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Supplementary appendix

This appendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

Supplement to: Blair VR, McLeod M, Carneiro F, et al. Hereditary diffuse gastric cancer: updated clinical practice guidelines. *Lancet Oncol* 2020; **21:** e385–96.

Supplementary Table 1: Cumulative cancer risk in carriers of pathogenic *CDH1* variants

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%)[ψ]	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%)	

*Families with ≥3 cases of DGC. **2010 IGCLC genetic testing criteria. [#]2015 IGCLC genetic testing criteria.
[ψ]Remaining 5/9 families did not meet IGCLC criteria due to unknown gastric histotype (M. Roberts, pers. comm).

Supplementary Text 1: Endoscopy Surveillance Protocol

Endoscopy should be performed in centres with endoscopists experienced in HDGC surveillance. A repeat endoscopy within 4-6 weeks is advised if the endoscopist suspects infiltrating lesions but histological outcome is negative.

The endoscopy should be performed using a white-light, high definition endoscope in a dedicated session of at least 30 minutes to allow for careful inspection of the mucosa on repeated inflation and deflation and for collection of biopsies. Before examination, the mucosa should be thoroughly cleaned with water combined with an antifoaming agent, such as simethicone. If required, mucolytics, such as N-acetylcysteine, can be used.

Given the procedure's length, propofol is preferred for moderate sedation to ensure patient comfort. Moderate sedation using midazolam, fentanyl, and/or other agents, or no sedation, is also possible if the patient is able to tolerate the 30-minute procedure.

Although an association between *H. pylori* infection and HDGC has not been proven, it is important to test for *H. pylori* to document the prevalence of infection. Since *H. pylori* is a WHO class 1 carcinogen, it is agreed that it should be eradicated when detected, especially in variant carriers opting for surveillance.

Little is known about the risk related to ectopic gastric mucosa in the proximal esophagus (inlet patches) in *CDH1* mutation carriers. Although there is a theoretical chance of developing SRCC lesions within inlet patches, which are prevalent in 1-12% of the general population, we are not aware of any reports of proximal oesophageal diffuse type adenocarcinoma in *CDH1* mutation carriers.[5] We would recommend systematically inspecting, reporting and biopsying inlet patches to increase knowledge on this subject.

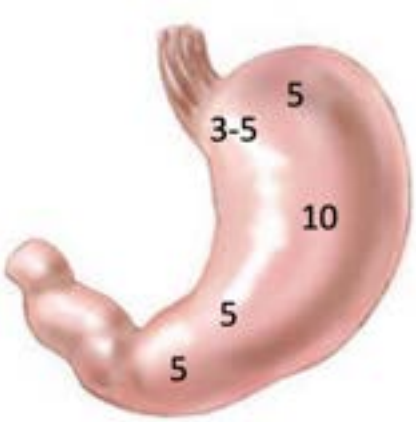
Distensibility
Prior to examination for visible mucosal abnormalities, the stomach should be assessed for distensibility. To assess for distensibility, the stomach should be maximally insufflated and then deflated using CO_2 or air. In cases of infiltrative disease, so-called '*linitis plastica*', the stomach becomes stiff, rigid and lacks typical distensibility with thickened or swollen appearance of the rugal folds. Any of these findings should prompt biopsies and further imaging - a high-resolution multidetector CT scan combined with endoscopic ultrasonography is suggested to visualise the gastric wall layers. No objective measures of distensibility are available, but this is an area that may warrant further research. In cases of *linitis plastica*, it is not uncommon that superficial biopsies are reported negative for cancer; therefore, deeper biopsies with bite-on-bite technique are advised for cases with suspected diffuse infiltration.

Targeted biopsies
The macroscopic appearance of the gastric mucosa, especially any focal visible lesion, should be recorded using still images or video for future reference. Prior to the collection of random biopsies, focal lesions should be sampled in a targeted manner for histology. A number of SRCC endoscopic findings have been described including pale lesions, erosive lesions, and subtle changes in vascular pattern. Superficial SRCC lesions can be seen in endoscopy as well-delineated, non-elevated pale lesions, first described by Shaw et al.[6] Two recent reports show that targeted biopsies can result in detection of SRCC foci in 28%-43%[7] (and Van Dieren, pers. comm) of patients, although smaller series have also reported no visible lesions.[8-12] The use of contrast enhancing techniques, such as narrow band imaging, optical enhancement or i-scan, is recommended as they enhance the visibility of these lesions.[7, 13] Infiltration of deeper wall layers can be associated with erosive lesions and subtle changes in the vascular pattern which is better appreciated on contrast enhanced magnification. The use of confocal endoscopic microscopy is currently under investigation.[14] Until evidence for its utility is produced it should only be used as part of research protocols. As noted in the previous guidelines, chromoendoscopy with Congo-red and methylene blue is no longer recommended due to theoretical concerns over toxicity.

Random biopsies
The yield of random biopsies varies substantially across different cohort studies (9-50% of surveilled mutation carriers.[7-10, 13 12, 15] Fujita *et al* estimated that for a 90% detection rate, 1768 random biopsies would be needed per patient to capture at least one single SRCC focus.[16] A disadvantage of taking extensive biopsies is the formation of scars that may hinder further recognition of SRCC lesions. The working group believes that a further increase of current detection rates should not come from the increase of random biopsies, but from a better recognition of SRCC lesions. The latter will also contribute to eliminating endoscopically missed advanced cancers. Centres that have demonstrable experience identifying SRCC lesions can consider limiting

the number of random biopsies during follow-up when baseline random biopsies according to protocol do not reveal any abnormalities.

The 2015 guideline recommended a minimum of 30 random biopsies (five from each of the following anatomical zones: pre-pyloric, antrum, transitional zone, body, fundus and cardia). However, several studies reported that SRCC lesions in the stomach body were more commonly missed compared to the antrum, transition zone and fundus.[6, 7, 13] This is likely due to the body's larger and folded surface area. Therefore, the current consensus is to obtain - spread over all quadrants – three-five biopsies from the cardia and five from each of the fundus, transition zone and the antrum, as well as ten biopsies from the body.



Supplementary Fig. 1. Recommended number and locations of random biopsies

Expert centres

Many countries have a limited number of established expert centres or reference centres for HDGC families. However, it is acknowledged that geographic location and health care systems may impact how *CDH1* carriers are managed. We would recommend that patients are surveilled and treated in an expert centre.[17] If this is not possible, for example due to country geography, experts should be involved or consulted in the diagnosis and management of HDGC families.

Supplementary Table 2: Summary of guidelines on management of breast cancer risk

	EviQ Australia	**ESMO Europe**	**NICE United Kingdom**	**NCCN United States**
Date/update	Updated 2019	2016	2013, Updated 2019	Updated 2019
Starting age	30yrs	20-30yrs	30yrs	30yrs
Clinical breast examination	Recommended	Every 6-12 months From age 20-25yrs		Every 6-12 months
Breast awareness	Encourage breast self-awareness and report changes	Encourage breast self-awareness and report changes	Women at increased risk should be 'breast aware' in line with advice for all women	
MRI **Mammogram* +/- tomosynthesis**	>30 yrs annual MRI +/- mammogram MRI may be superior for detection of LBC	20-29yrs: annual MRI 30-75yrs: annual MRI and/or mammogram	30-39yrs: offer annual MRI *and* consider annual mammography* 40-49yrs: offer annual MRI *and* annual mammography >50yrs: Do not offer annual MRI unless mammogram has shown a dense breast pattern	30yrs: consider breast MRI with contrast** Annual mammogram; consider tomosynthesis
Ultrasound	+/- ultrasound	Generic statement***: Ultrasound may be considered as an adjunct to mammography at all ages and as an alternative when MRI is not available. In women <30yrs – breast ultrasound can be considered if MRI unavailable.	Generic statement***: Do not routinely offer, but consider it when MRI is not suitable (e.g claustrophomia, contrast reaction, renal impairment), or when results of MRI or mammogram are difficult to interpret	
Bilateral risk reducing mastectomy (BRRM)	May be considered	May be considered	Bilateral mastectomy should be raised as a risk-reducing strategy option with all women at high risk	Evidence insufficient, manage based on family history[#]

*Recent evidence questions whether mammogram at the same time as MRI adds value. Mammography < 40 years should take into consideration breast density - see text.
**NCCN: May be modified based on family history, typically beginning 5–10 years earlier than youngest diagnosis in family but not later than stated in the table.
*** Generic advice for all women at high risk of breast cancer – no discussion of LBC phenotype.
# For women with pathogenic/likely pathogenic variants who are treated for breast cancer and have not had bilateral mastectomy, surveillance should continue as described.

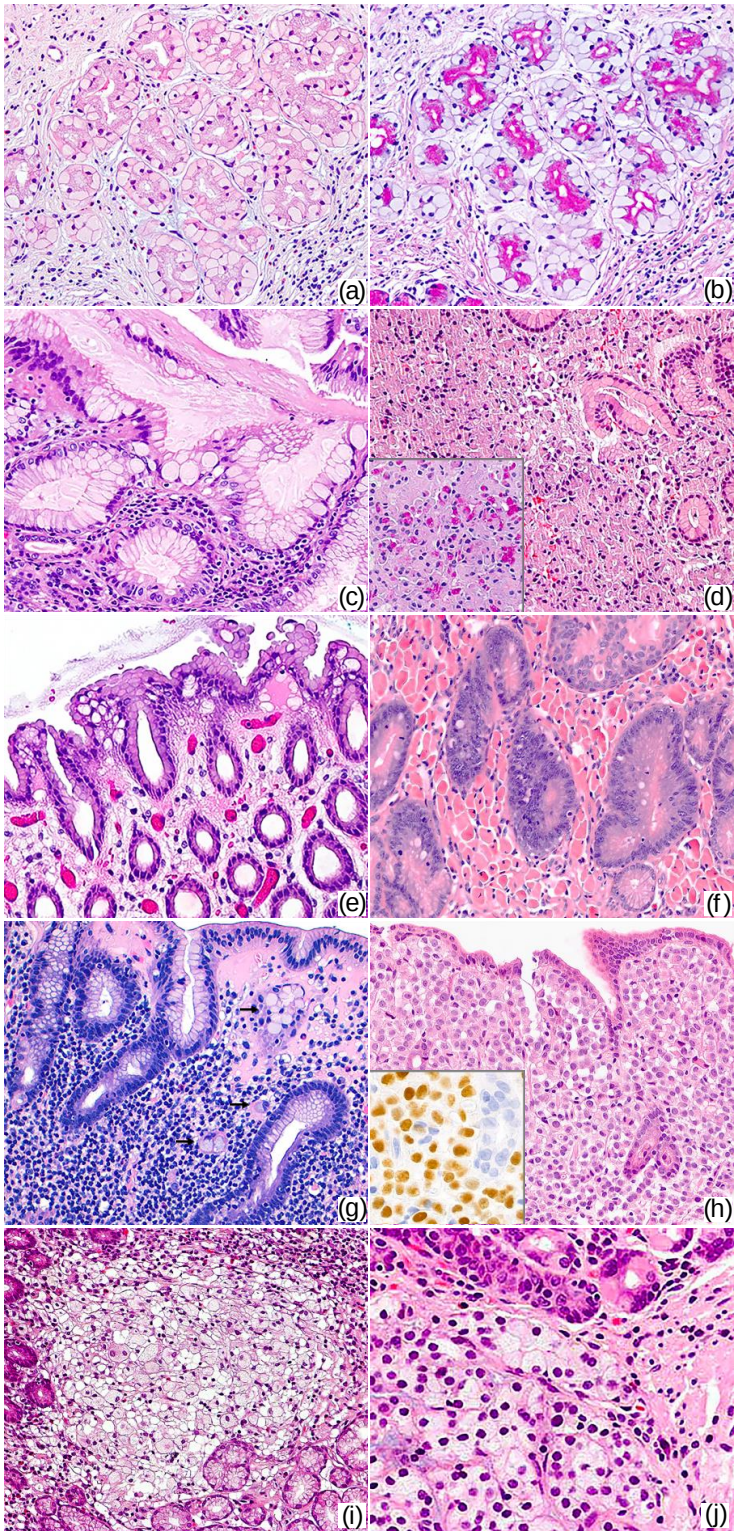
Supplementary Text 2: Surgery and recovery

Reconstruction of the GI tract is usually performed with a Roux Y diversion of the pancreaticobiliary contents 40-50 cm downstream from the esophageal anastomosis to avoid chronic bile reflux. The length of the Roux limb can be made longer for morbidly obese patients to facilitate optimal postoperative weight loss. Mesenteric defects should be closed to minimise the incidence of internal bowel herniation. The use of non-absorbable sutures is recommended, although formal evidence to support this is not yet available. Other surgical details, such as positioning the Roux limb relative to the colonic mesentery, the use of a jejunal pouch, and the technique of the esophagojejunal anastomosis should be left to the clinical discretion of the operating surgeon. On rare occasions, if access to the duodenum is required for endoscopic surveillance, a retrocolic isoperistaltic jejunal interposition may be used. Although somewhat controversial and often subject to individual surgeon preference, the practice of routinely inserting decompressing naso-enteric tubes and/or jejunostomy feeding tubes is not generally supported by prospective randomised clinical trials.

Adequate opioid-limiting pain control is the bedrock of uncomplicated recovery, enabling adequate pulmonary recruitment, and early ambulation. Oral intake can generally begin on the first postoperative day and advance as the patient and clinician judge appropriate. Contrast upper GI series are not mandatory prior to initiation of oral intake, but should be performed if there is clinical suspicion of an anastomotic leak. Other potential early complications should be aggressively screened for, recognised, and managed early, to minimise their impact on recovery.

There appears to be slightly increased risk of subsequent cholelithiasis in patients who have undergone gastrectomy compared to a case matched non-gastrectomy control population.[18] Among several series with relatively short follow-up, the absolute risk of cholelithiasis after gastrectomy is estimated at around 3.5-12%, with the risk of symptomatic cholecystitis estimated to be one quarter to one third that population. The incidence of post-gastrectomy cholelithiasis appears to be consistently higher after total compared to subtotal gastrectomy.[19-21] One underpowered trial of prophylactic cholecystectomy at the time of gastrectomy concluded that one would need to perform more than 32 prophylactic cholecystectomies to prevent one episode of symptomatic cholecystitis.[22] At present, the data are not strong enough to support a recommendation for routine prophylactic cholecystectomy at the time of prophylactic total gastrectomy.

A word about the impact of serious postoperative complications unique to the setting of elective prophylactic surgery is appropriate. The incidence of these complications, how they are managed, and the ultimate outcome affect not only the patient sustaining the complication, but also impact the decision making of other family members contemplating similar surgery.



Supplementary Fig. 2. Mimickers and pitfalls of HDGC. (a) Glassy cell change (HE) and (b) PAS-D staining: the glassy vacuole is negative, while the luminal portion of the cytoplasm is positive. (c) Globoid change of foveolar epithelium. (d) Artifactual pseudo-SRCs induced by procedural trauma; inset (PAS-D staining) shows scattered positive mucopeptic cells. (e) Vacuolisation of superficial epithelium, with globoid change and tufting of foveolar cells. (f) Russel bodies gastritis. (g) Isolated and clustered pseudo-SRCs (arrows) in the context of chronic gastritis. (h) Metastatic lobular breast cancer; inset shows immunoreactivity for estrogen receptor. (i) Xanthomatous cells. (j) Neuroendocrine tumour.

Supplementary Text 3: Protocol for macroscopic examination and sampling of *CDH1* mutation-related gastrectomy specimens

Total gastric mucosa embedding and mapping is the gold standard for pathology examination and is pivotal to to determine the stage of cancer and additionally to better understand the phenotype and biology of *CDH1* mutation-related gastric cancer. However, experience in the examination of prophylactic gastrectomies for HDGC is quite limited in many pathology departments due to the rarity of these surgical specimens. Additionally, the routine workload may be incompatible with performing the detailed examination of hundreds of sections typically obtained after totally embedding these stomachs. Actually, total gastric mapping requires approximately 120-270 blocks (a higher number of blocks has even been described in some studies[23]), with up to three slices per block resulting in an average of 9.6m of mucosa to examine per gastrectomy.[16, 24] As an approximation, total gastric mucosa embedding consumes ten-fold the resources compared to a conventional gastrectomy specimen. The resources are mainly in staff time required for mapped macroscopic dissection, laboratory embedding and cutting, and pathologist time required to examine the slides and map microscopic lesions to the macroscopic photo. To address these shortcomings, a three level protocol for pathological examination of gastrectomy specimens, depending on availability of resources, is herein proposed (Supplementary Table 4).

Macroscopic examination and sampling of prophylactic gastrectomies should follow specific protocols. Begin with painting the margins or removing the margins before fixation. Then dissect the omentum and retrieve lymph nodes. Fresh gastrectomy specimens should be opened along the greater curve and pinned onto a cork board. A life size specimen photo should be used as a template to identify the exact location of the tissue blocks. The collection of fresh tissue samples from any macroscopic lesion and normal looking mucosa should be considered for research purposes. Overnight fixation in buffered formalin is recommended before sampling for routine histopathology, including any macroscopically abnormal areas such as pale lesions. Sections of the margins should be taken and labelled. The remainder of the stomach should be sectioned according to the level selected for pathological examination depending on availability of resources (see Supplementary Table 4). Regardless of the selected protocol, each section (2 cm x 0.3 cm, full thickness) is blocked (paraffin-embedded). The location of each section should be marked on the map of the stomach. Any macroscopic lesions identified should be precisely localised within the map. An alternative for pathologists experienced in the method is to use an adaptive version of the Swiss roll technique.[25] With this technique, the gastrectomy should only be fixed briefly, for 2-3 hours, after which the mucosa is dissected from the submucosa and muscle layers. Another technique is to use giant histological sections with the whole-mount technique, also called large-format histology. This method will save time and blocks, as each stomach is represented in approximately 25 blocks. The histological examination should be made using a checklist focusing on the items listed in Supplementary Table 3.

Regardless of the level selected for pathological examination depending on availability of resources, the minimum examination of a macroscopically normal gastrectomy should include: 1. Proximal and distal margins to confirm all the gastric mucosa has been resected. 2. All lymph nodes should be sampled as per a usual gastrectomy. 3. Photograph. 4. Mapped sampling from all zones: antrum, transitional zone (*incisura angularis*), body, and fundus. 5. If no foci of carcinoma are found, then to go back to the specimen and take more blocks. If no foci of SRCC are found, the gastrectomy should not be reported as negative for carcinoma, but as 'no carcinoma found in xx% of the mucosa examined'.

The pathology of HDGC and HLBC is unique and expertise is needed to provide high quality diagnosis, both in biopsies and in resection specimens. In order to increase the experience of pathologists and the accuracy of the diagnosis, it would be useful to build a free, online open-access digital slide bank of the different types of lesions observed in the setting of *CDH1*-related cancer. The use of (scanned) slides to be submitted for evaluation by experienced pathologists in the field should be seriously considered.

In the event of a lack of pathologist experience in dealing with these cases, or restricted time available due to the pathologist's workload and laboratory resources, the entire formalin-fixed gastrectomy or mastectomy specimen can be sent to an experienced pathology laboratory. An alternative option is to totally embed the stomach or breast, perform H&E and PAS-D stain on all blocks and send the slides and blocks to an experienced centre for specialist pathology reporting. If these alternative strategies are not feasible, and it is not possible to totally embed the gastric (or breast specimen), this should be communicated to clinicians and the patient.

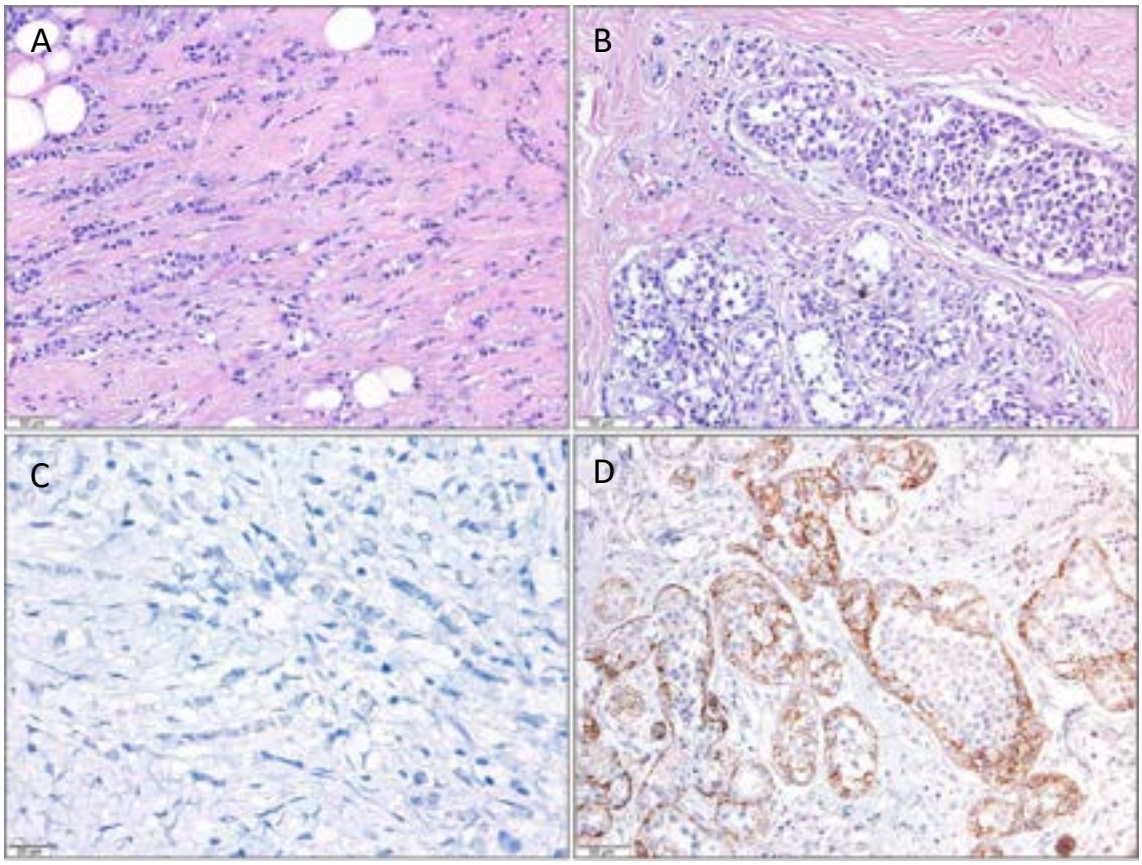
Supplementary Table 3: Checklist for reporting of prophylactic gastrectomy specimens

(1) Features of ≥pT1b carcinoma(s)	Growth pattern (diffuse infiltration versus localized tumour) Anatomic location (cardia, fundus, body, transitional zone, antrum) Measurements Histological type according to WHO 2019 and Laurén's classifications Lymphatic, venous and neural invasion (present or absent) TNM stage
(2) Features of intraepithelial precursor lesions and intramucosal (pT1a) signet ring cell carcinoma	Number of lesions Anatomic location (cardia, fundus, body, transitional zone, antrum) Measurements Aggressive features: pleomorphism, loss of mucin, spindle cells, small cells, mitoses Stromal reaction related to lesions: desmoplasia; lymphocytic, eosinophilic or granulomatous inflammatory reaction Surgical margin status (proximal oesophageal, distal duodenal mucosa, including donuts), to confirm there is no residual gastric mucosa and no tumour at margins. Lymph node status
(3) Non-neoplastic mucosa: changes more commonly seen in this condition	Tufting/ hyperplastic mucosal changes Surface epithelial vacuolisation Globoid change
(4) Other findings in surrounding mucosa	Inflammation (acute, chronic, erosion, ulceration) *Helicobacter pylori* Intraepithelial lymphocytes Lymphoid infiltrates Glandular atrophy Intestinal metaplasia Adenomatous dysplasia Hyperplastic polyps Fundic gland polyps

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.



Supplementary Fig. 3. Lobular breast cancer. (A) Invasive lobular breast cancer. (B) Lobular carcinoma *in situ*. Loss of E-cadherin immunoexpression is shown both in the invasive (C) and *in situ* (D) components.

Supplementary Table 5: HDGC emerging research areas divided into sections based on patient groups with different genetic risk factors

Emerging Research Areas	
Carriers of likely pathogenic and pathogenic variants in CDH1 or CTNNA1	
Main Topic	**Sub-topics**
Penetrance and risk prediction analysis	• Establish cancer registries combining clinical, phenotypic, pathological, and molecular data. A database on the likely pathogenicity of known germline *CDH1* variants is currently under construction (contact Carla Oliveira, on behalf of the European Reference Network GENTURIS at carlaol@ipatimup.pt). • Study extended family pedigrees to understand variant-specific penetrance and variant-specific disease phenotypes • Evaluate environmental and physiological risk factors • Identify genes that modify *CDH1* mutation penetrance • Evaluate gastric cancer risk in families with no history of DGC
Genotype-phenotype correlations	• Understand differences and similarities between *CDH1*- and *CTNNA1*-associated disease phenotypes • Further investigate the gastric and breast cancer histological and molecular subtypes associated with *CDH1* and *CTNNA1* deleterious variants • Identification of congenital malformations or other non-cancer phenotypes • Correlation of cancer-phenotypes and non-cancer phenotypes with variant molecular type (truncating *vs* missense)
Somatic events and triggers of cancer development	• Correlation of numbers of precursor, indolent SRC foci, and aggressive SRC foci with risk of progression • Identification of the cell compartment (differentiated *vs* progenitor *vs* stem cells) where cancer initiates • Identification of genetic, epigenetic and environmental triggers of transition from intramucosal *foci* to deeper, invasive cancer • Frequency of *H. pylori* infection and associated strains
Cancer diagnosis, chemoprevention, and treatment	• Identification of early diagnostic biomarkers • Evaluation of the potential of gene replacement as a germline therapy • Evaluation of the potential of synthetic lethality as a chemoprevention approach
Cancer surveillance and risk reduction measures	• Definition of cost-effective surveillance methodologies and their periodicity • Determination of the age-range of onset for DGC and LBC to optimise the timing for risk reduction interventions • Determining patient factors in choosing surveillance vs. surgery • Assessing quality of life; psychological interventions and outcomes
Gastroenterology/Pathology	• Determination of whether CRC is a minor part of the *CDH1* and/or *CTNNA1* spectrum, and if yes, its histological type
Long term follow-up: Nutrition post-gastrectomy	• Relationship between diet, nutrition, drug absorption, changes in body composition and quality of life
Pharmacology	• Impact of gastrectomy on uptake of common medications including SSRIs, SERMs, and anti-inflammatories.
Carriers of variants of unknown significance (VUS)	
Main Topic	**Sub-topics**

Variants of unknown significance in *CDH1 and CTNNA1*	For missense variants, regulatory or deep intronic variants, large gene duplications, and full-gene deletions: • Classification according to their impact on: (i) normal splicing, (ii) transcription, and (iii) protein function • Validation and standardisation of methodologies for *in silico, in vitro* and *in vivo* molecular analysis
Families meeting HDGC genetic testing criteria but lacking clinically-relevant variants in CDH1 or CTNNA1	
Main Topic	**Sub-topics**
Novel disease causative events	• Alternative loss of function mechanisms affecting *CDH1* and *CTNNA1*, such as epimutations or defects in regulatory regions • Alternative genes to *CDH1* and *CTNNA1* • Somatic mosaicism associated with *CDH1* and *CTNNA1* loss of function
Surveillance endoscopy	• Risk estimation and benefit of endoscopic surveillance
All patient groups	
Main Topic	**Sub-topics**
Improved endoscopic methods	• Confocal endoscopy • Artificial intelligence • Measurements of resistance of the gastric wall for detection of (larger) submucosal infiltrative lesions
Model systems	• Development of pre-clinical and clinical models to better estimate risk and inform surveillance strategies

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