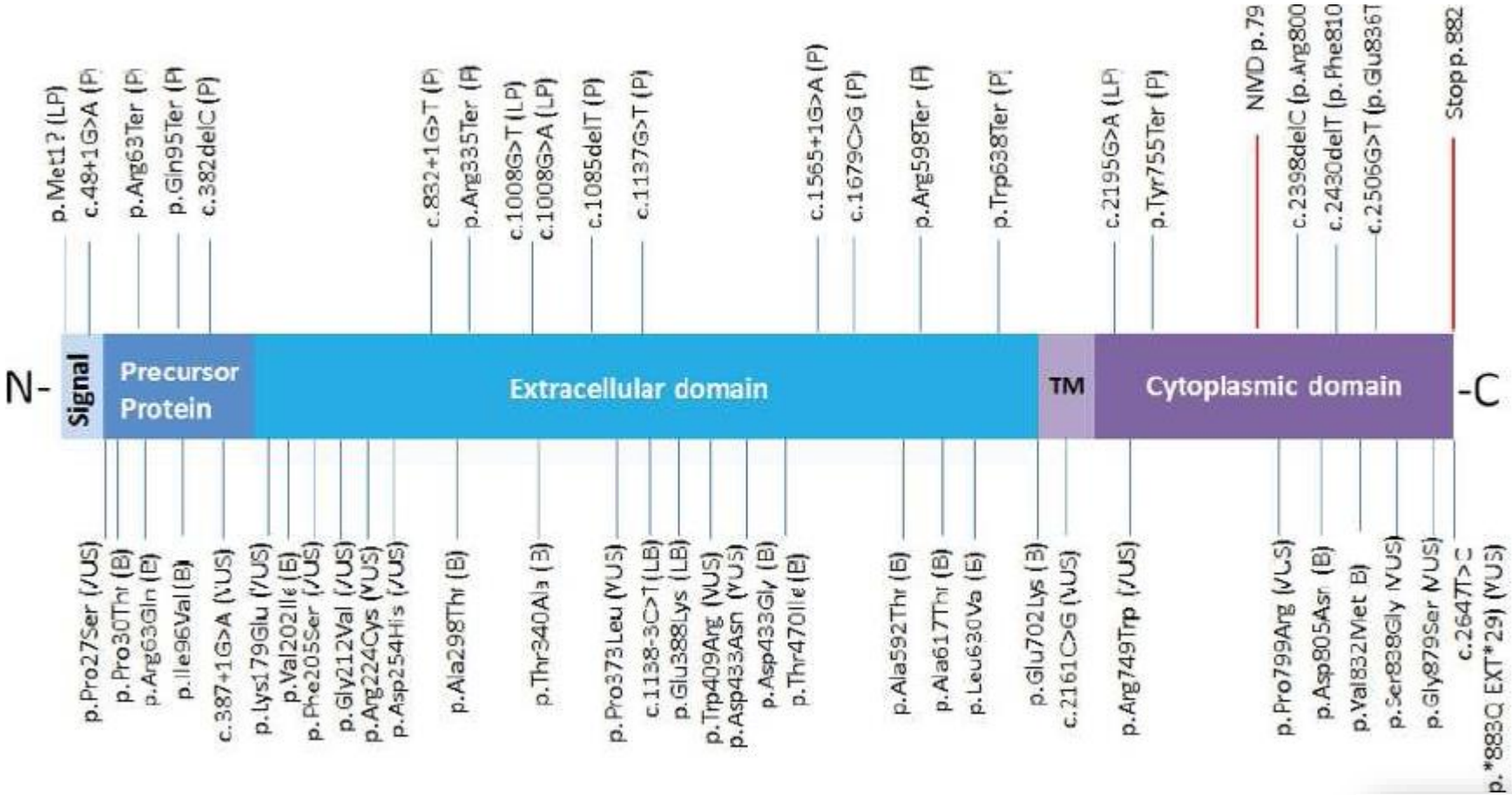


Guilford et al , Nat Genet 1998
Gayther et al, Cancer Res 1999
Oliveira et al, Hum Mutat 2002
Oliveira C et al, EJC 2004
Oliveira C et al, HMG 2009
Pinheiro H et al, HMG 2010
Pinheiro H et al, HMG 2012
Majewsky IJ et al, J Pathol 2013
Gaston D et al. PLoS Genet 2014
Hansford S et al, JAMA Oncol 2015
Vogelaar IP et al, Fam Cancer 2015
Donner I et al, Fam Cancer 2015
Oliveira et al, Lancet Oncol 2015
Vogelaar IP et al, EJHG 2017
Weren RDA et al, JMG 2018
Sahasrabudhe et al, Gastroenterology. 2017
Fewings E et al, Lancet Gastroenterol Hepatol. 201

Targeted DNAseq *and* ***Exome seq*** *in hundreds of probands identified few new candidate genes*

CTNNA1 (~10 families)
PALB2 (very rare)
TP53 (very rare)
BRCA2 (very rare)
ATM (rare; controversial)
MAP3K6 (rare; controversial)
STK11 (very, very rare)
MYD88 (very rare; controversial)

E-cadherin schematic representation demonstrating its major domains in relation to the 50 pilot variants curated by an Expert Panel



Clinically actionable variants (P, LP) are shown in the top; VUS, LB, and B variants are shown in the bottom. TM = transmembrane domain.

Received: 30 April 2018 | Revised: 30 August 2018 | Accepted: 6 September 2018
DOI: 10.1002/humu.23650
Human Mutation, 2018
SPECIAL ARTICLE
WILEY HGVS HUMAN GENOME VARIATION SOCIETY

Specifications of the ACMG/AMP variant curation guidelines for the analysis of germline *CDH1* sequence variants

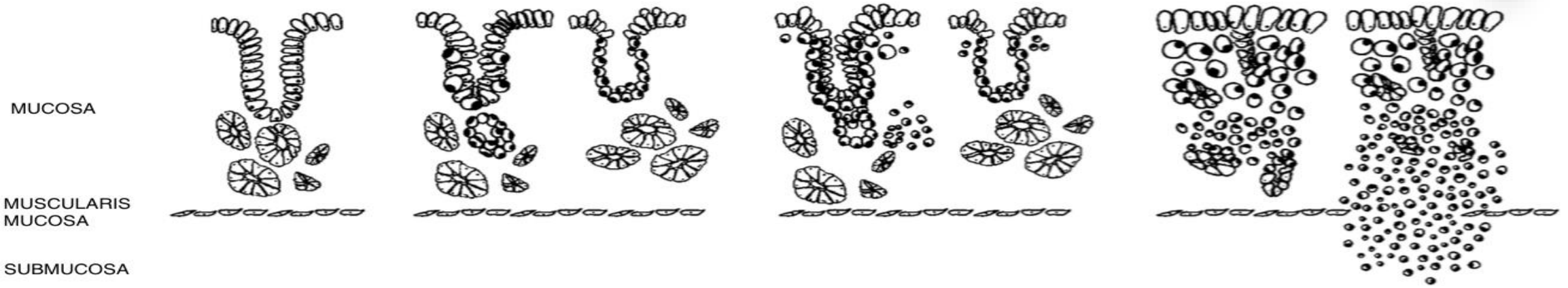
Hereditary Diffuse Gastric Cancer

MORPHO-MOLECULAR MODEL OF PATHOGENESIS

"1st HIT"
CDH1 germline inactivation

"2nd HIT"
CDH1 somatic inactivation
(promoter methylation, LOH, mutations, intragenic deletions)

?



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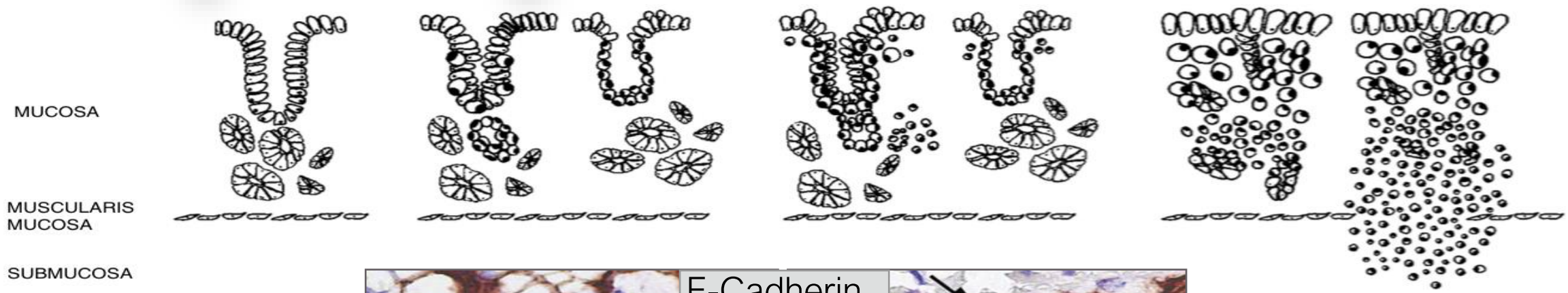

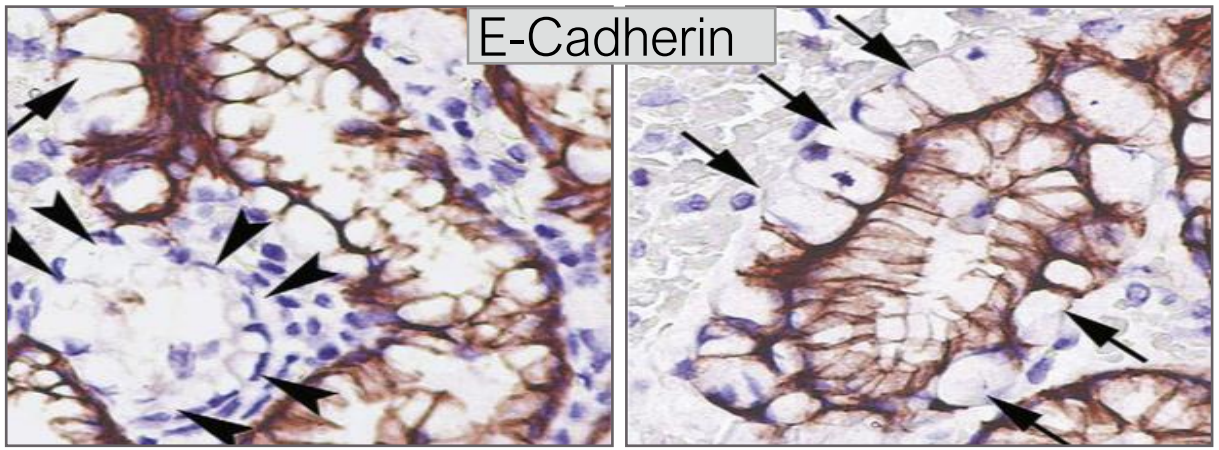

Carneiro F et al J Pathol 2004; WHO Classification of Tumours. Digestive System Tumours (2019)

Hereditary Diffuse Gastric Cancer

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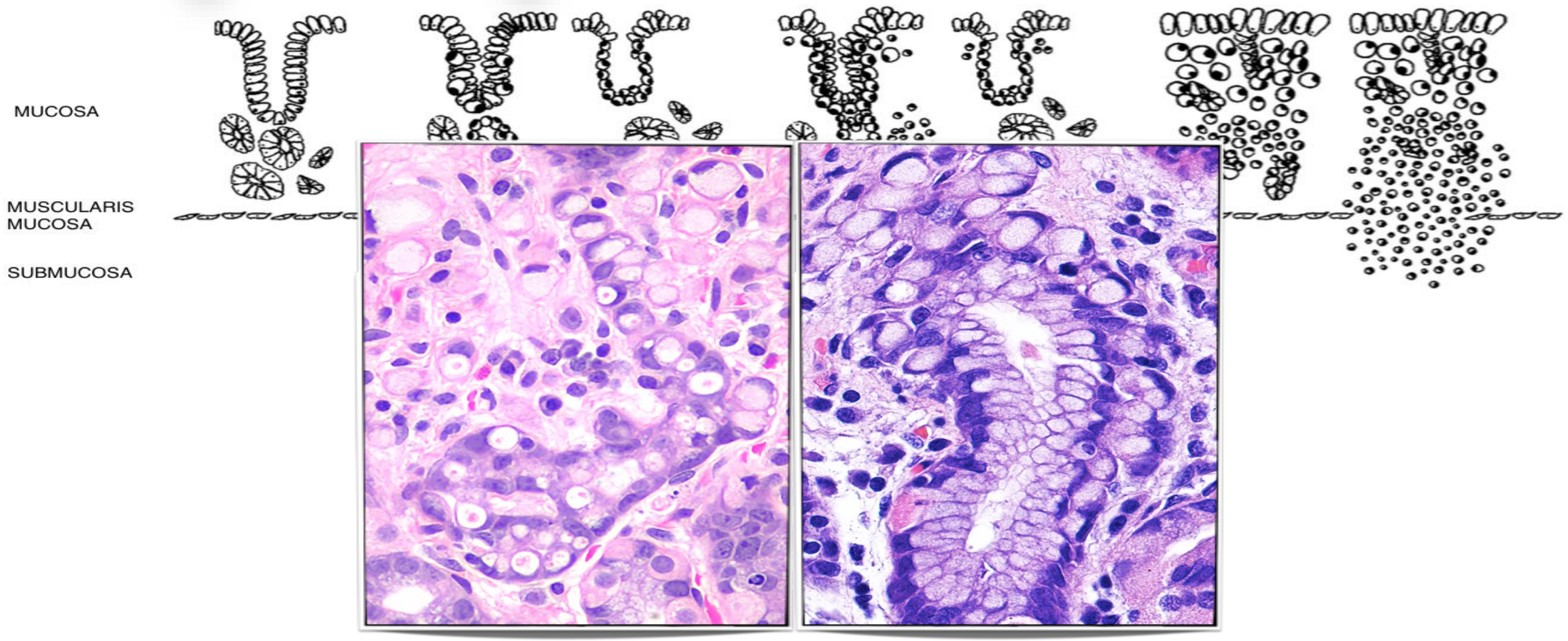
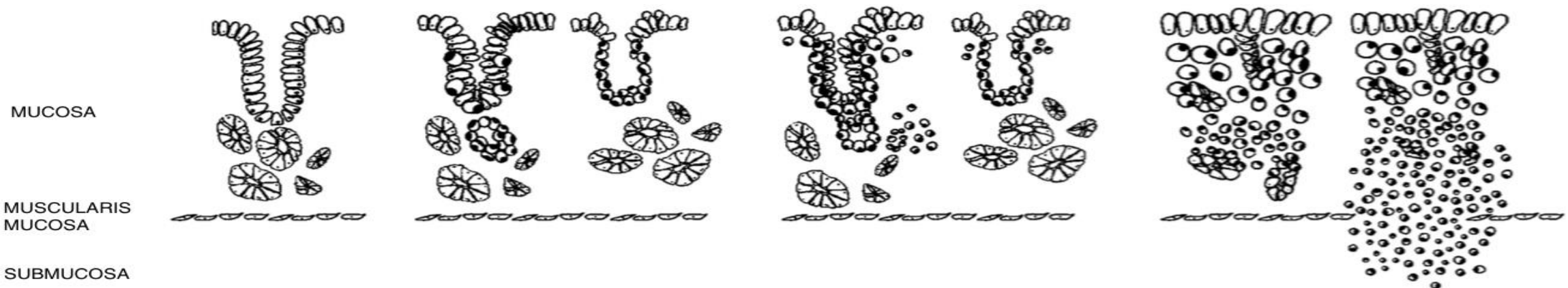


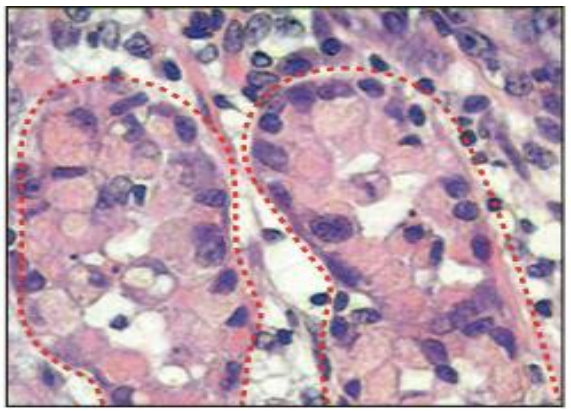
Carneiro F et al J Pathol 2004; WHO Classification of Tumours. Digestive System Tumours (2019)

Hereditary Diffuse Gastric Cancer

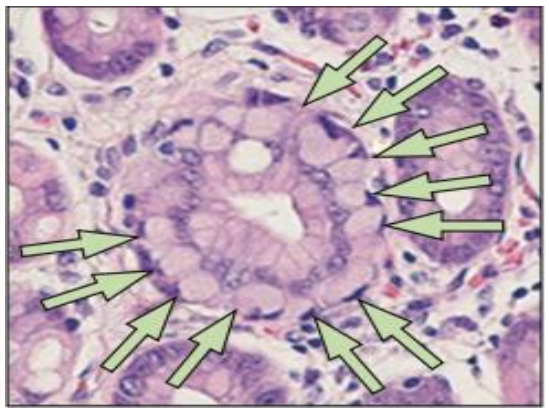
MORPHO-MOLECULAR MODEL OF PATHOGENESIS



Precursor lesions

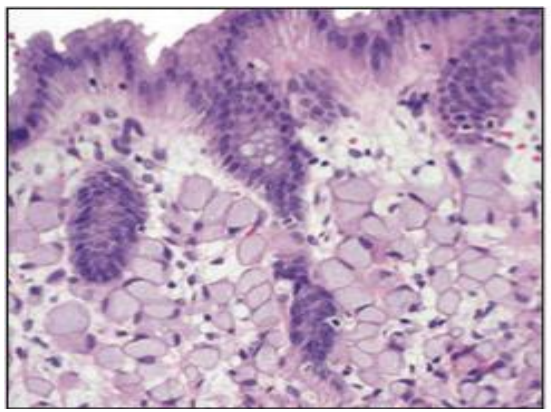


"*In situ*" SRCC



Pagetoid spread of SRCs

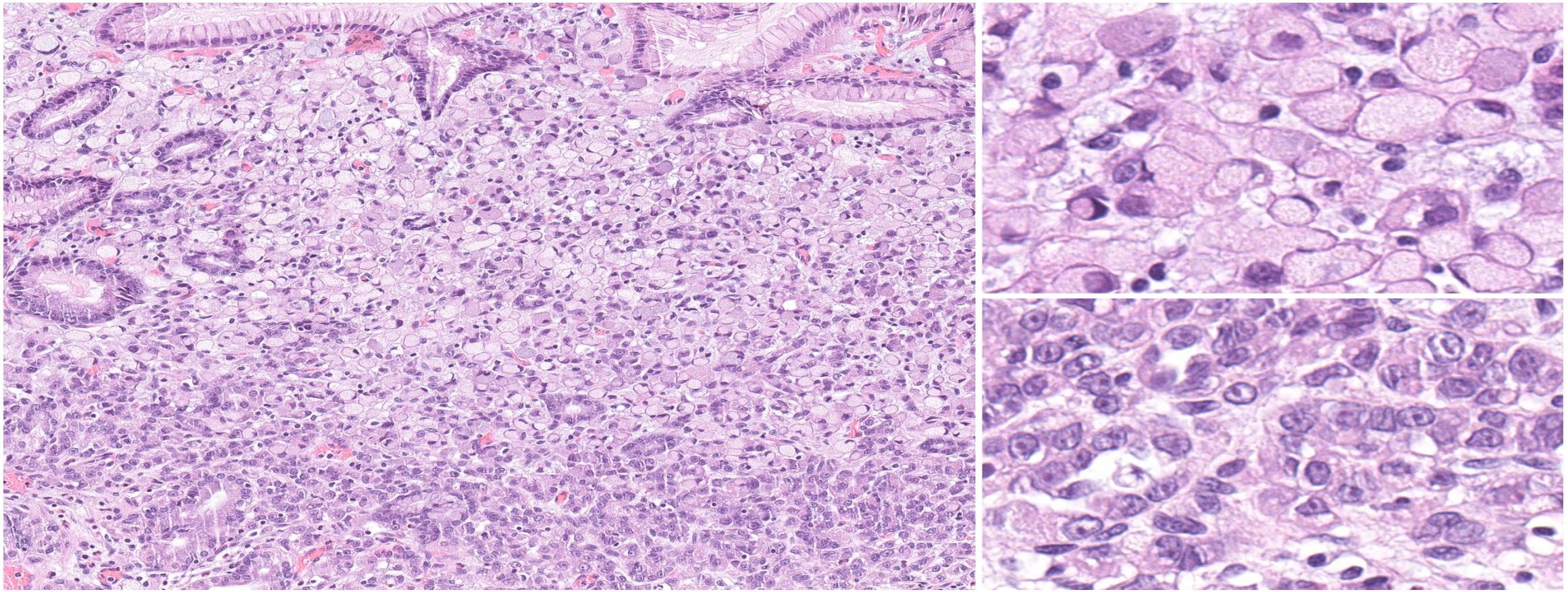
Intramucosal SRCC



Carneiro F et al J Pathol 2004; WHO Classification of Tumours. Digestive System Tumours (2019)

Hereditary Diffuse Gastric Cancer

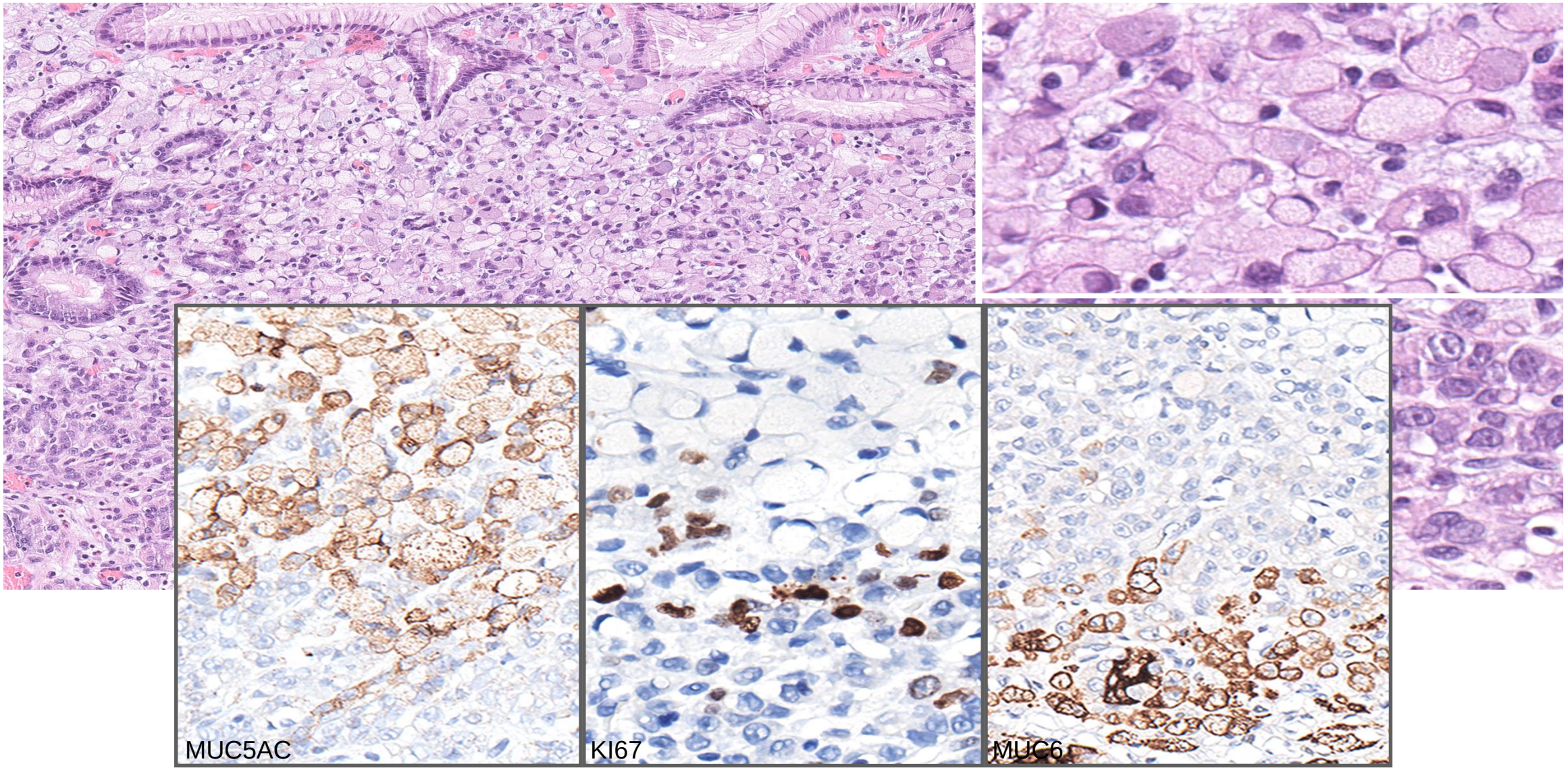
MORPHOLOGIC SPECTRUM



Gullo I et al. Histopathology 2020

Hereditary Diffuse Gastric Cancer

MORPHOLOGIC SPECTRUM

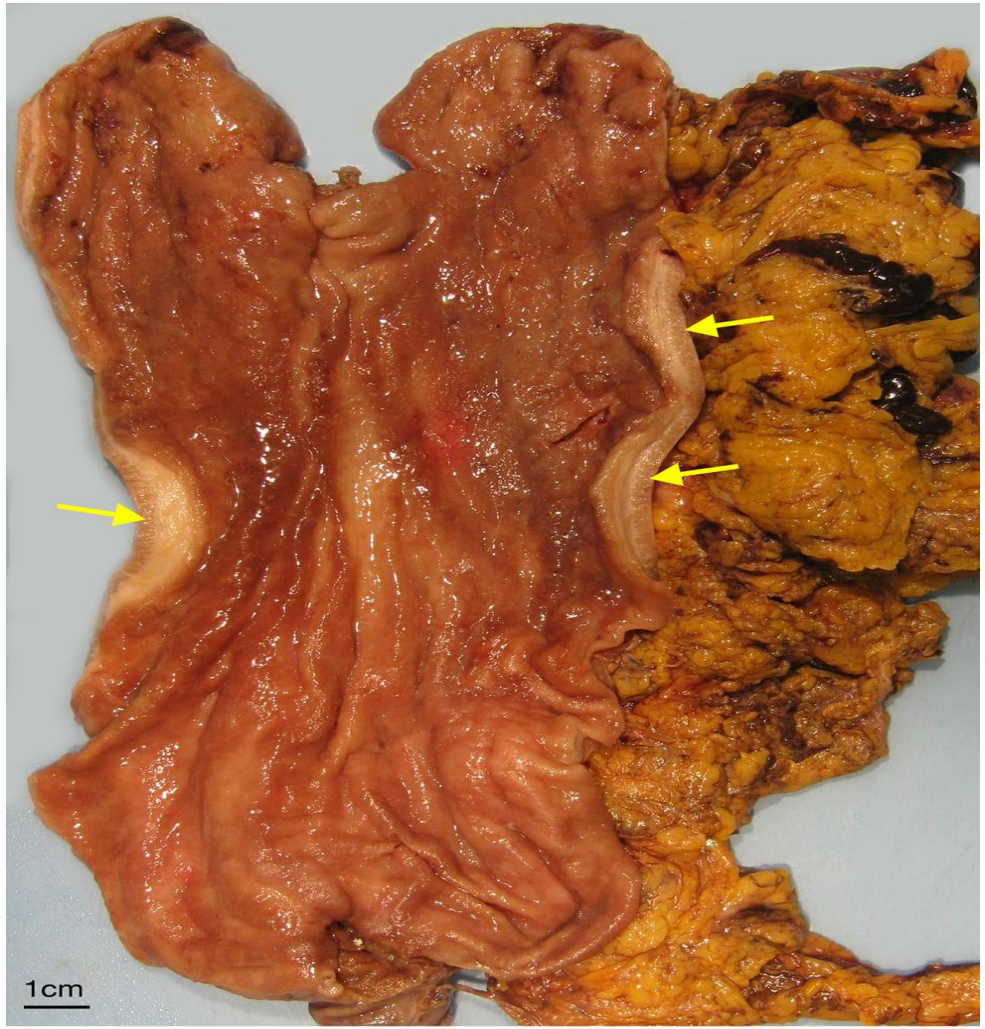


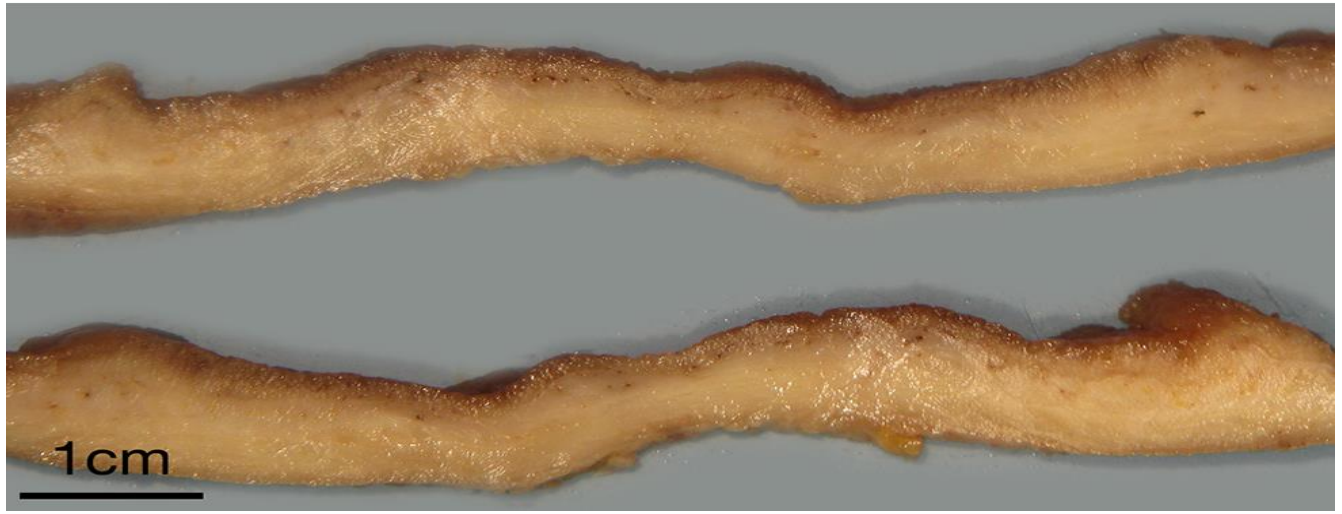
Gullo I et al. Histopathology 2020

Hereditary Diffuse Gastric Cancer

"AGGRESSIVE" PHENOTYPE

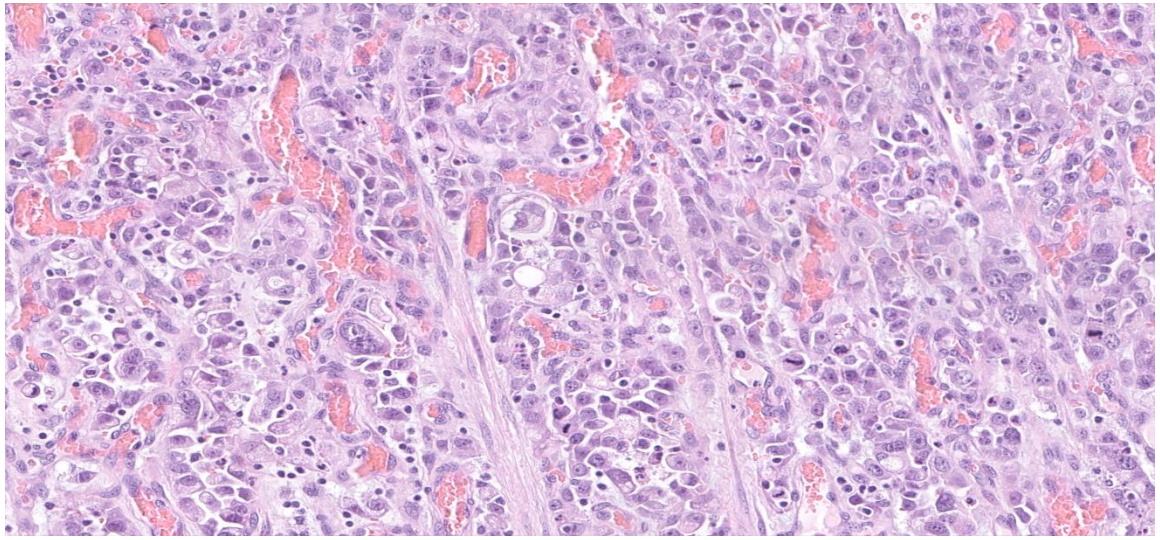
Linitis plastica ("leather bottle" stomach) in a CDH1 carrier

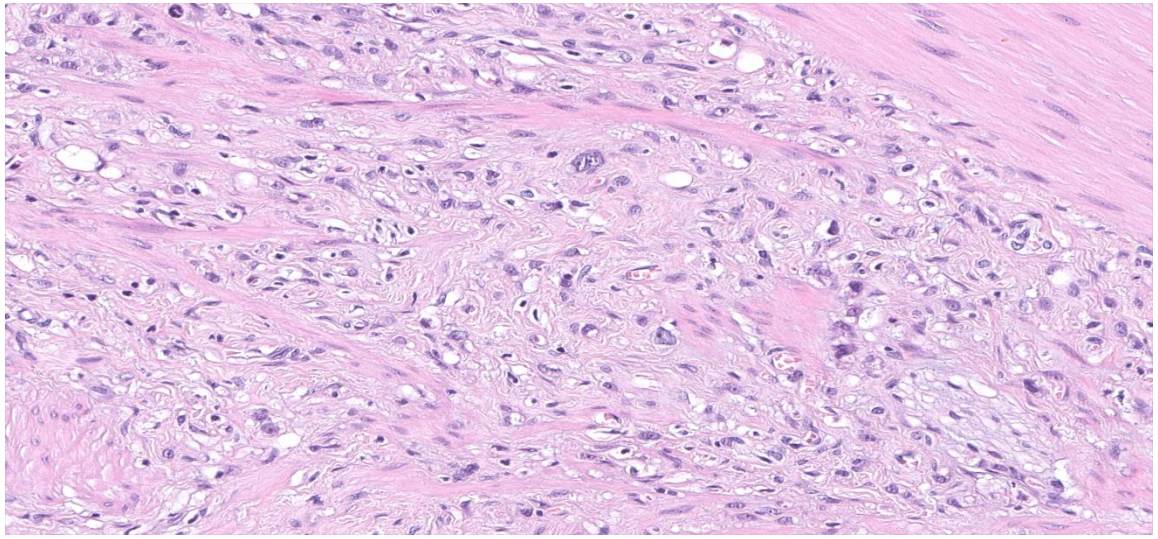


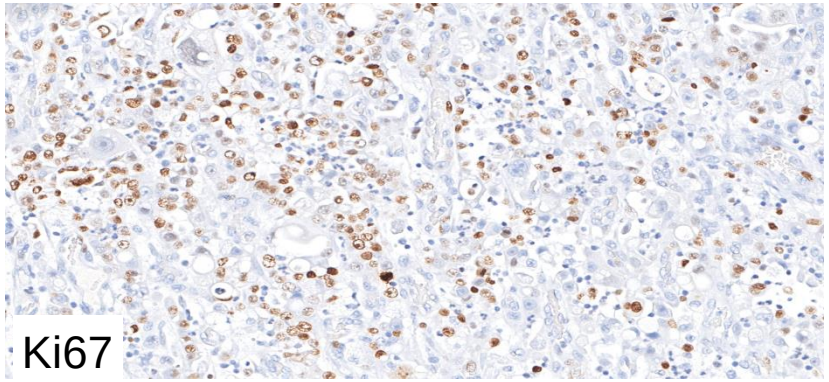


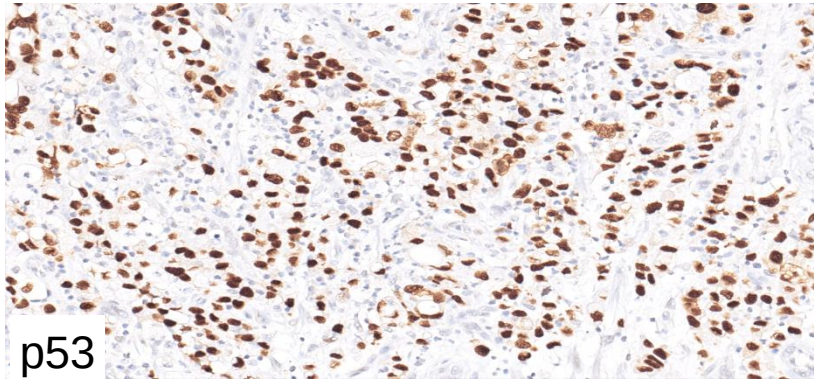
Hereditary Diffuse Gastric Cancer

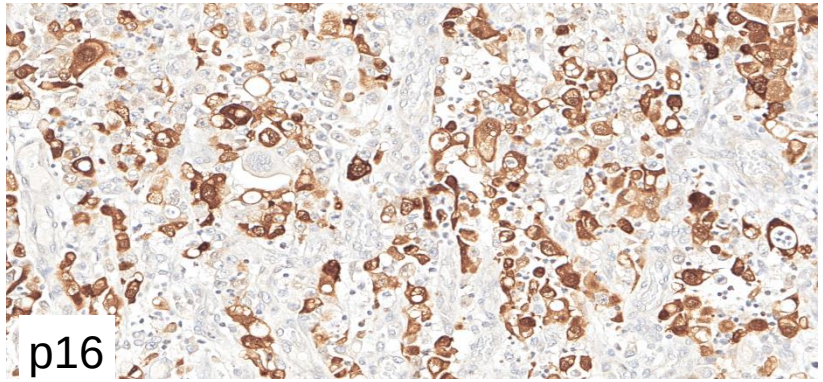
“AGGRESSIVE” PHENOTYPE









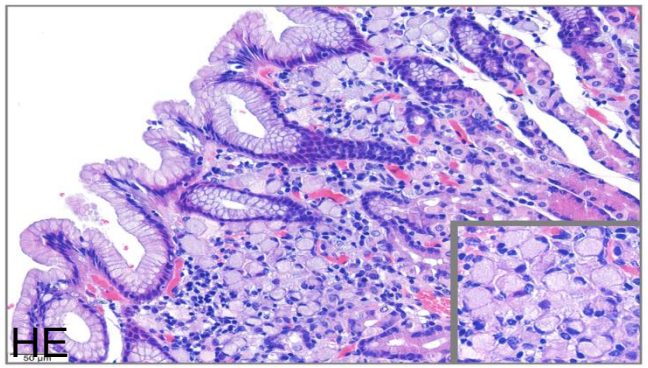


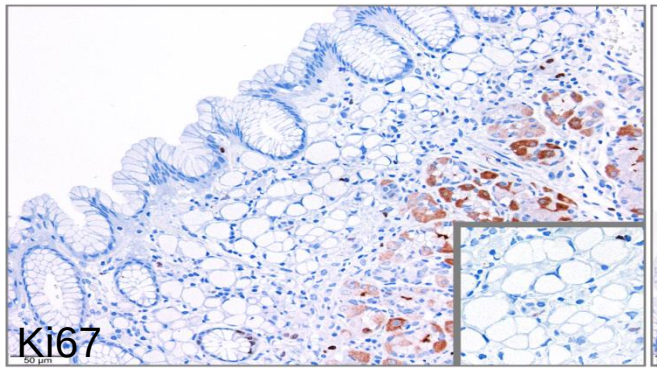
Hereditary Diffuse Gastric Cancer

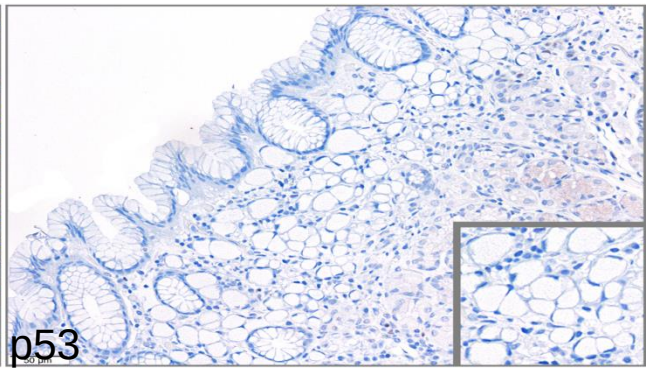
MORPHO-MOLECULAR MODEL OF PATHOGENESIS

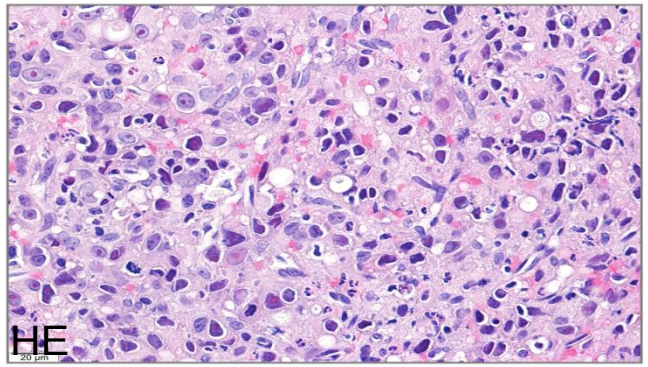
“**Indolent**”
early HDGC

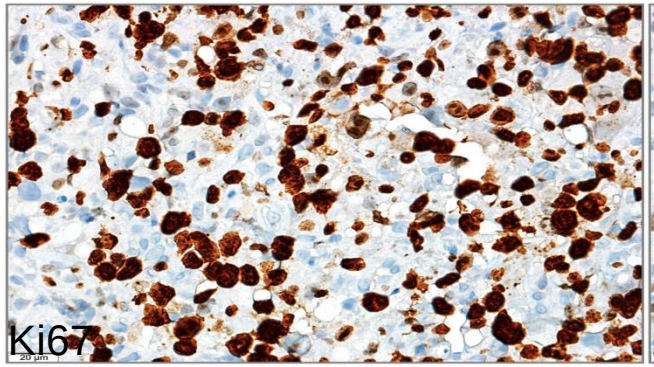
“**Aggressive**”
advanced
HDGC

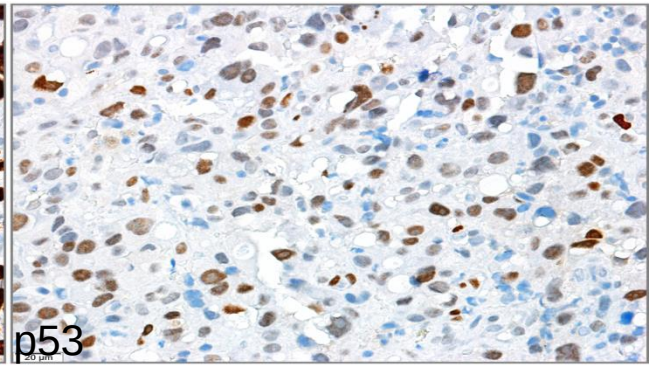


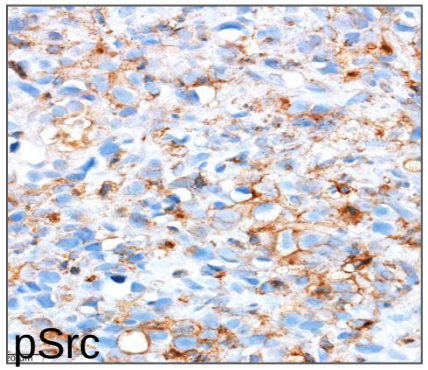


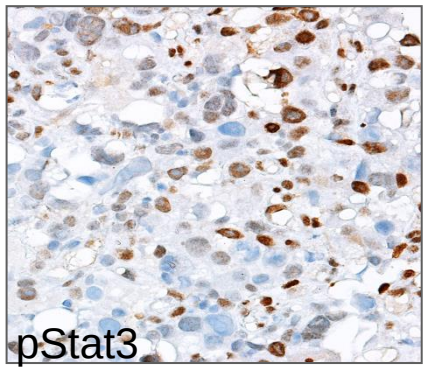


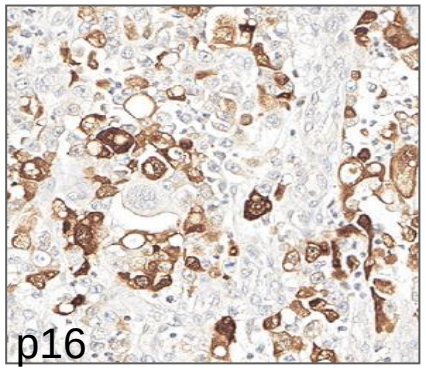












Gullo I *et al* Gastrointestinal Endoscopy. 2018

Hereditary Diffuse Gastric Cancer

PATHOLOGY ARTICLE

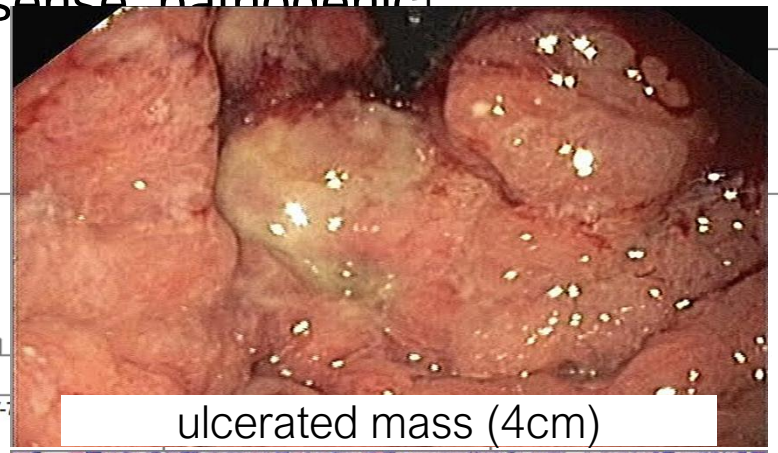
Phenotypic heterogeneity of hereditary diffuse gastric cancer: report of a family with early-onset disease

Gullo I *et al* Gastrointestinal Endoscopy. 2018

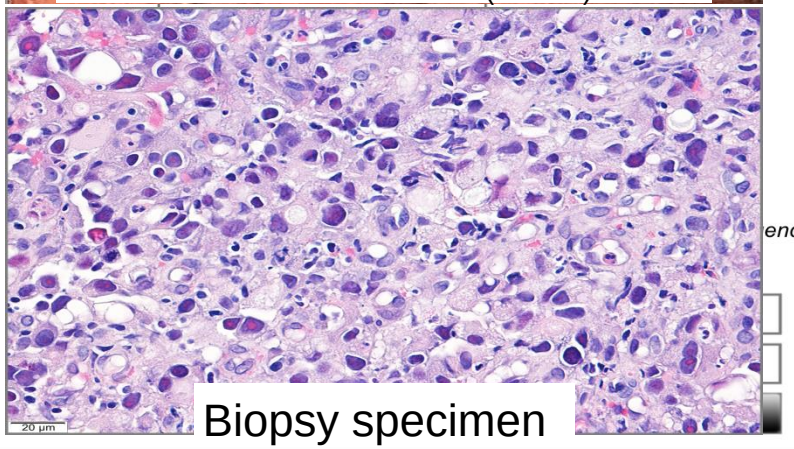
HETEROGENEITY OF CLINICAL PHENOTYPE

Germline ***CDH1*** variant:

c.1901C>T (p.Ala634Val) - rare*, missense, pathogenic†



ulcerated mass (4cm)



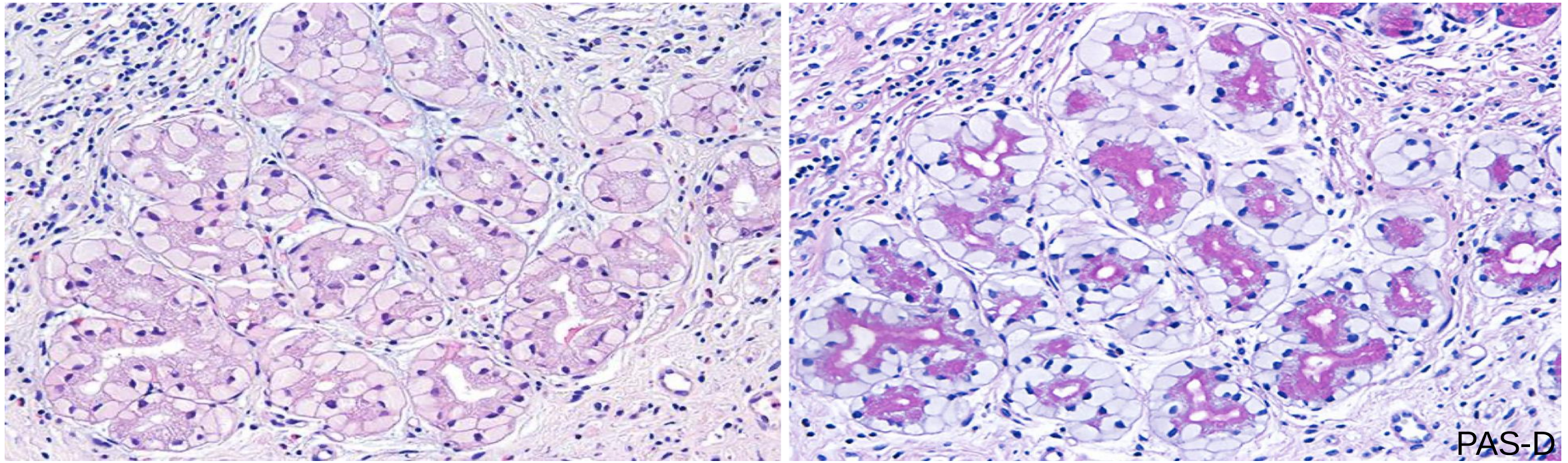
Biopsy specimen

* Suriano G et al Hum Mol Genet 2003; Oliveira C et al Eur J Cancer 2004; Kaurah P et al JAMA 2007; More H et al Hum Mutat 2007; Molinaro V et al Genes Chromosomes Cancer 2014

† Suriano G et al J Mol Med (Berl) 2006; Vecsey-Semjen B et al Oncogene 2002

Hereditary Diffuse Gastric Cancer

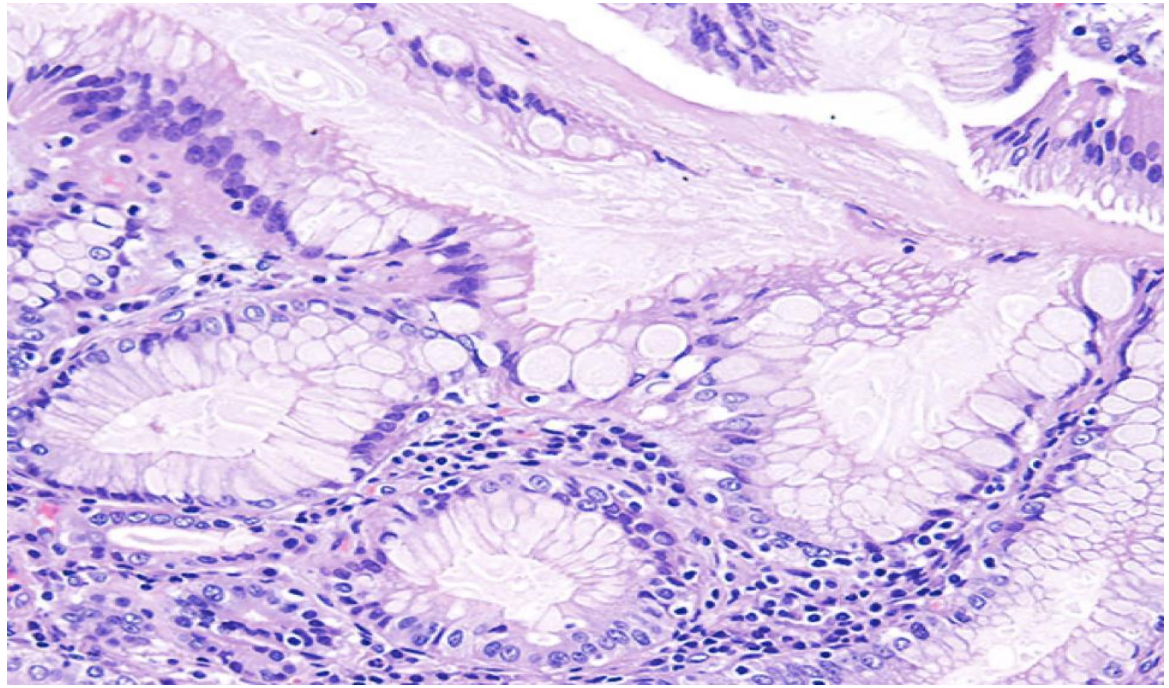
HISTOLOGIC MIMICS OF SIGNET RING CELLS

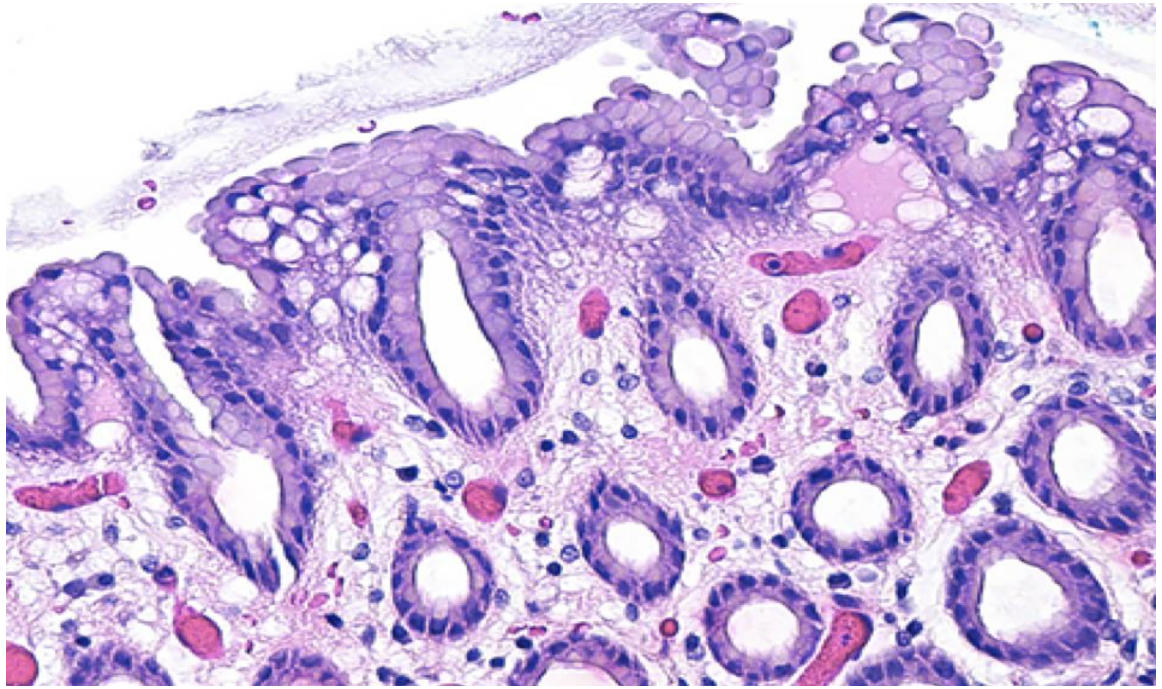


Clear/glassy cell change

Hereditary Diffuse Gastric Cancer

HISTOLOGIC MIMICS OF SIGNET RING CELLS



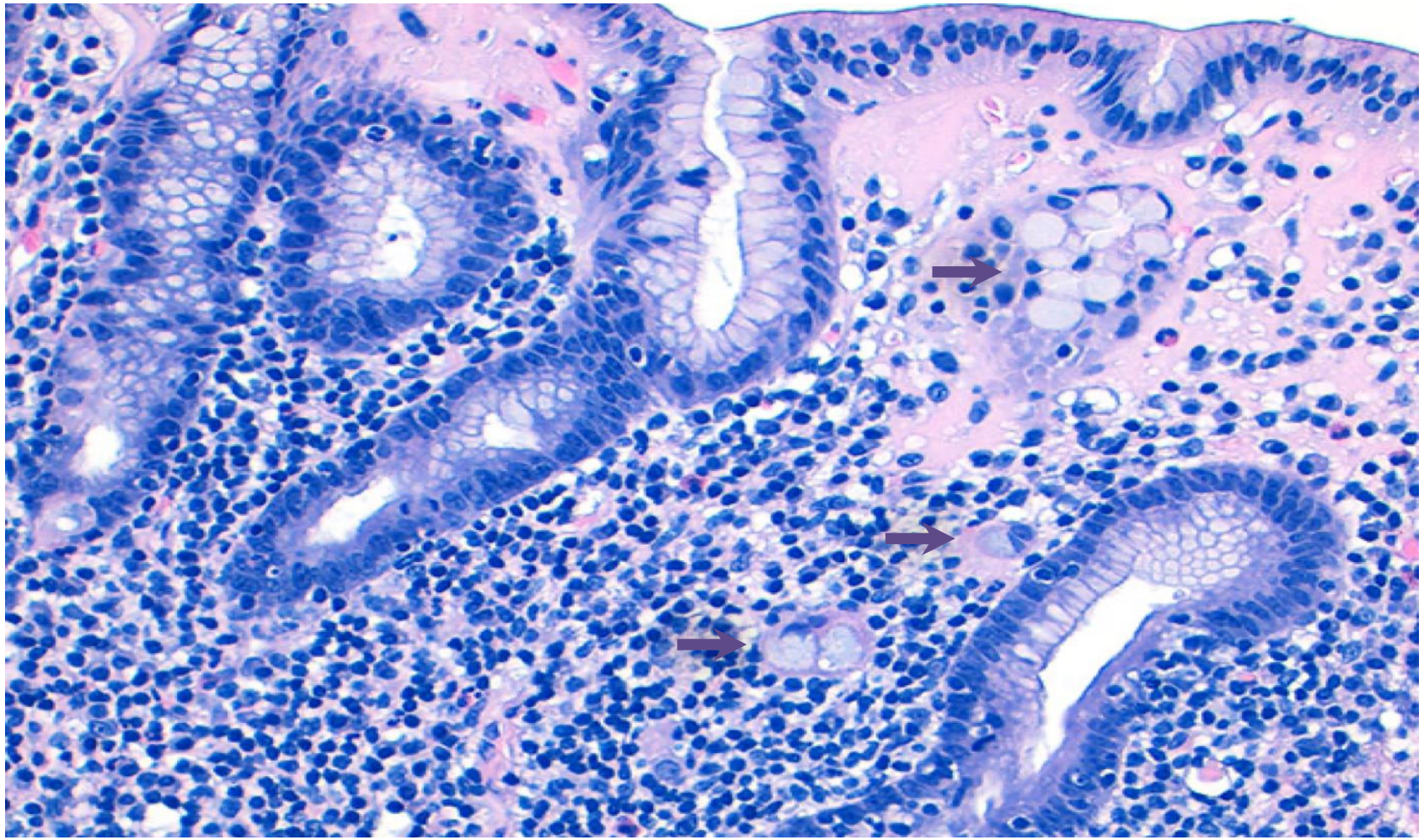


Globoid change and vacuolisation of superficial epithelium

Hereditary Diffuse Gastric Cancer

!

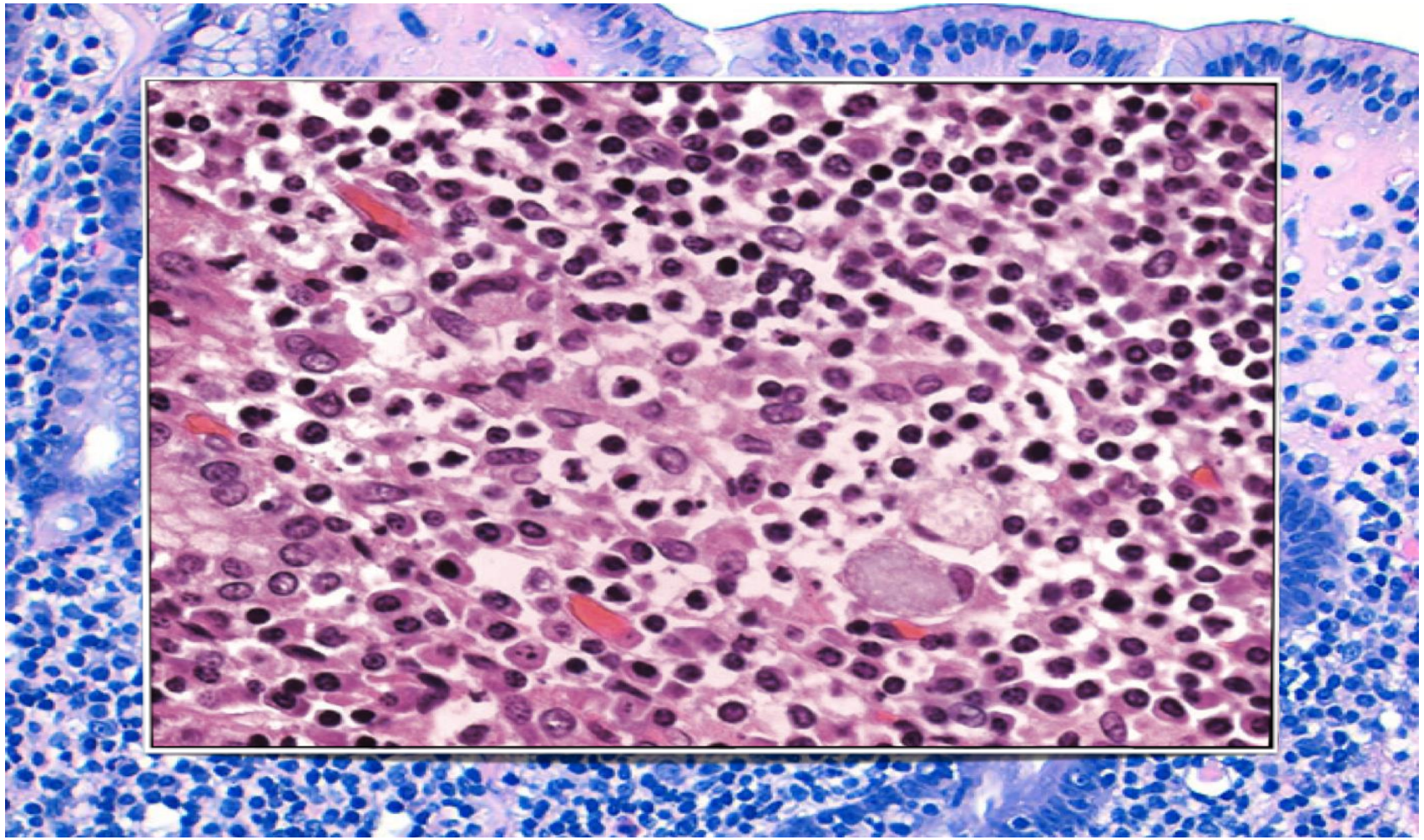
HISTOLOGIC MIMICS OF SIGNET RING CELLS



Pseudo-SRC associated with chronic gastritis

Hereditary Diffuse Gastric Cancer

HISTOLOGIC MIMICS OF SIGNET RING CELLS

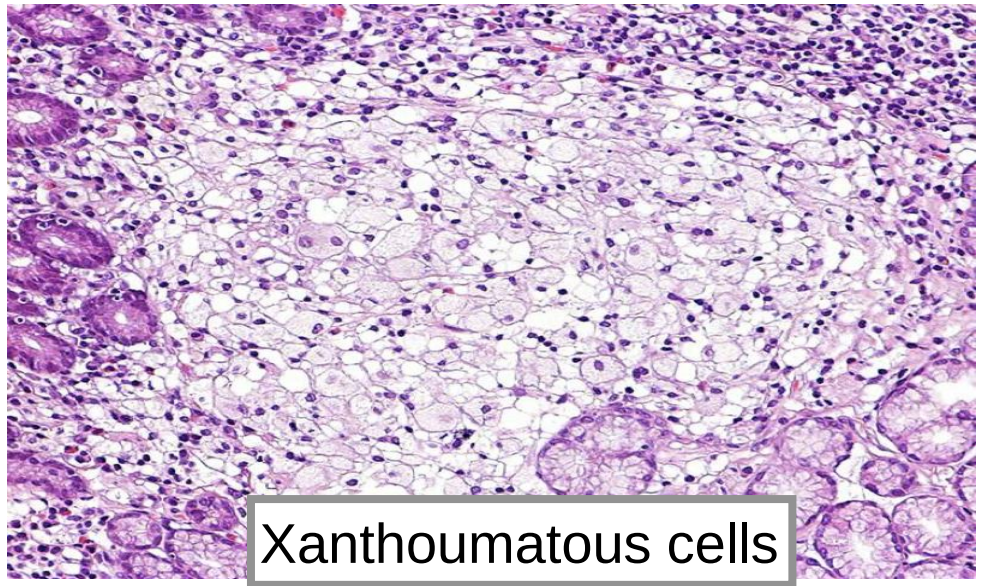


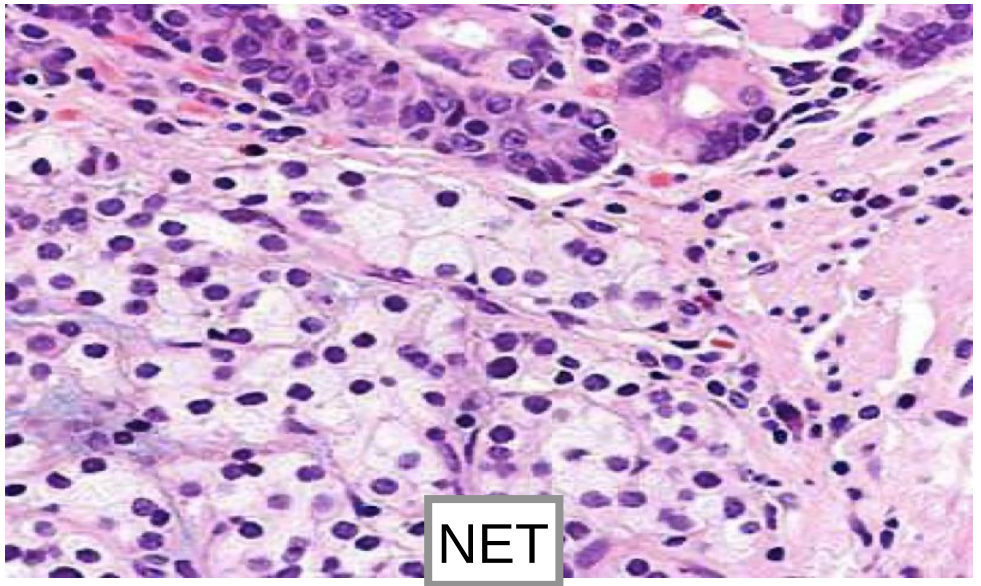
Carcinoma-like signet-ring cells in gastric MALT lymphoma

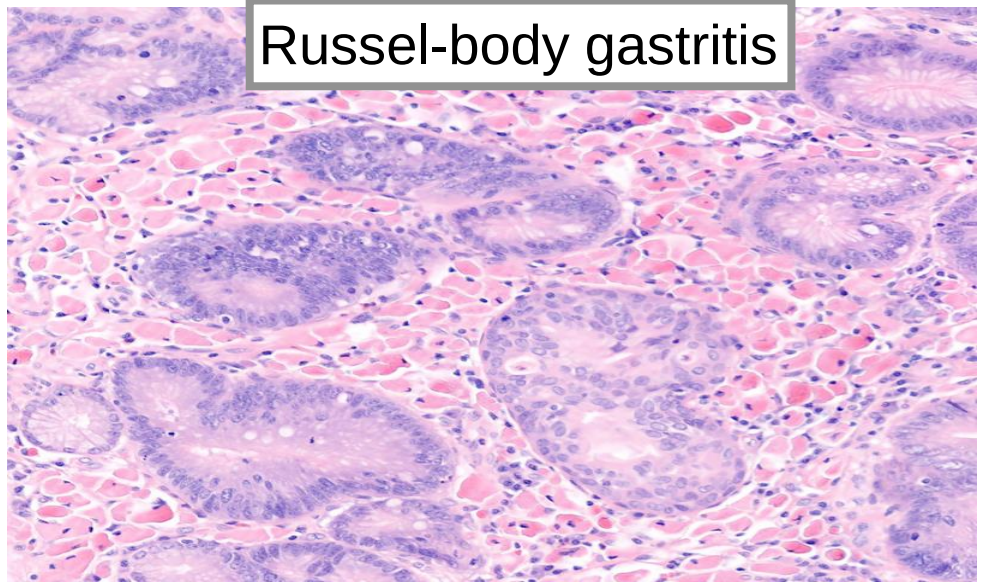
Zamboni G *et al.* Am J Surg Pathol. 1996 May;20(5):588-98

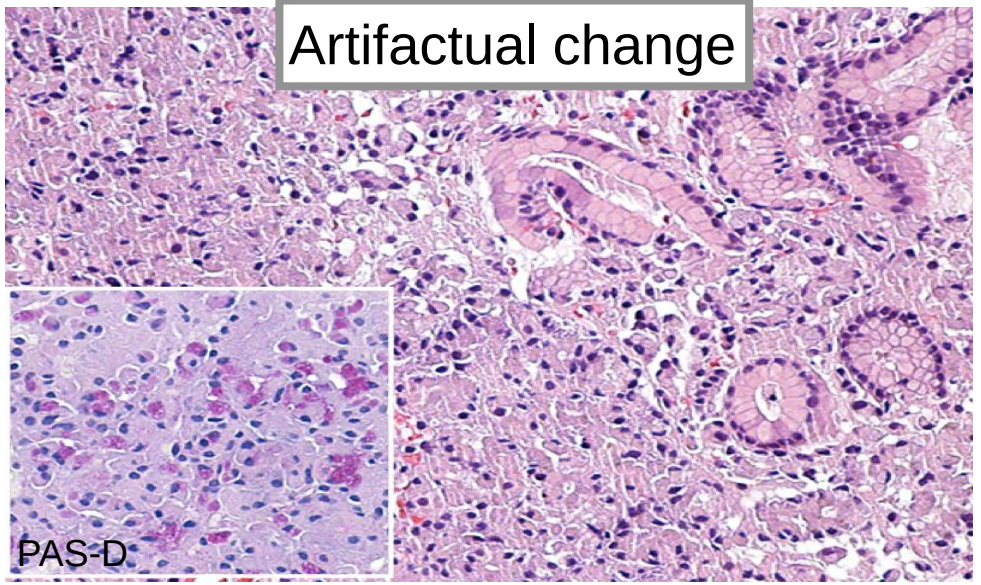
Hereditary Diffuse Gastric Cancer

HISTOLOGIC MIMICS OF SIGNET RING CELLS









Hereditary Diffuse Gastric Cancer

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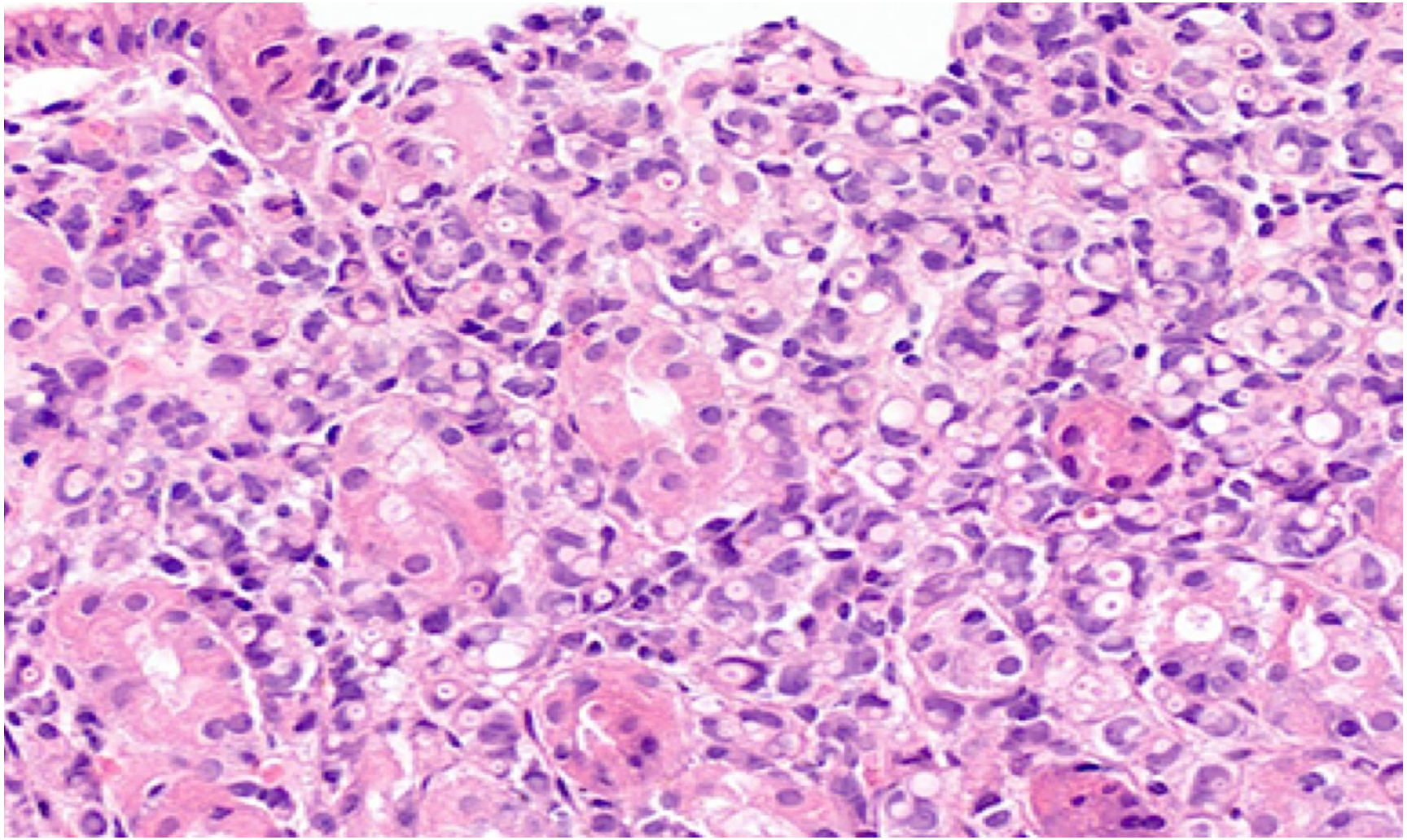
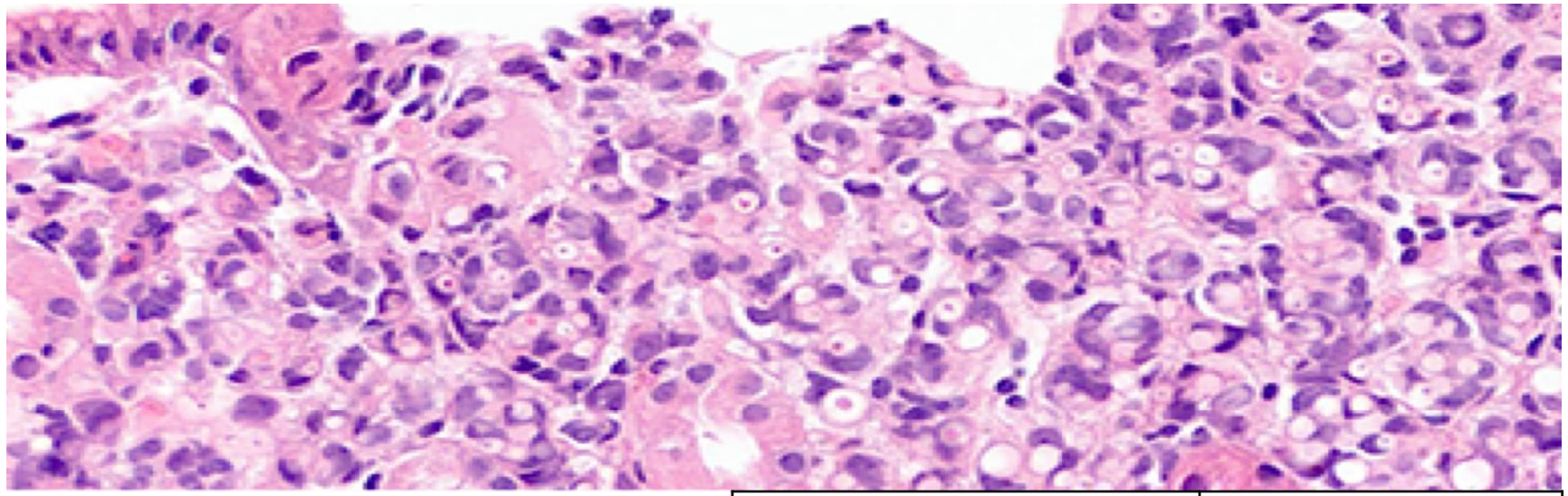
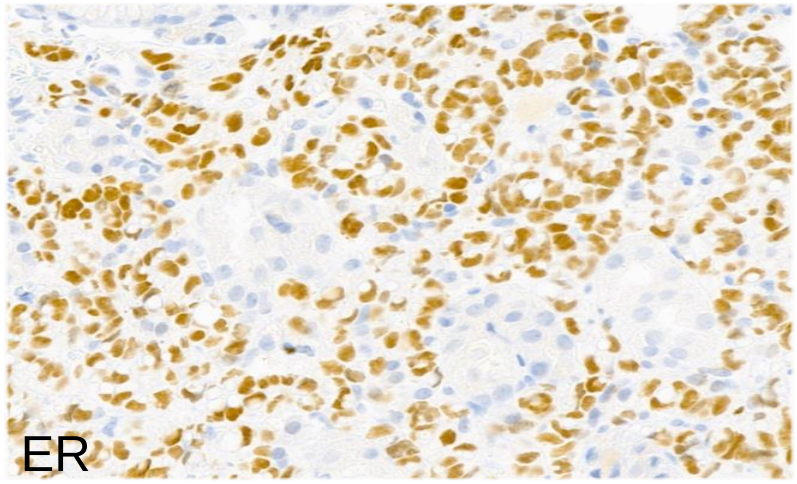
HISTOLOGIC MIMICS OF SIGNET RING CELLS



Hereditary Diffuse Gastric Cancer

HISTOLOGIC MIMICS OF SIGNET RING CELLS





LBC	DGC
ER	HNFA4
PR	
GCDFP-15	
GATA3	

International Gastric Cancer Linkage Consortium

Hereditary diffuse gastric cancer: updated clinical practice guidelines

Blair V *et al.* Lancet Oncol 2020; 21: e386–97

Panel 1: 2020 hereditary diffuse gastric cancer (HDGC) genetic testing criteria

CDH1 testing is recommended when one of the following criteria have been met and cancer diagnoses have been confirmed. When a criterion involves two or more cancers, at least one cancer should have confirmed histology. Where possible, other relevant cancers should also be confirmed. Histologically confirmed intestinal-type gastric cancer and non-lobular breast cancer cases should not be used to fulfil testing criteria, because these cancers are not part of HDGC. Individuals who fulfil criteria for genetic testing but are found to be negative for a *CDH1* variant should subsequently be considered for *CTNNA1* analysis.

Family criteria*

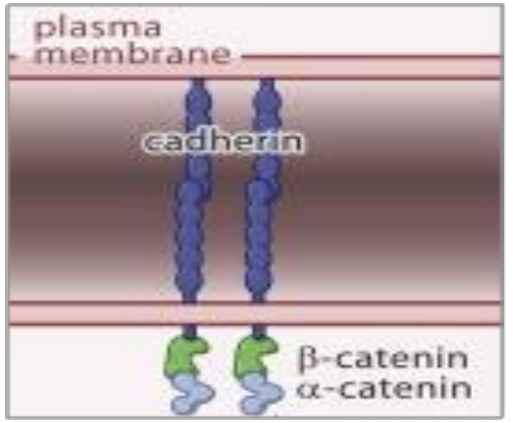
1 ≥2 cases of gastric cancer in family regardless of age, with at least one diffuse gastric cancer (DGC)
2 ≥1 case of DGC at any age, and ≥1 case of lobular breast cancer at age <70 years, in different family members
3 ≥2 cases of lobular breast cancer in family members <50 years of age

Individual criteria

4 DGC at age <50 years
5 DGC at any age in individuals of Māori ethnicity
6 DGC at any age in individuals with a personal or family history (first-degree relative) of cleft lip or cleft palate
7 History of DGC and lobular breast cancer, both diagnosed at age <70 years
8 Bilateral lobular breast cancer, diagnosed at age <70 years
9 Gastric in situ signet ring cells or pagetoid spread of signet ring cells in individuals <50 years of age

*Family members must be first-degree or second-degree blood relatives of each other. Where possible, test an affected pers… If there are no living affected relatives, consider tissue testing (tumour tissue or healthy tissue) from an affected deceased relative. If these options are not possible, consider indirect testing in unaffected family members.

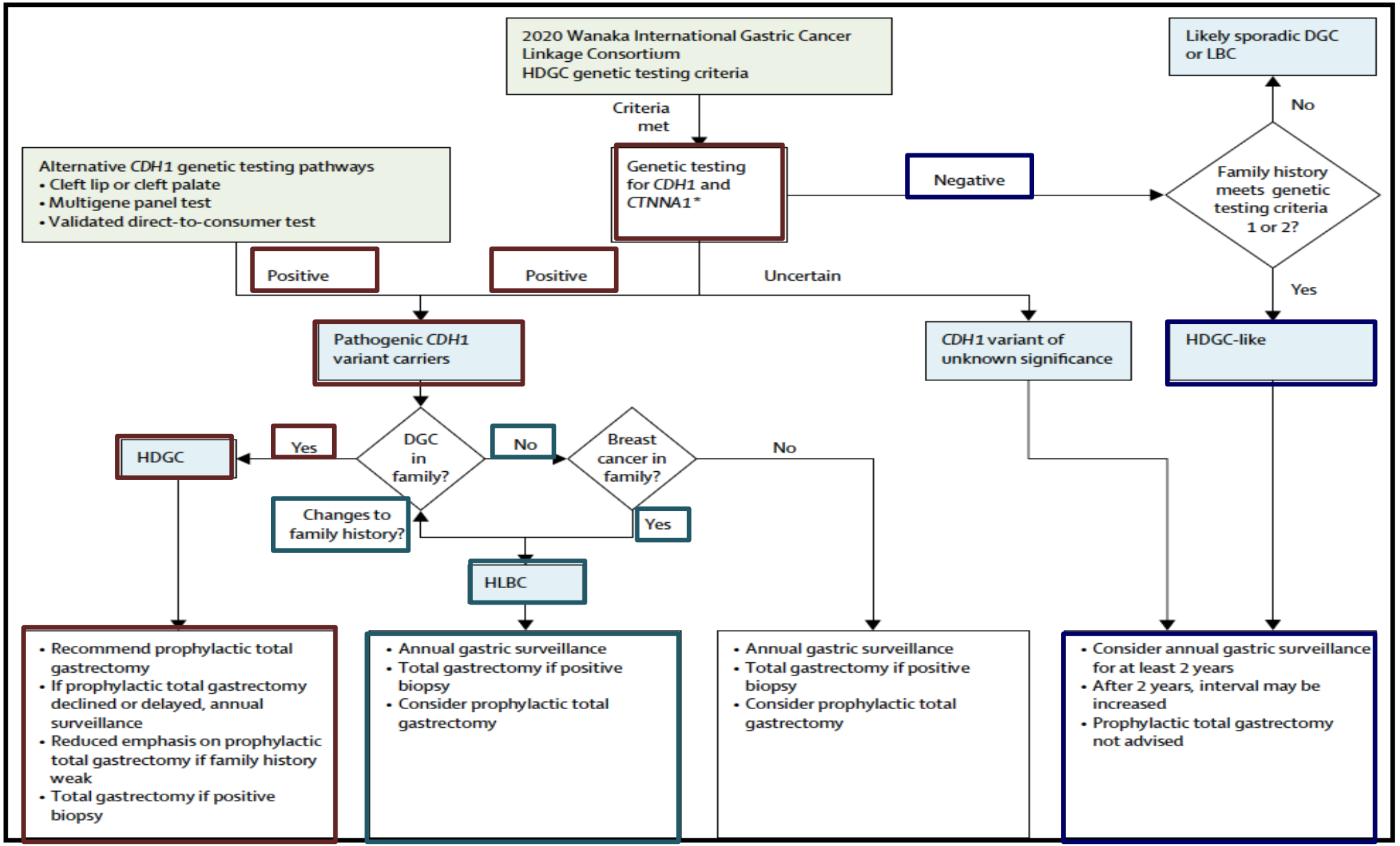
CDH1 testing
CTNNA1 testing



Hereditary diffuse gastric cancer: updated clinical practice guidelines

Blair V *et al.* Lancet Oncol 2020; 21: e386–97

Hereditary Diffuse Gastric Cancer



Hereditary Diffuse Gastric Cancer

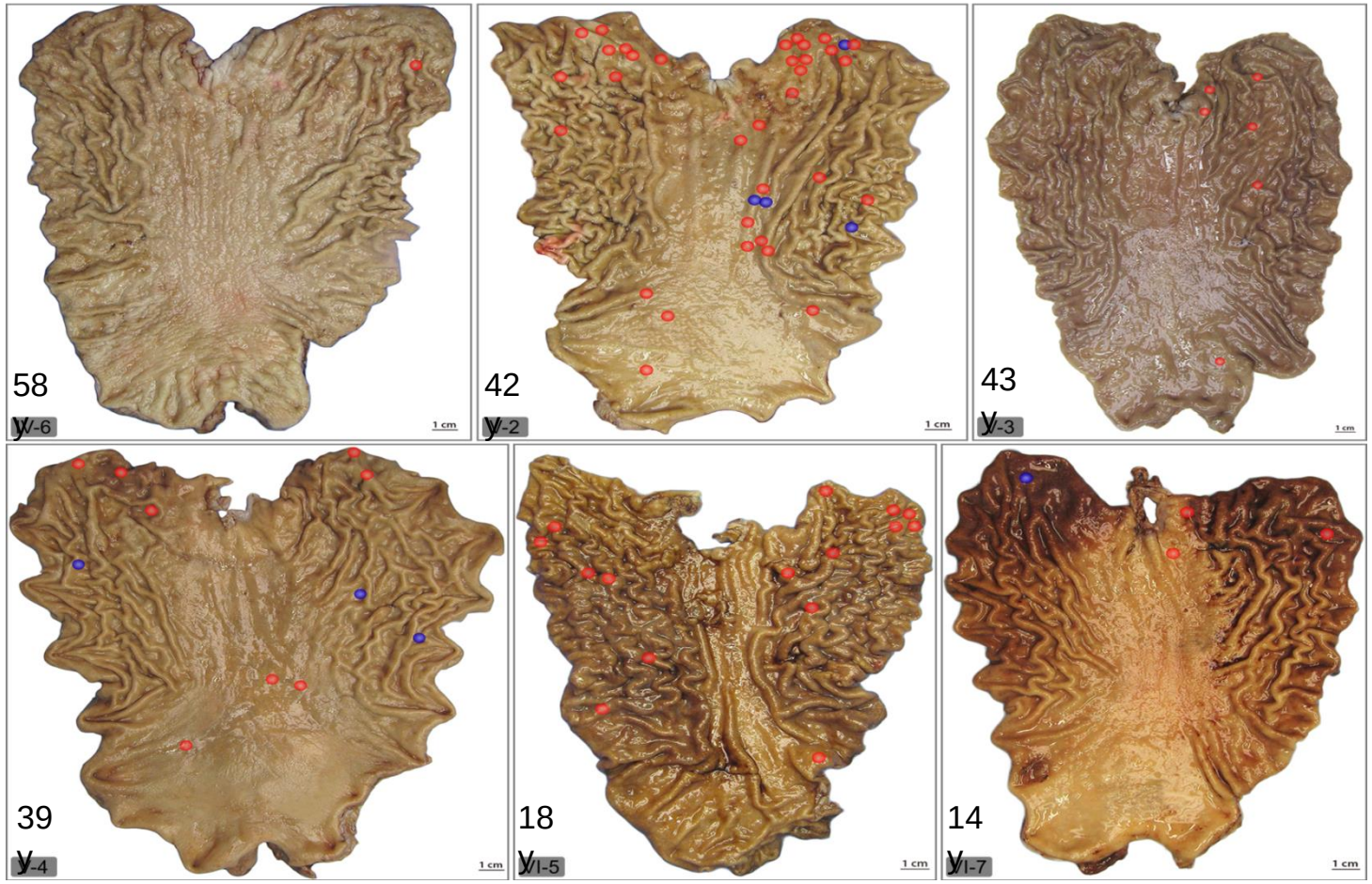
PATHOLOGY ARTICLE

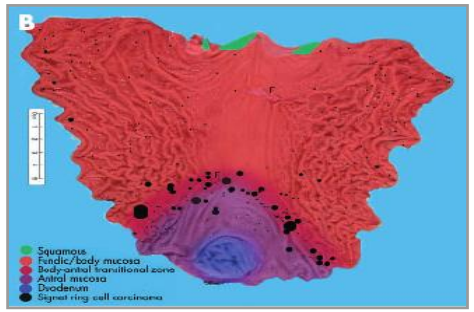
Phenotypic heterogeneity of hereditary diffuse gastric cancer: report of a family with early-onset disease

Gullo I *et al* Gastrointestinal Endoscopy. 2018

PROPHYLACTIC TOTAL GASTRECTOMY SPECIMENS

Variability of number and spatial distribution of the cancer foci





New Zealand

Charlton A et al Gut 2004

Blair V et al Clin Gastroenterol Hepatol 2006

Europe and USA

Lim YC et al Gastrointest Endosc 2014; Barber ME et al J Pathol 2008

Rogers WM et al Am J Surg Pathol 2008 ; Fujita H et al Am J Surg Pathol 2012

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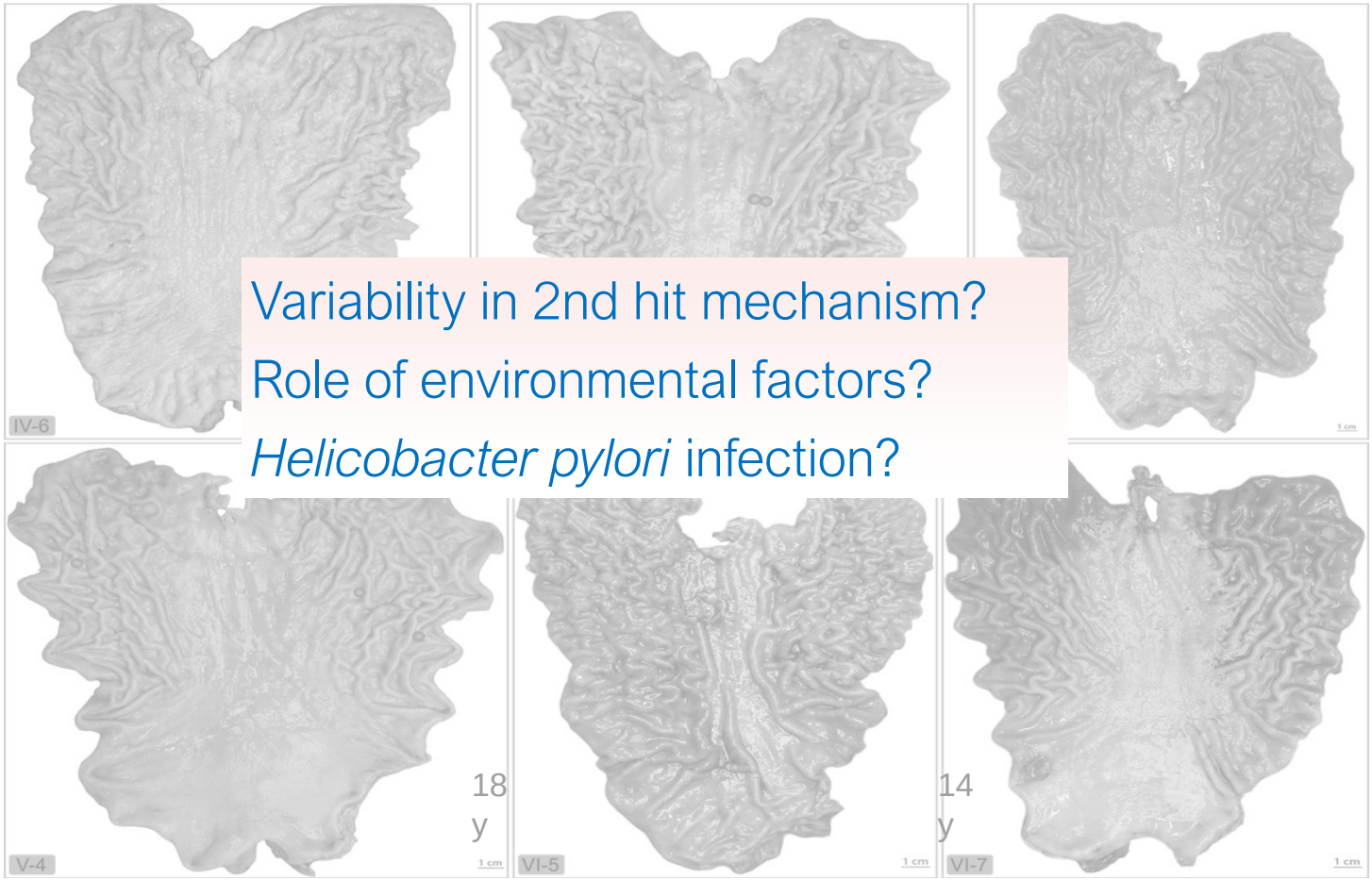


58 y

39 y

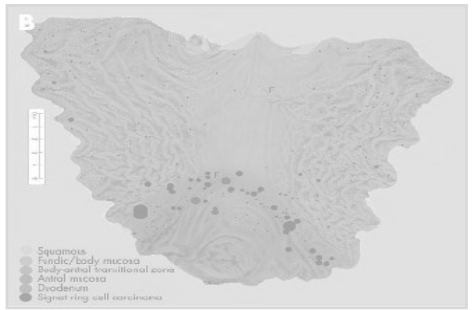
18 y

14 y

Variability in 2nd hit mechanism?

Role of environmental factors?

Helicobacter pylori infection?



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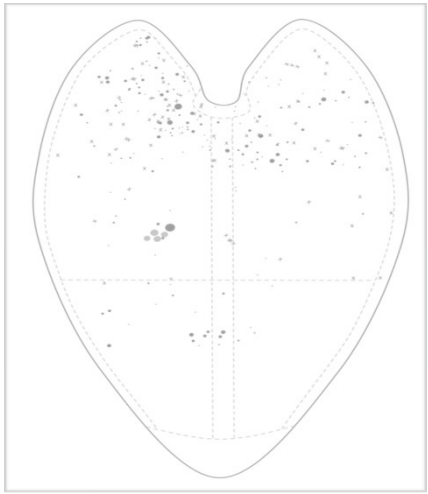

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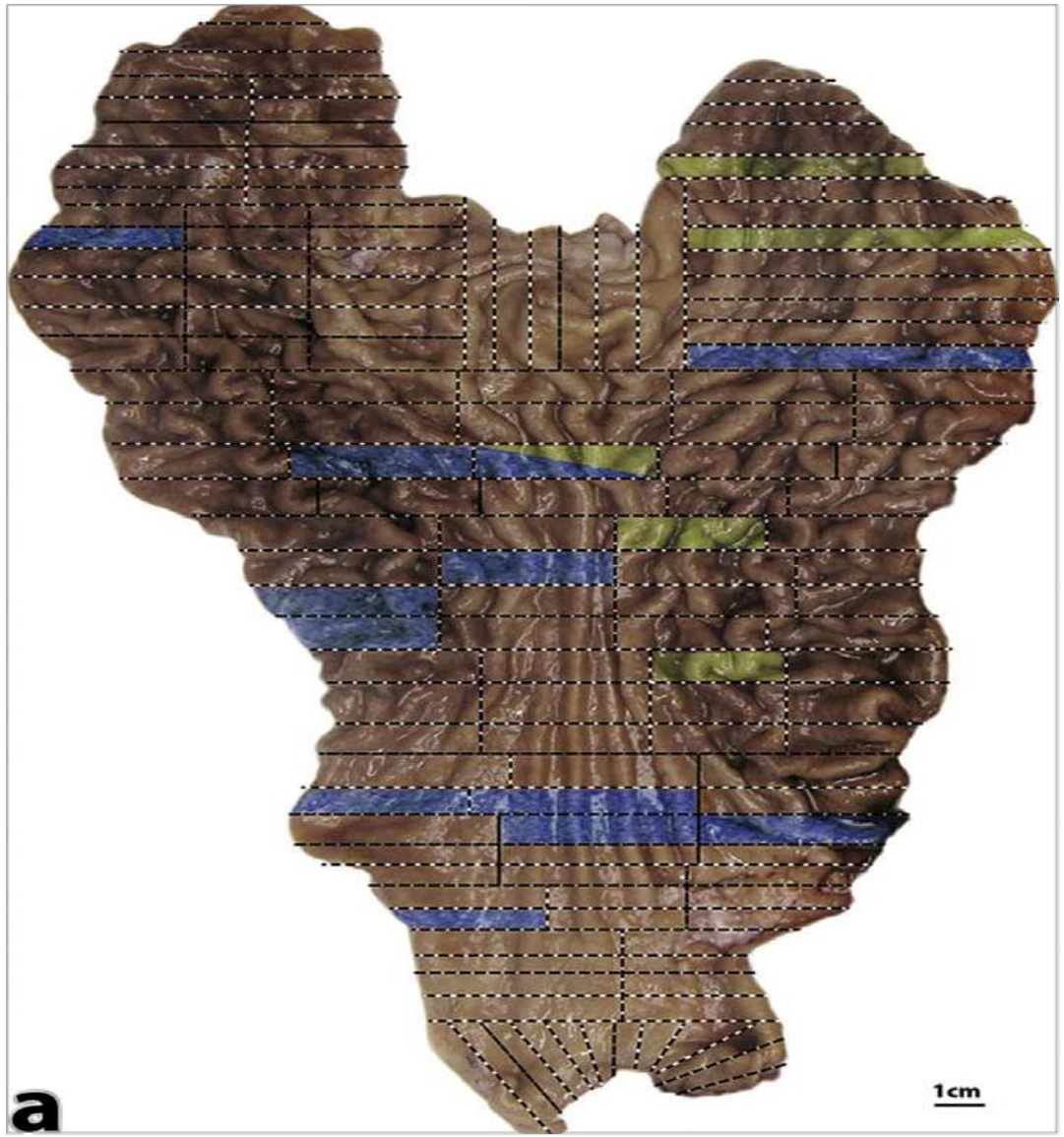
Hereditary Diffuse Gastric Cancer

PROPHYLACTIC TOTAL GASTRECTOMY SPECIMENS



Gold standard

Total-embedding protocol and thorough histopathological examination of the entire gastric mucosa

Review article

Hereditary gastrointestinal carcinomas and their precursors: An algorithm for genetic testing

Spoto CPE, **Gullo I** et al Semin Diagn Pathol. 2018

Hereditary Diffuse Gastric Cancer

HANDLING PTG SPECIMENS

Histopathology

Histopathology 2018 DOI: 10.1111/his.13715

REVIEW

Pathological features of total gastrectomy specimens from asymptomatic hereditary diffuse gastric cancer patients and implications for clinical management

João P Rocha,[1] Irene Gullo,[2,3,4,5] Xiaogang Wen,[4,5,6] Vítor Devezas,[7,8,9] Manuela Baptista,[7,8,9] Carla Oliveira[3,4,5] & Fátima Carneiro[2,3,4,5]

Macroscopy			
Abnormal	11	6.3	11.7
Normal	83	47.7	88.3
NA	80	46.0	–

Table 1. Description of 174 hereditary diffuse gastric cancer patients undergoing gastrectomy and major clinicopathological features

	n	%	% excluding NA cases
Total TGs	174	100	–
Sex			
Male	69	39.7	41.1
Female	99	56.9	58.9
NA	6	3.4	–
Endoscopic biopsy			
Positive	36	20.7	28.3
Negative	91	52.3	71.7
NA	47	27.0	–
Type of surgery			
Laparoscopic	16	9.2	11.2
Open	127	73.0	88.8
NA	31	17.8	–
Macroscopy			
Abnormal	11	6.3	11.7
Normal	83	47.7	88.3
NA	80	46.0	–
Total-embedding protocol*			
Yes	129	74.1	76.3
No	40	23.0	23.7
NA	5	2.9	–
Precursor lesions and/or invasive (SRC) carcinoma			
Present†	152	87.4	87.9
With total-embedding protocol‡	122/128	95.3	–
Without total-embedding protocol‡	25/40	62.5	–
Absent†	21	12.0	12.1
With total-embedding protocol	6/128	4.7	–
Without total-embedding protocol	15/40	37.5	–
NA	1	0.6	–
In-situ SRC carcinoma			
Present	48	27.6	48.5
Absent	51	29.3	51.5
NA	75	43.1	–
Pagetoid spread of SRCs			
Present	10	5.7	12.2
Absent	72	41.4	87.8
NA	92	52.9	–
Helicobacter pylori infection			
Present	15	8.6	23.4
Not detected	49	28.2	76.6
NA	110	63.2	–
Intestinal metaplasia			
Present	15	8.6	22.1
Absent	53	30.5	77.9
NA	106	60.9	–
Lymph node metastasis			
Present§	1	0.6	0.99
Absent	100	57.5	99.01
NA	73	42.0	–

NA, not available; SRC, signet ring cell; TG, total gastrectomy.
*Total-embedding protocol: Yes—specimens subjected to total embedding; No—cases with partial/incomplete embedding; NA—cases without information on how the embedding was performed.
†In one case, information on histopathological analysis was not available.
‡In five cases, information on the total-embedding protocol was not available.
§Reported in Frebourg *et al.*[22]

Rocha J, **Gullo I** et al Histopathology 2018

Hereditary Diffuse Gastric Cancer

HANDLING PTG SPECIMENS

Histopathology

Histopathology 2018 DOI: 10.1111/his.13715

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p<0.001

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Lymph node metastasis			
Present§	1	0.6	0.99
Absent	100	57.5	99.01
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NA, not available; SRC, signet ring cell; TG, total gastrectomy.
*Total-embedding protocol: Yes—specimens subjected to total embedding; No—cases with partial/incomplete embedding; NA—cases without information on how the embedding was performed.
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Rocha J, **Gullo I** et al Histopathology 2018

Hereditary Diffuse Gastric Cancer

HANDLING PTG SPECIMENS

Supplementary Table 4. Levels of pathological examination depending on availability of resources

Levels of pathological examination depending on availability of resources			
Level	Level 1 Minimum required	Level 2 [level 1 plus…]	Level 3 [Level 2 plus…]
Morphologic	• Pin out and photograph • Sample margins and lymph nodes • Sample tissue from all gastric zones • Map blocks to photo • Examine all slides	• Embed all mucosa, process to paraffin blocks. • Cut a subset of blocks, sampling all gastric zones • Examine sampled slides.	• Cut all blocks. Examine all slides.
Repeat	• Sample tissue from all zones • Map blocks • Examine all slides	• Cut a subset of blocks, sampling all zones • Examine sampled slides.	
Stop	When invasive carcinoma is found or up to arbitrary limit for example 50 blocks	When invasive carcinoma is found, or up to arbitrary limit for example 50 slides.	When all mucosa is examined.
Report	Multiple of foci of pT stage carcinoma in xx% of mucosa examined microscopically	Number of foci of pT stage carcinoma in xx% of mucosa examined microscopically	Number of foci of pT stage carcinoma, all mucosa examined microscopically
Blocks	~ 20-50*	~ 120-270	~ 120-270
Slides	~ 20-50*	~ 20-50*	~ 120-270

A three level protocol is suggested where Level 1 is the minimum examination to obtain sufficient data (margins, carcinoma stage, lymph node status) necessary for patient care. Level 2 represents a compromise between clinical reporting and preserving tissue for future research, and Level 3 is total gastric embedding and mapping. *The upper limit number of blocks and slides required to find foci of stage pT1a carcinoma, or pTis (signet ring cell carcinoma *in situ*) is variable.

Blair V *et al.* Lancet Oncol 2020; 21: e386–97

Hereditary Diffuse Gastric Cancer

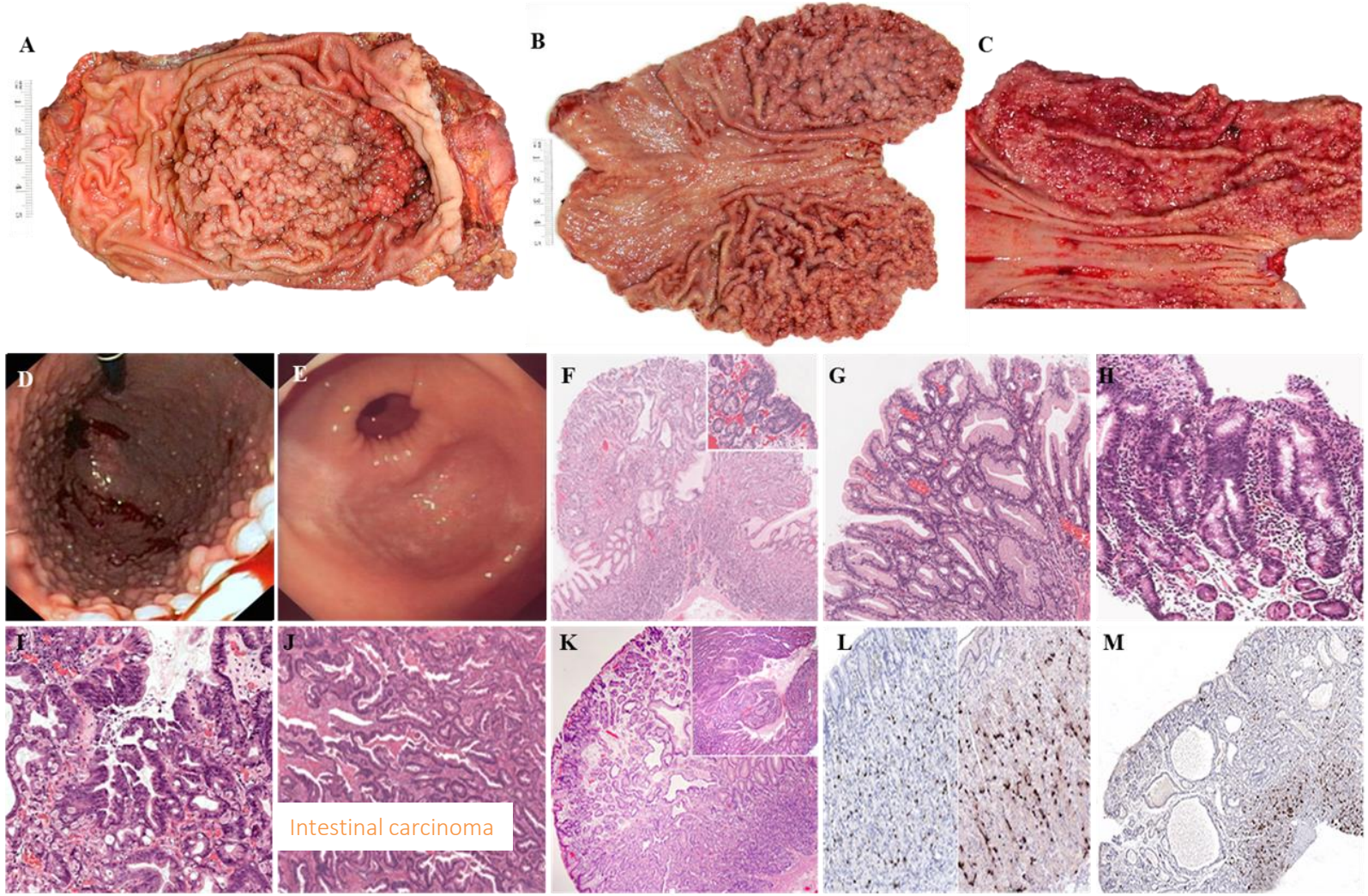
- The definition of HDGC and HLBC is based on the presence of pathogenic germline *CDH1*/*CTNNA1* variants.
- Total embedding protocol is the gold standard workup for correct identification and staging of HDGC lesions.
- HDGC in *CDH1* carriers is **heterogenous**, in terms of clinical presentation, morphology and immunophenotypic profile.
- The clinical course and progression of HDGC is **unpredictable**: total gastrectomy is still the recommended strategy to prevent aggressive disease.
- The “**aggressive**” phenotype (aberrant p53 expression, high Ki-67 proliferative index) should be reported by the pathologist as it strongly predicts advanced disease.

WHO Classification of Tumours of the Digestive System, 5th edition, 2019

Genetic tumour syndromes of the digestive system

- Genetic tumour syndromes of the digestive system: Introduction
- Genetics
- Genetic tumour syndromes of the digestive system
  - Lynch syndrome
  - Familial adenomatous polyposis 1
  - GAPPS and other fundic gland polyposes
  - Other adenomatous polyposes
  - Serrated polyposis
  - Hereditary diffuse gastric cancer
  - Familial pancreatic cancer
  - Juvenile polyposis syndrome
  - Peutz-Jeghers syndrome
  - Cowden syndrome
  - Other genetic tumour syndromes

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



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

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]

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 exclusi involvement of the gastric body and fundus, the app inverse association with current *Helicobacter pylor* 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 autoso dominant transmission of fundic gland polyposis, including areas of dysplasia or intestinal-type gastr adenocarcinoma, restricted to the proximal stomach with no evidence of colorectal or duodenal polypos other heritable gastrointestinal cancer syndromes.

include *MUTYH*-associated polypo generalised juvenile polyposis syndr Peutz Jeghers syndrome (PJS) an syndrome.[5 6] However, FGPs are relat MAP, an autosomal recessive disorder, a PJS are often characterised by the specific hamartomatous (rather t dysplastic fundic gland) polyps.[5 6]

Sporadic FGPs are usually inno syndromic FGPs can progress to dy gastric adenocarcinoma.[7 9] Therefor must distinguish patients with spo

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 *Helicobacter pylori*. Upper endoscopy revealed nd polyps covering the rpus (figure 1A). In the so a flat and discoloured y polyps (figure 1B). A revealed well-differen- na. No other polyps or d in the duodenum. The t show any colorectal scan of the chest and al. A total gastrectomy roscopically, there were poid lesions. There was ea measuring 6×5.5 cm s (figure 1C). Histologi- ll fundic gland polyps buted (figure 1D). The differentiated adenocar- vading the superficial ucosa (figure 1E). Since matous polyposis was rmed an upper endos- family members: two two daughters, one son result, five of the seven gastric FGP (figure 2).

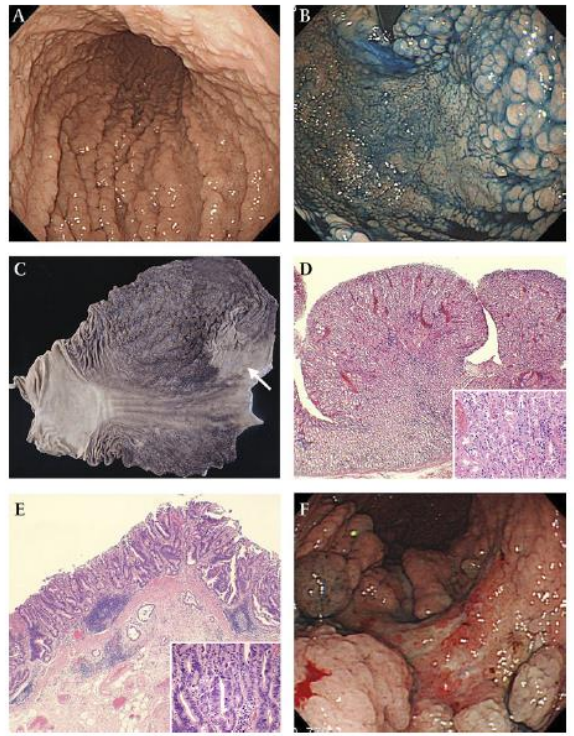
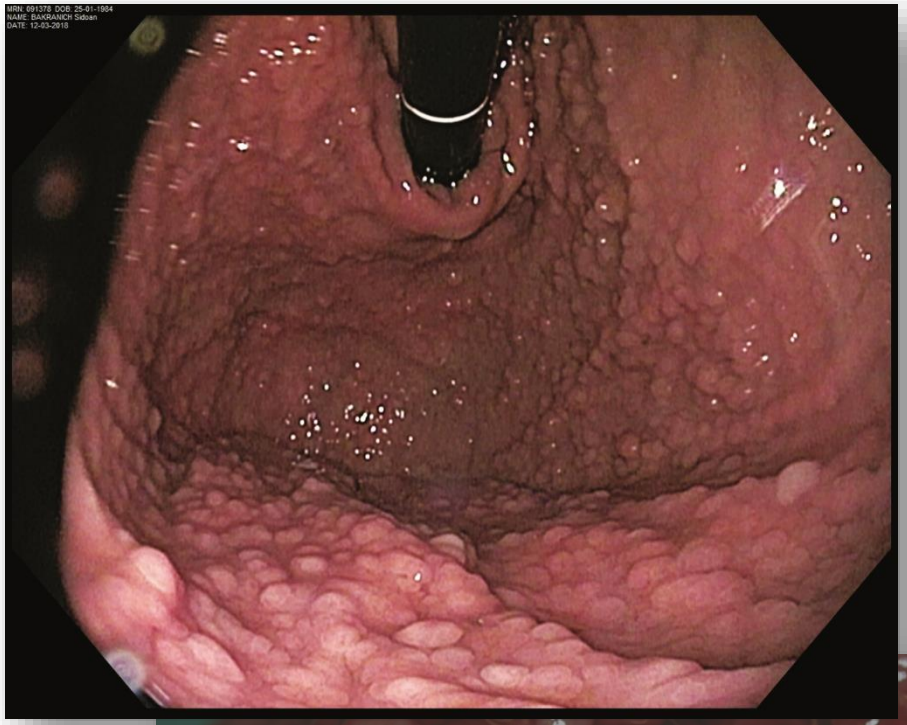
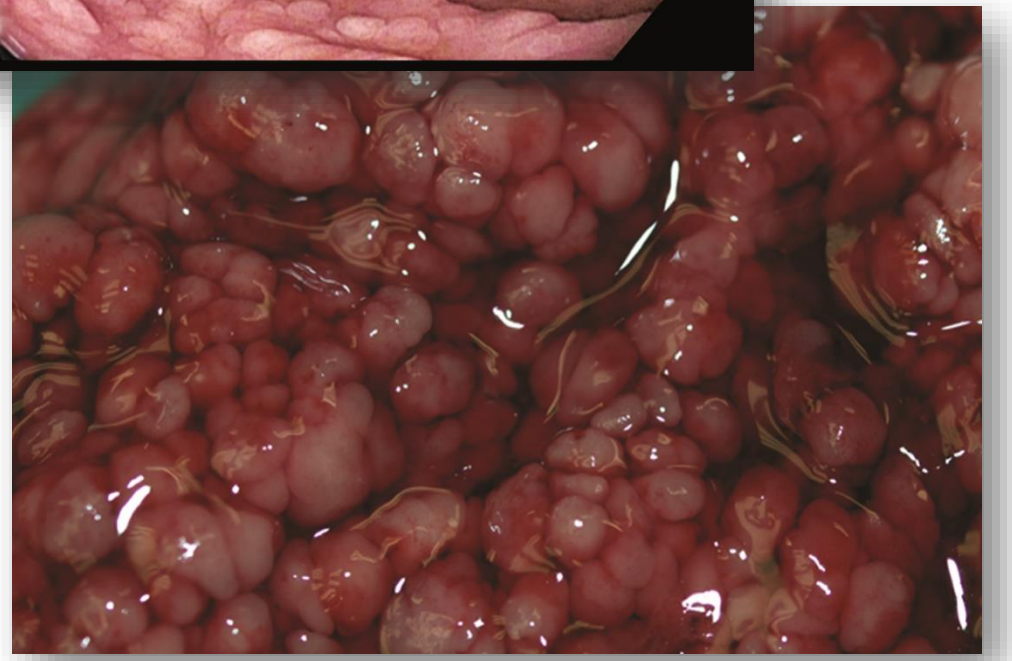


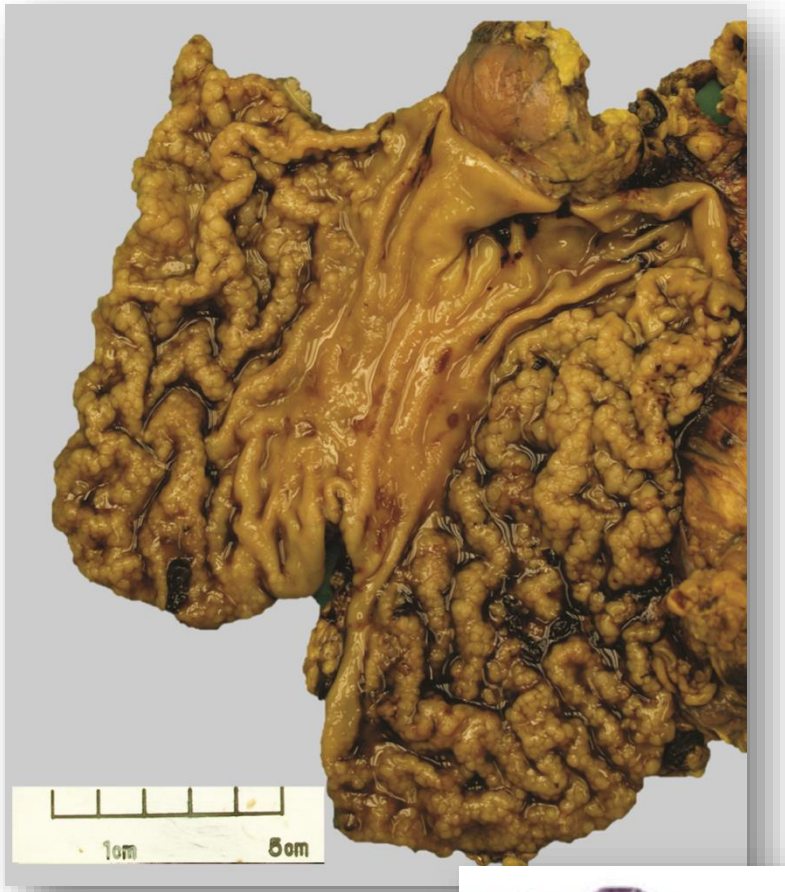
Figure 1 Endoscopic and pathological findings. (A and B) Case 1. Endoscopic images reveal numerous fundic gland polyps in the corpus (A), while a flat area circumscribed by polyps can be seen in the fundus (B). (C) Macroscopic finding of the gastrectomy specimen showing numerous

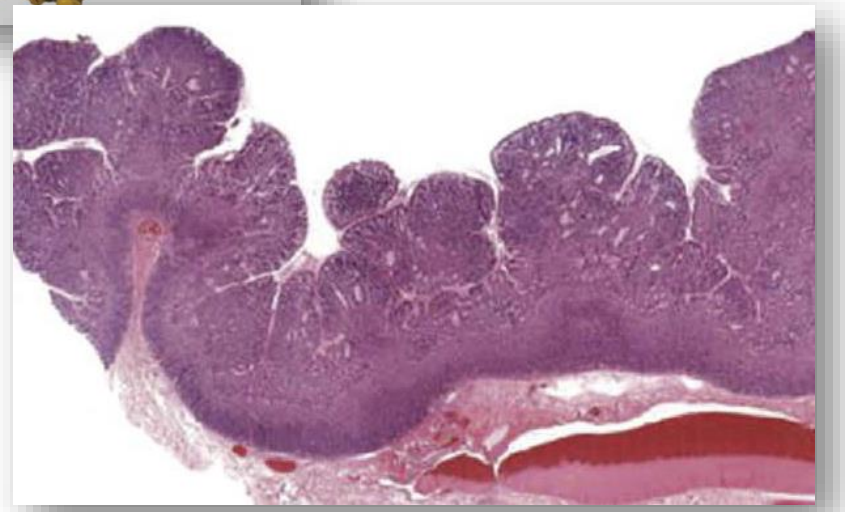
Mutations were excluded in the following genes:

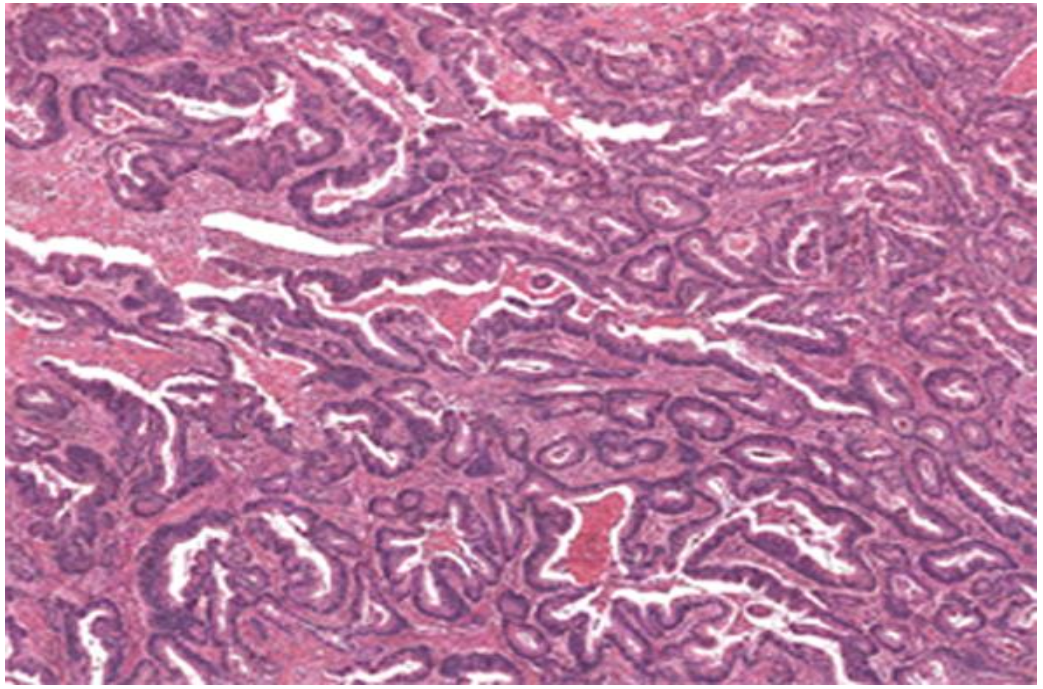
- *APC*
- *MUTYH*
- *CDH1*
- *SMAD4*
- *BMPR1A*
- *STK11*
- *PTEN*

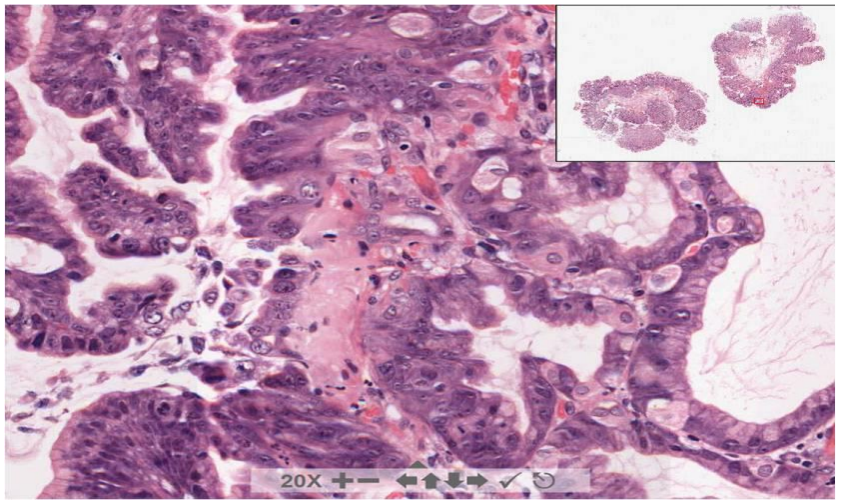

MRN: 691378 DOB: 25-01-1964
NAME: BAKRANICH Sidoan
DATE: 12-03-2018



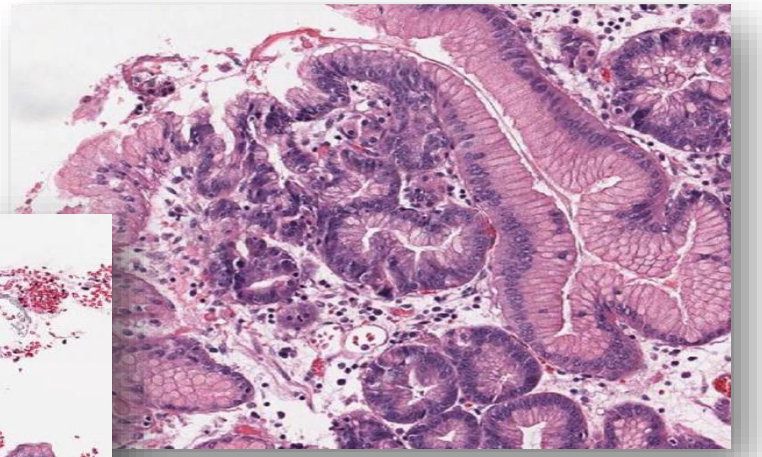

1cm
5cm

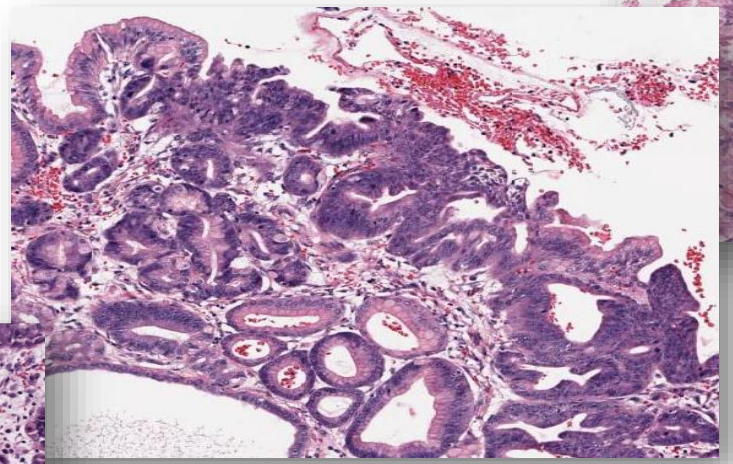


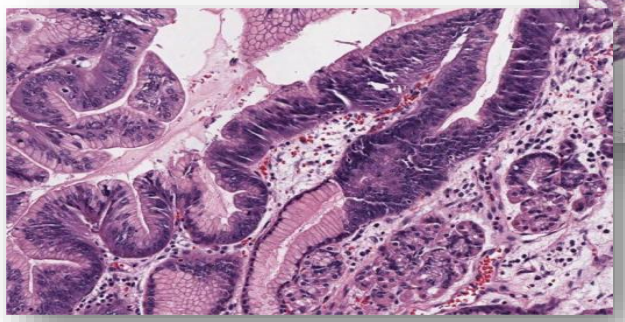




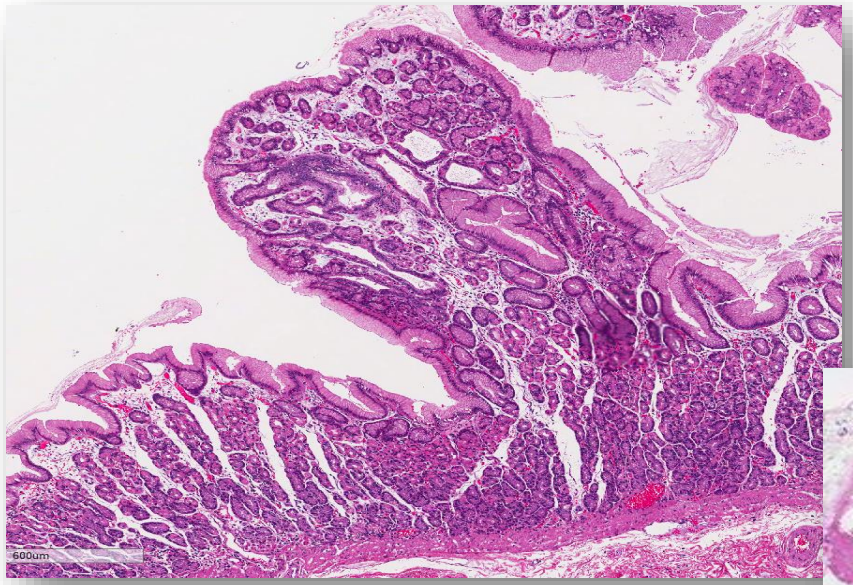
- Gastric Adenocarcinoma
- Fundic Gland Polyposis



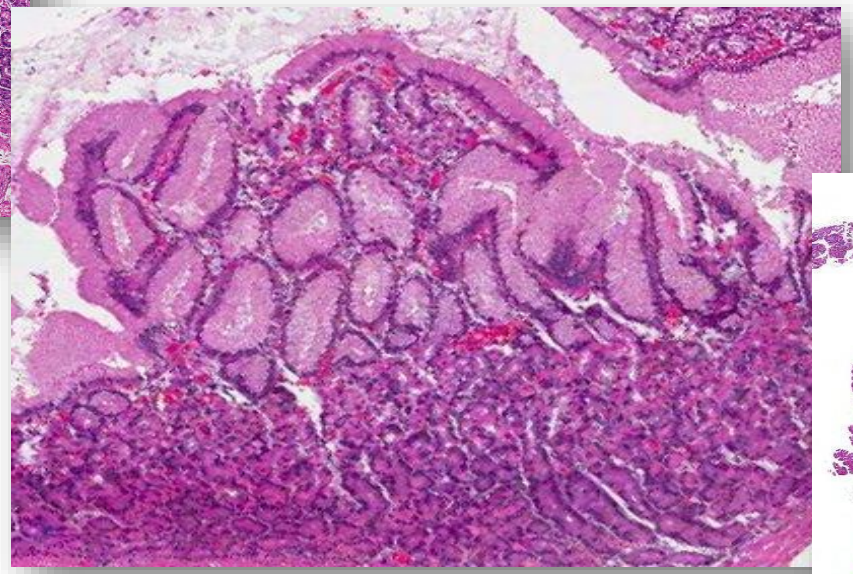




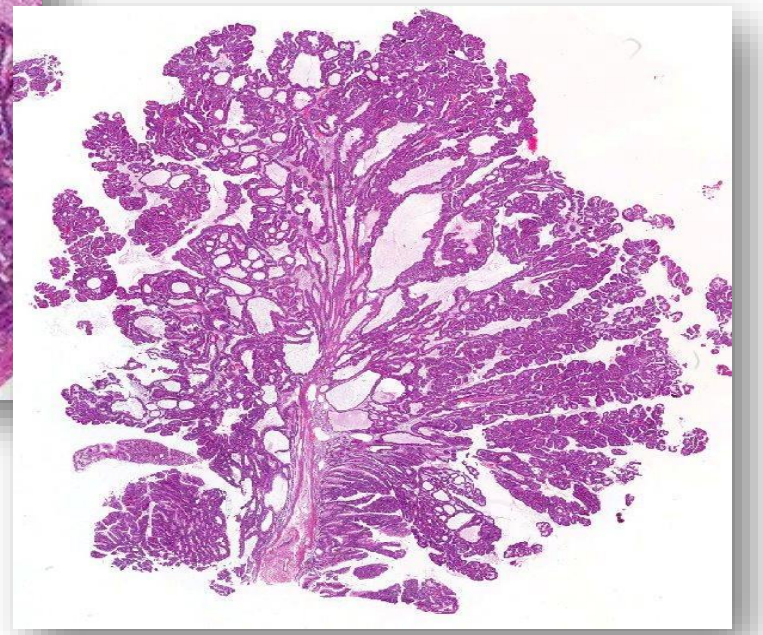
Fundic gland-type polyp



Inverted foveolar hyperplasia



Foveolar adenoma

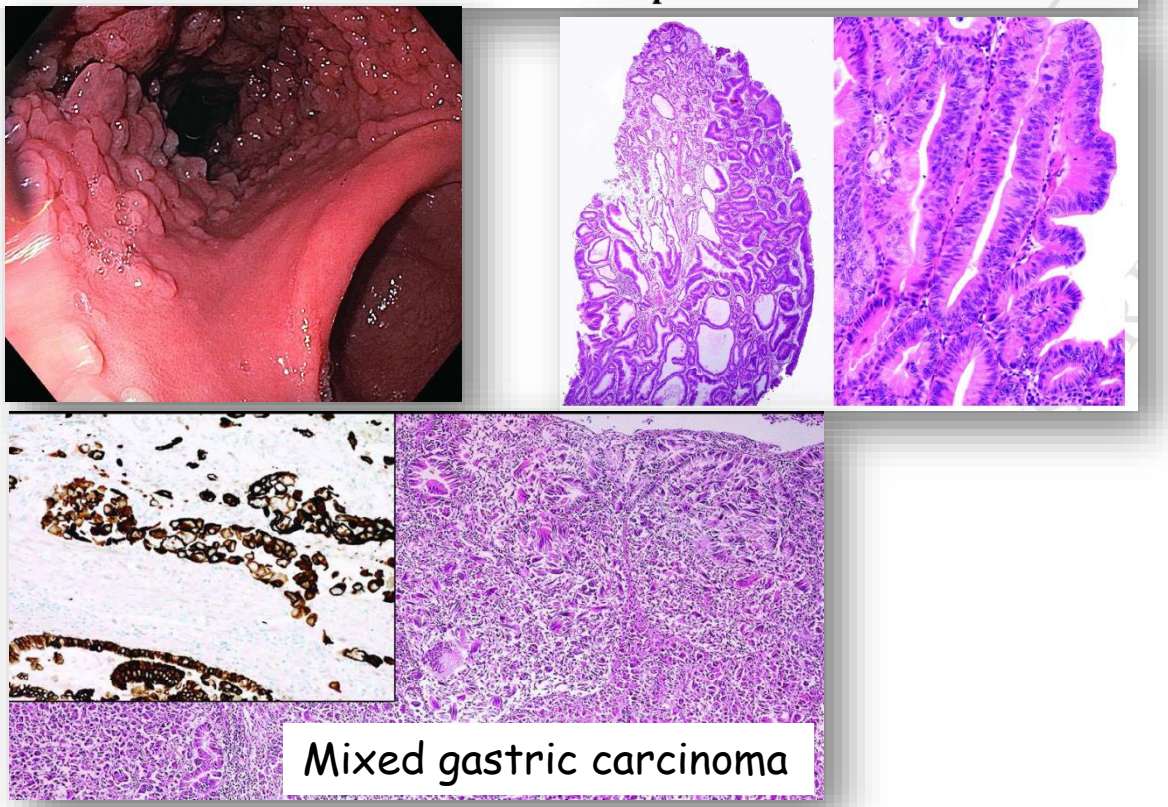


De Boer WB and Kuamarasinghe MP: Am J Surg Pathol .2018 Jan;42(1):1-8.

ACCEPTED MANUSCRIPT

The first European family with gastric adenocarcinoma and proximal polyposis of the stomach: case report and review of the literature

Short title: First case of GAPPS in Europe



Repak R *et al*: Gastrointestinal EndoscopyDOI: 10.1016/j.gie.2016.06.023

GAPPS (Gastric Adenocarcinoma and Proximal Polyposis of the Stomach)

More recently, another GAPPS family in Europe

Kasuistik

Thieme

Gastric adenocarcinoma and proximal polyposis of the stomach (GAPPS) – a rare recently described gastric polyposis syndrome – report of a case

GAPPS – eine seltene, 2012 erstmals beschriebene Magenpolypose – ein Fallbericht

Authors

Andrea Beer[1], Berthold Streubel[1], Reza Asari[2], Clemens Dejaco[3], Georg Oberhuber[1]

IGCC-0038 & IGCC-1172: 8 families from Czech Republic

Table 2
Characteristics of gastric polyposis syndromes

Syndrome	Gene Mutation	Mode of Inheritance	Associated Gastric Polyps	Estimates of Gastric Cancer Lifetime Risk	Histology Gastric Cancer	Important Histologic Clues	Locations of Associated Other Malignancies	Important Clinical Clues
Gastric adenocarcinoma with proximal polyposis	Point mutations in Exon 1B of *APC*	Autosomal dominant	Fundic gland polyps, few hyperplastic polyps and adenomas	Increased	Intestinal and mixed	Fundic gland polyposis with antral sparing	None	Gastric polyposis without colorectal polyposis and without use of acid-suppression therapy
Attenuated familial adenomatous polyposis	*APC*	Autosomal dominant	Predominantly fundic gland polyps, foveolar adenomas, and pyloric gland adenomas	Not increased	Intestinal	Fundic gland polyps	Colorectum, thyroid, duodenum, adrenal gland, small bowel, brain	Colorectal and duodenal polyposis

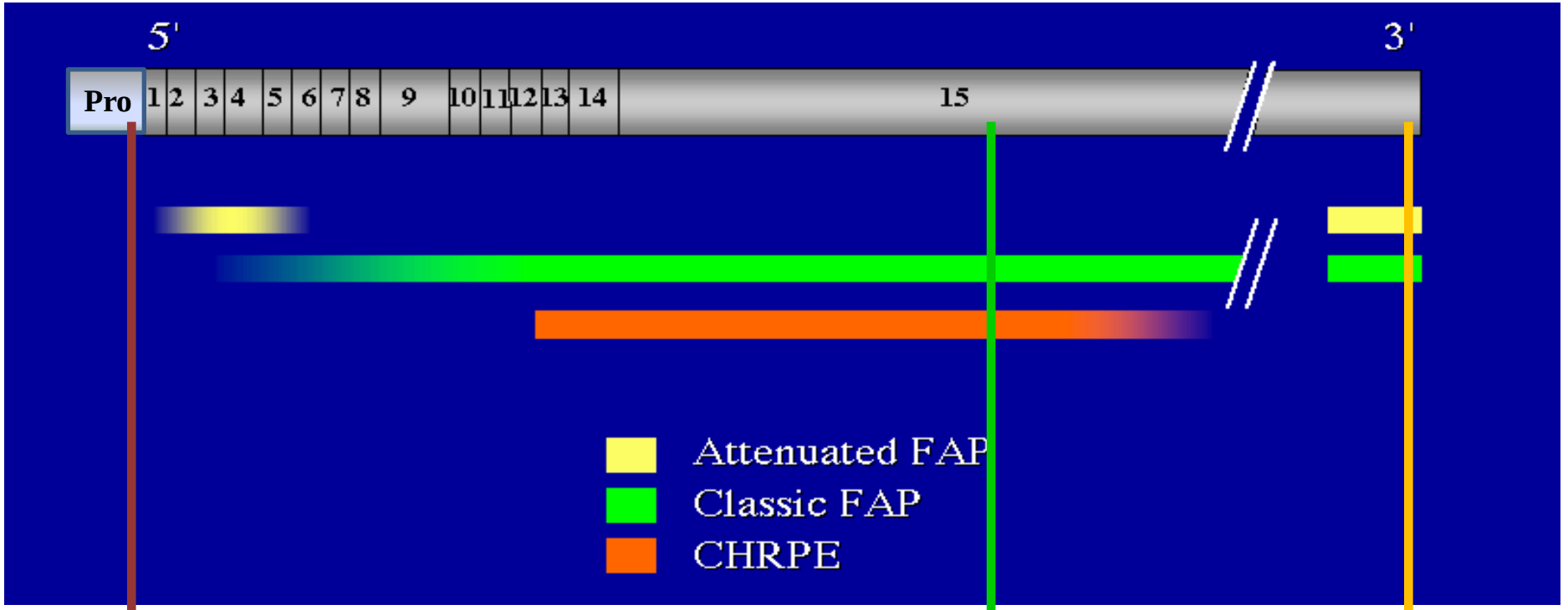
Point Mutations in Exon 1B of *APC* Reveal Gastric Adenocarcinoma and Proximal Polyposis of the Stomach as a Familial Adenomatous Polyposis Variant

Jun Li,[1] Susan L. Woods,[2] Sue Healey,[1] Jonathan Beesley,[1] Xiaoqing Chen,[1] Jason S. Lee,[1] Haran Sivakumaran,[1] Nicci Wayte,[1] Katia Nones,[1] Joshua J. Waterfall,[3] John Pearson,[1,4] Anne-Marie Patch,[1] Janine Senz,[5] Manuel A. Ferreira,[1] Pardeep Kaurah,[6] Robertson Mackenzie,[7] Alireza Heravi-Moussavi,[8] Samantha Hansford,[5] Tamsin R.M. Lannagan,[2] Amanda B. Spurdle,[1] Peter T. Simpson,[9,10] Leonard da Silva,[9,10] Sunil R. Lakhani,[9,10,11] Andrew D. Clouston,[12,13] Mark Bettington,[10,13,14] Florian Grimpen,[15] Rita A. Busuttil,[16,17,18] Natasha Di Costanzo,[16] Alex Boussioutas,[16,17,18,19] Marie Jeanjean,[20] George Chong,[21] Aurélie Fabre,[22,23,24] Sylviane Olschwang,[22,23,24] Geoffrey J. Faulkner,[25] Evangelos Bellos,[4,26] Lachlan Coin,[4] Kevin Rioux,[27] Oliver F. Bathe,[28,29] Xiaogang Wen,[30,31] Hilary C. Martin,[32] Deborah W. Neklason,[33] Sean R. Davis,[3] Robert L. Walker,[3] Kathleen A. Calzone,[3] Itzhak Avital,[34] Theo Heller,[35] Christopher Koh,[35] Marbin Pineda,[3] Udo Rudloff,[36] Martha Quezado,[37] Pavel N. Pichurin,[38] Peter J. Hulick,[39] Scott M. Weissman,[40] Anna Newlin,[39] Wendy S. Rubinstein,[41] Jone E. Sampson,[42] Kelly Hamman,[42] David Goldgar,[43] Nicola Poplawski,[44,45] Kerry Phillips,[44,45] Lyn Schofield,[46] Jacqueline Armstrong,[44] Cathy Kiraly-Borri,[46] Graeme K. Suthers,[45] David G. Huntsman,[7,47] William D. Foulkes,[20,48] Fatima Carneiro,[30,49] Noralane M. Lindor,[50] Stacey L. Edwards,[1] Juliet D. French,[1] Nicola Waddell,[1,4] Paul S. Meltzer,[3] Daniel L. Worthley,[2] Kasmintan A. Schrader,[6,7] and Georgia Chenevix-Trench,[1,*]

The genetic defect is now identified

The American Journal of Human Genetics (2016),
http://dx.doi.org/10.1016/j.ajhg.2016.03.001

APC: Genotype – Phenotype correlations



GAPPS
(the stomach is
the single target)

Severe FAP
(the colon is
the main target)

Attenuated FAP
(colon & stomach
are the targets)

Clinical criteria	WHO 2019
Essential criteria	1. Phenotypic features: - Proximal (body and fundus) gastric polyposis with antral sparing. No evidence of colorectal or duodenal polyposis* - >100 polyps carpeting the proximal stomach in the index case or >30 polyps in a first-degree relative of another case - Predominantly fundic gland polyps (FGP) and/or fundic gland-like polyps
	2. Proband or family member with either dysplastic FGPs or gastric adenocarcinoma
	3. Mutation in the chr5: 112,043,220–12,043,224 region of promoter 1B of APC**,***
Supportive criteria **(families in whom genetic testing could be considered)**	1. Family history (autosomal dominant pattern of inheritance)
	2. Spectrum of other histological lesions: hyper-proliferative aberrant pits (HPAPs), hyperplastic polyps, gastric type adenomas

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

** The point mutations that segregate with GAPPS (c.-191T>C, c.-192A>G and c.-195A>C) are all positioned within the Ying Yang 1(YY1) binding motif of the APC gene.

*** FAP has also been caused by these mutations. Although criteria for GAPPS means there is no colorectal polyposis, testing for 1b promoter variants should still be considered for patients with FAP that are APC negative - especially if they also have FGPs.

Hereditary Gastric Cancer Syndromes

Genotype or Phenotype – What matters most in GI cancers?

BOTH

Obrigada pela atenção