סרטן קיבה דיפוזי תורשתי – HDGC
האמנם עדיין ניתוח מניעתי או ביופסיות מרובות?

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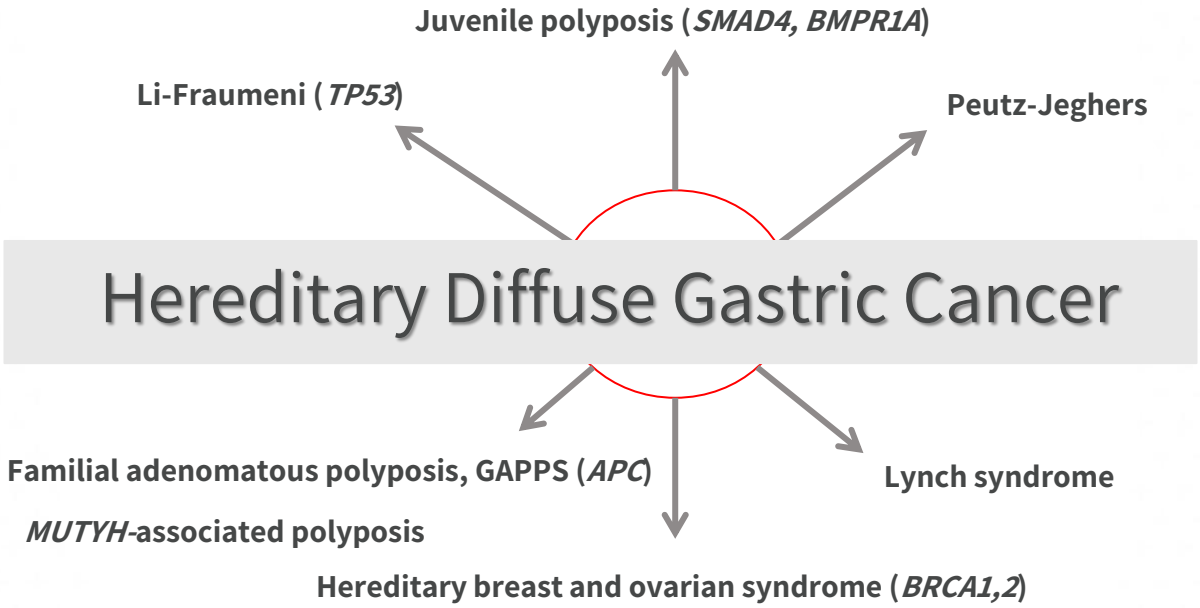
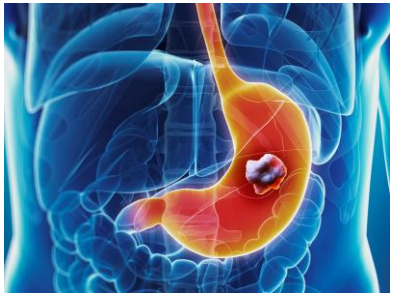
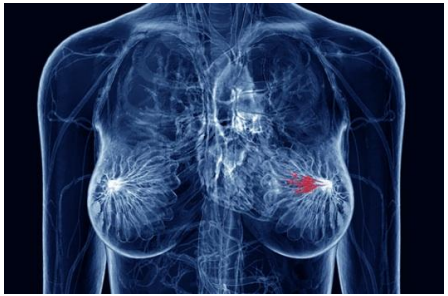
Syndromes associated with inherited gastric cancer



Hereditary Diffuse Gastric Cancer

Pathogenic variant in CDH1 or CTNNA1 genes





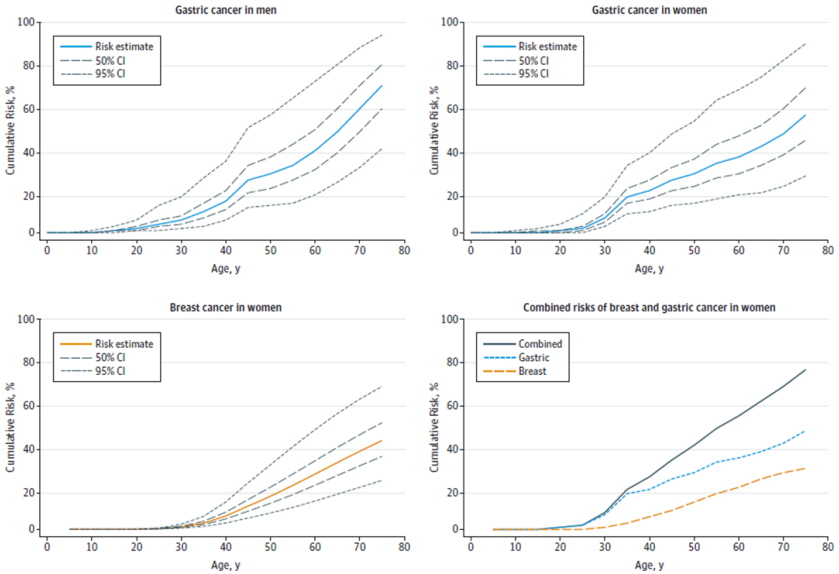
CDH1 encodes E-cadherin, a transmembrane protein that is localised to the adherens junctions in epithelial tissues and has functions in cell to cell adhesion, tension sensing, and signal transduction.

CTNNA1 – a new minor player. Encodes α catenin.

HDGC - epidemiology

- First described in 1998 in New-Zeland
- worldwide population incidence of 5–10 per 10^5 births
- Average age of gastric cancer onset – 38 years (14-69)
- Although the incidence of gastric cancer is higher in Japan and China, most of the CDH1 pathogenic variants have been reported in Europe and in New-Zeland Maori families
- No data published from Israel

Cancer risk in CDH1 mutation carriers



Hansford S et-al, JAMA oncol. 2015

The 2020 HDGC guidelines –IGCLC International Gastric Cancer Linkage Consortium

Hereditary diffuse gastric cancer: updated clinical practice guidelines

Vanessa R Blair, Maybelle McLeod, Fátima Carneiro, Daniel G Coit, Johanna L D'Addario, Jolanda M van Dieren, Kirsty L Harris, Nicoline Hoogerbrugge, Carla Oliveira, Rachel S van der Post, Julie Arnold, Patrick R Benusiglio, Tanya M Bisseling, Alex Boussioutas, Annemieke Cats, Amanda Charlton, Karen E Chelcun Schreiber, Jeremy L Davis, Massimiliano di Pietro, Rebecca C Fitzgerald, James M Ford, Kimberley Gamet, Irene Gullo, Richard H Hardwick, David G Huntsman, Pardeep Kaurah, Sonia S Kupfer, Andrew Latchford, Paul F Mansfield, Takeshi Nakajima, Susan Parry, Jeremy Rossaak, Haruhiko Sugimura, Magali Svrcek, Marc Tischkowitz, Toshikazu Ushijima, Hidetaka Yamada, Han-Kwang Yang, Adrian Claydon, Joana Figueiredo, Karyn Paringatai, Raquel Seruca, Nicola Bougen-Zhukov, Tom Brew, Simone Busija, Patricia Carneiro, Lynn DeGregorio, Helen Fisher, Erin Gardner, Tanis D Godwin, Katharine N Holm, Bostjan Humar, Caroline J Lintott, Elizabeth C Monroe, Mark D Muller, Enrique Norero, Yasmin Nouri, Joana Paredes, João M Sanches, Emily Schulpen, Ana S Ribeiro, Andrew Sporle, James Whitworth, Liying Zhang, Anthony E Reeve, Parry Guilford

Blair VR et al *Lancet Onc* August 2020

Cancer risk in CDH1 mutation carriers – actual numbers - 2020

Study	% families meeting genetic testing criteria	Subsets	Cumulative risk		
			Gastric cancer (males)	Gastric cancer (females)	Breast cancer
Pharoah *et al.*[1]	11/11 (100%)	-	**67%** (95% CI 39-99%)	**83%** (95% CI 58-99%)	**39%** (95% CI 12-84%)
Hansford *et al.*[2]	75/75 (100%)	-	**70%** (95% CI 59-80%)	**56%** (95% CI 44-69%)	**42%** (95% CI 23-68%)
Xicola *et al.*[3]	15/38 (39%)	-	**37·2%** (95% CI 8.7- 89.5%)	**24.7%** (95% CI 6.1- 68·9%)	**42·9%** (95% CI 33.4- 53.9%)
Roberts *et al.*[4]	14/41 (37%)	-	**42%** (95% CI 30-56%)	**33%** (95% CI 21-43%)	**55%** (95% CI 39-68%)
	4/9 (44%)	families with ≥3 gastric cancers	**64%** (95% CI 43-87%)	**47%** (95% CI 29-60%)	
	11/32 (34%)	families with ≤2 gastric cancers	**27%** (95% CI 15-41%)	**24%** (95% CI 12-36%)	

**insufficient evidence of increased risk of colorectal cancer

[1]Pharoah et al *Gastroenterol* 2001
[2]Hansford S et al *JAMA Oncol* 2015
[3]Xicola R et al *J Med Genet* 2019
[4]Roberts M et al *JAMA Oncol* 2019

Family history should be considered when estimating an individual carrier's risk.

Kupfer S, CGA-IGC meeting, 2020
Blair VR, Lancet oncol, 2020

Topics covered by the guidelines

- Genetic testing criteria
- Clinical practice recommendations
  - UGI endoscopy protocol
  - Histopathology
  - breast cancer
- Gastrectomy
- Long-term sequelae and follow-up

2020 genetic testing criteria

Family criteria

1) ≥2 cases of gastric cancer in family regardless of age, with at least one 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

Kupfer S, CGA-IGC meeting, 2020
Blair VR, Lancet oncol, 2020

Genetic counseling and testing

- Testing starting at age 16-18
- Where possible histopathological confirmation of cancer diagnoses or any precursor lesions should be taken
- Multidisciplinary discussion
  - benefits and risks of gastric and breast cancer surveillance and risk-reducing surgery, including the long-term sequelae of prophylactic total gastrectomy
- Uncertainty of incidental finding of pathogenic mutation by genetic panel when no FH exists

HDGC - definitions

- **Hereditary diffuse gastric cancer (HDGC)**
  CDH1 pathogenic or likely pathogenic (P/LP) variant in individual or family with 1 or more diffuse gastric cancer (DGC) in 1st & 2nd degree relatives
- **Hereditary lobular breast cancer (HLBC)**
  CDH1 P/LP variant in individual or family with 1 or more LBC in 1st & 2nd degree relatives *but no DGC*
- **HDGC-like**
  Families that fulfil HDGC criteria (1 or 2) but no identified P/LP *CDH1* or *CTNNA1* variants

Kupfer S, CGA-IGC meeting, 2020
Blair VR, Lancet oncol, 2020

Clinical practice recommendations

Management summary by syndrome

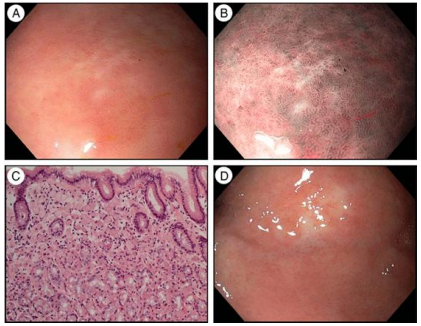
Syndrome	Management
HDGC	Consider prophylactic total gastrectomy (PTG) If no PTG, yearly endoscopic surveillance High-risk breast cancer surveillance or bilateral risk-reducing mastectomy
HBLC	Annual endoscopic surveillance Consider PTG (uncertain DGC risk) High-risk breast cancer surveillance or bilateral risk-reducing mastectomy
HDGC-like	Annual endoscopic surveillance for at least 2 years PTG only if positive biopsies Breast cancer surveillance individualized
CDH1 VUS	If personal or family history of DGC, lack of consensus about endoscopic surveillance PTG not recommended Breast cancer surveillance individualized
CTNNA1	Endoscopic surveillance PTG based on biopsies and/or penetrance of DGC in family Breast cancer surveillance individualized

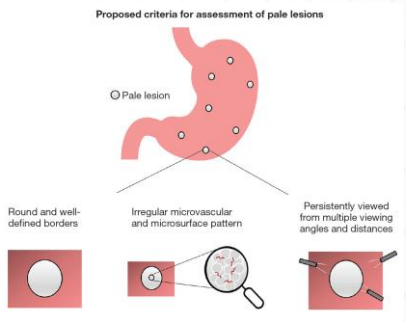
Biopsies (Cambridge protocol)

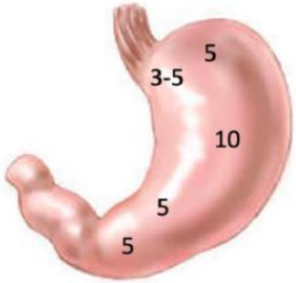
- Targeted and random biopsies:
  - Any endoscopically visible lesions including pale areas – NBI, magnification
  - Random sampling comprising five biopsies taken from each of the following anatomical zones:
    - Pre-pyloric area, antrum, transitional zone, body, fundus, cardia
  - Minimum 30 biopsies during 30 minutes
  - Random Bx appear better than targeted biopsies (39% vs. 3% in initial endoscopy; 50% vs. 26% in surveillance)

Mi, GI Endoscopy, 2018, Lee Lancet Oncol, 2023

- Test for HP







Prophylactic total gastrectomy

- Perform at age 20-30 till 70
- Onset of clinical cancer in probands, should be taken into account
- The surgical approach is not as important as the experience of the surgeon
- Total gastrectomy with intraoperative confirmation of esophageal and duodenal mucosa in margins
- Extended D2 lymphadenectomy is not needed
- A dormant period in which the signet ring cell adenocarcinoma does not spread may explain why many individuals are found to have T-1 N-0 stage tumors after prophylactic gastrectomy

Long-term sequelae and follow-up

- Mortality – 1%; morbidity – 100%
- Psychological, physiological and metabolic impact of a total gastrectomy
- Global quality-of-life scores recover to presurgery levels at around 12 months postoperatively
  - Maintaining weight
    - The median weight loss 1 year postsurgery is 10 kg.

Worster E. Ann Surg. 2014

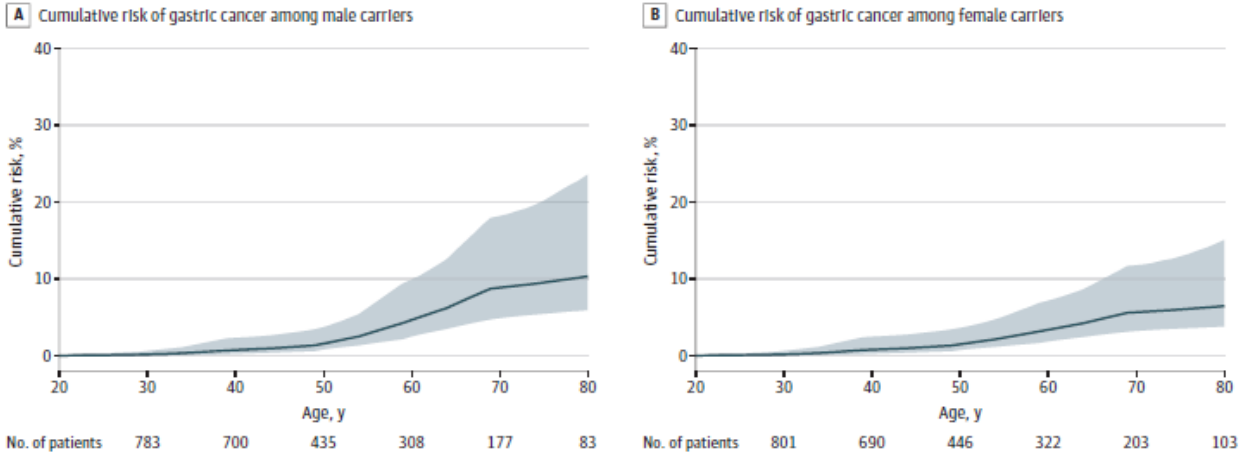
- Adjustments with regard to diet and nutrition postgastrectomy:

Interim conclusion 2020

Individuals with HDGC should be advised to consider *prophylactic gastrectomy*, regardless of endoscopic findings

HDGC 2025 – Lifetime risk of GC is lower than initial estimation

	Advanced gastric cancer[a]					Breast cancer in female carriers[b]		
		Male carriers		Female carriers				
Age, y	Hazard ratio (95% CI)	No.[c]	Cumulative risk, % (95% CI)	No.[c]	Cumulative risk, % (95% CI)	Hazard ratio (95% CI)	No.[c]	Cumulative risk, % (95% CI)
30	33.5 (9.8-112)	783	0.2 (0.1-0.6)	801	0.2 (0.1-0.6)	5.7 (2.5-13.2)	800	0.5 (0.2-1.2)
40	13.9 (4.4-42.6)	700	0.7 (0.3-2.3)	690	0.8 (0.3-2.5)	4.2 (2.2-7.9)	682	3.6 (1.9-7.4)
50	24.1 (8.4-67.9)	435	1.6 (0.8-3.7)	446	1.5 (0.8-3.6)	4.3 (2.3-8.1)	423	10.5 (6.9-16.9)
60	19 (5.7-59)	308	4.7 (2.5-9.9)	322	3.4 (1.9-7.2)	1.2 (0.4-3.6)	281	19.3 (13.7-28.6)
70	3.5 (0.4-30.3)	177	8.9 (4.9-18.2)	203	5.7 (3.2-11.8)	3.9 (1.1-13.7)	169	24.2 (18.3-35.5)
80	3.5 (0.4-26.2)	83	10.3 (6-23.6)	103	6.5 (3.8-15.1)	3.9 (1.1-13.7)	84	36.8 (25.7-62.9)



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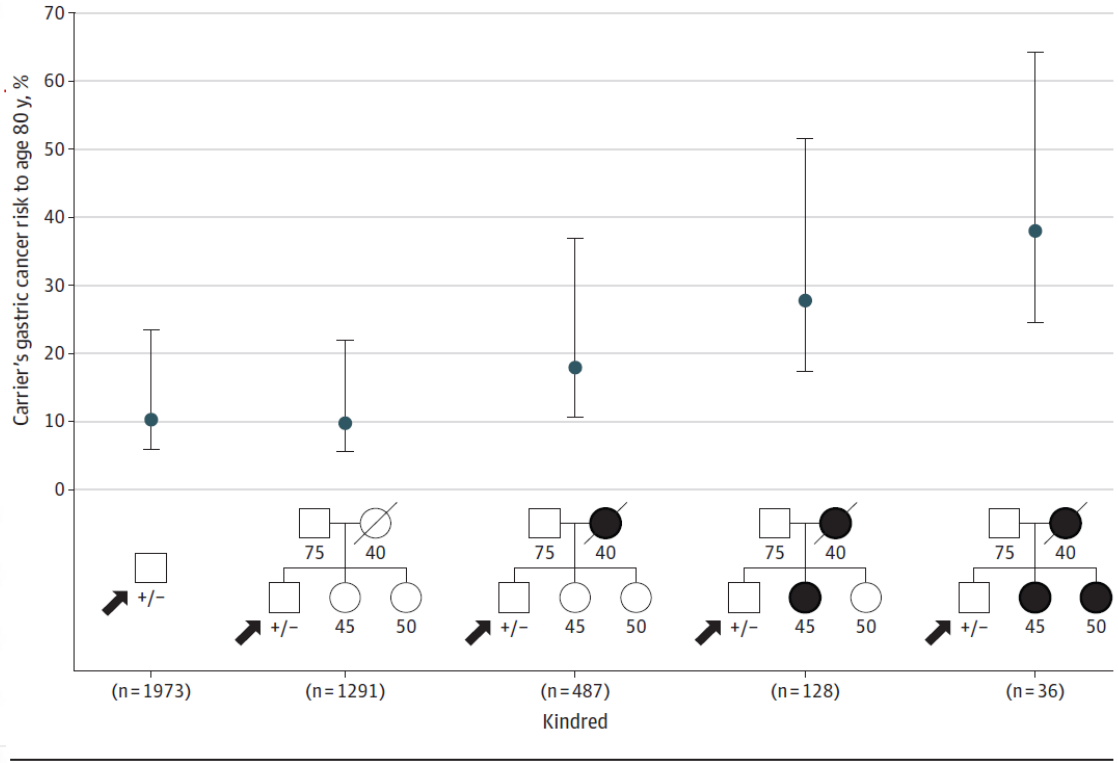
Ryan CE et-al JAMA, 2024

HDGC 2025 – Lifetime risk of GC is lower than initial estimation, and depend on family history



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Ryan CE et-al JAMA, 2024

HDGC 2025 –Surveillance appears to be safe and effective - EVIDENCE

Endoscopic surveillance with systematic random biopsy for the early diagnosis of hereditary diffuse gastric cancer: a prospective 16-year longitudinal cohort study

Colin Y C Lee, Adriaan Olivier, Judith Honing, Anne-Marie Lydon, Susan Richardson, Maria O'Donovan, Marc Tischkowitz, Rebecca C Fitzgerald, Massimiliano di Pietro

- 145 carriers
- Median f/u 51 months
- SRCC in 58 carriers:
  - Most were diagnosed by random biopsies
  - 22 continued surveillance
  - None with advanced cancer

Cancer surveillance as an alternative to prophylactic total gastrectomy in hereditary diffuse gastric cancer: a prospective cohort study

Bilal Asif*, Amber Leila Sarvestani*, Lauren A Gamble, Sarah G Samaranayake, Amber L Famiglietti, Grace-Ann Fasaye, Martha Quezado, Markku Miettinen, Louis Korman, Christopher Koh, Theo Heller, Jeremy L Davis

- 270 carriers
- Median f/u 31 months
- 120 underwent surveillance (including 51 with SRCC)
  - 2 had visible lesions
  - Gastrectomy – stage II cancer
  - 91/118 continued surveillance – no advanced cancer

Lee CYC, Lancet Oncol, 2023; Asif B, Lancet Oncol, 2024

HDGC 2025 – To biopsy or not to biopsy?

Enhanced endoscopic surveillance is safe and feasible for individuals with germline CDH1 P/LP variants, at least in the short term

T1a lesions are ubiquitously present in more than 95% of prophylactic total gastrectomy samples

Therefore, T1a signet ring cell carcinoma should be an expected finding on random endoscopic biopsy of normal-appearing gastric mucosa in HDGC patients

However, because the lifetime risk of developing advanced diffuse-type gastric cancer is 25–40%, most superficial T1a lesions supposedly display an indolent behavior

The goal of endoscopic surveillance should not be to find every single mucosal (pT1a) lesion, but rather to detect abnormal lesions that tend to infiltrate deeper towards the submucosa

Advanced gastric cancer (pT2 or greater) occurs in the setting of intramucosal signet ring cells **detected on the biopsy of a focal mucosal abnormality**

The biggest challenge is recognizing subtle mucosal changes and diagnosing a lesion when it is still restricted to the mucosa but shows features of tendency towards deeper infiltration. Effort should be put in inspection and taking multiple targeted biopsy samples from mucosal abnormalities

Ryan CE et-al JAMA, 2024; Davis JL et-al ASCO Percis Oncol, 2024; vd Post RL et-al, Lancet Oncol, 2023
Asif B, Lancet Oncol, 2024; Davis JL et-al ASCO Percis Oncol, 2024

HDGC 2025 – Appropriate target biopsies

Now, the paradigm has shifted to identification and targeted biopsy of gross mucosal abnormalities such as ulceration, abnormal pit patterns, and mucosal thickening that may indicate a progressing signet ring cell lesion

	Endoscopy	Histology
Type 1 (T1a)	Small lesions, mostly <0·5 cm; not-visible (random) or pale, roundish lesion; irregular	Superficial lesion in the top layer of the mucosa; well differentiated; predominantly
		some inflammatory or stromal reaction; increased proliferation; and usually wild-type p53 expression
Type 3 (≥T2)	Larger lesions (generally >1 cm) and not uniform focal tumour mass, ulceration, diffuse abnormal aspect with thickened rigid gastric folds	Increased atypia,high nucleus-to-cytoplasm ratio; infiltrative growth pattern; no signs of maturation; low mucin; loss of normal epithelium; increased proliferation; p53 often mutational pattern; and p16 might be positive

Table: Categorisation of endoscopic lesions and corresponding histology in hereditary diffuse-type gastric cancer

Should we continue with random biopsies???

conclusions

- HDGC is an autosomal dominant susceptibility for diffuse gastric cancer
- Women are also at risk for lobular breast cancer
- The cumulative risk of gastric cancer by age 80 years in families affected by DGC is lower than was previously thought
- Prophylactic total gastrectomy used to be the cornerstone of HDGC management, and still should be seriously considered for patients with alarming endoscopic findings, >T1a lesions or a strong family history
- Alternatively, endoscopic surveillance in expert centers is safe and effective with an effort towards multiple targeted biopsies, as well as random biopsies and should be continued even when signet ring cell lesions are detected by random mucosal biopsy

Thanks!

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