Hereditary diffuse gastric cancer: updated clinical practice guidelines

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Hereditary diffuse gastric cancer (HDGC) is an autosomal dominant cancer syndrome that is characterised by a high prevalence of diffuse gastric cancer and lobular breast cancer. It is largely caused by inactivating germline mutations in the tumour suppressor gene *CDH1*, although pathogenic variants in *CTNNA1* occur in a minority of families with HDGC. In this Policy Review, we present updated clinical practice guidelines for HDGC from the International Gastric Cancer Linkage Consortium (IGCLC), which recognise the emerging evidence of variability in gastric cancer risk between families with HDGC, the growing capability of endoscopic and histological surveillance in HDGC, and increased experience of managing long-term sequelae of total gastrectomy in young patients. To redress the balance between the accessibility, cost, and acceptance of genetic testing and the increased identification of pathogenic variant carriers, the HDGC genetic testing criteria have been relaxed, mainly through less restrictive age limits. Prophylactic total gastrectomy remains the recommended option for gastric cancer risk management in pathogenic *CDH1* variant carriers. However, there is increasing confidence from the IGCLC that endoscopic surveillance in expert centres can be safely offered to patients who wish to postpone surgery, or to those whose risk of developing gastric cancer is not well defined.

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Introduction

Hereditary diffuse gastric cancer (HDGC) is a cancer syndrome characterised by a high prevalence of diffuse gastric cancer (DGC) and lobular breast cancer (LBC). HDGC was first described in an extended New Zealand Māori family in 1998,[1] and is now estimated to have a worldwide population incidence of 5–10 per 100 000 births. Most confirmed HDGC cases are caused by inactivating germline mutations in the *CDH1* tumour suppressor gene.[2] *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.[3] Mutations in a second adherens junction protein, α-catenin (*CTNNA1*), are also found in a small minority of HDGC cases.[4]

In the past 5 years the genetic testing landscape has been changing, with lower costs, increased accessibility, more public awareness, and greater adoption of cancer gene panels, particularly for breast cancer. For the *CDH1* gene, this change has led to the increased identification of genetic variants in individuals with a family history of breast cancer but little or no family history of gastric cancer, challenging the existing DGC-centric genetic testing criteria.[5] This changing landscape, combined with deeper experience of both HDGC endoscopic surveillance and long-term follow-up after gastrectomy, has demanded an update to the previous International Gastric Cancer Linkage Consortium (IGCLC) management guidelines for HDGC published in 2015.[6]

Guideline development

From March 16 to 18, 2019, a group of 19 genetic researchers, seven pathologists, ten gastroenterologists, seven breast and gastric surgeons, seven clinical geneticists and genetic counsellors, a pharmacist, and 13 HDGC advocates or family members met in Wānaka, New Zealand to update the IGCLC guidelines and identify areas of emerging research in this field. The shared vision was to build a consensus for HDGC management that was tightly connected to the experience of families with HDGC. The group was identified through prior IGCLC engagement and active involvement in HDGC research, management, or advocacy. Focus groups reviewed new data and identified required updates to the guidelines and research priorities. After the Wānaka meeting, expert writing panels (geneticists, gastroenterologists, pathologists, surgeons, and advocates) achieved consensus within their specialties and drafted the manuscript. Because of the relatively low incidence of HDGC, randomised clinical trial data specific to HDGC are scarce. Therefore, as for other rare diseases, the recommendations in these guidelines have relied on consensus expert opinion, anecdotal evidence from experts, and observational studies, instead of using trial data.[7,8] Therefore, the strength of the evidence for our recommendations is categorised as low to moderate according to the Grading of Recommendations, Assessment, Development, and Evaluation system.[9] This categorisation means that further research is likely or very likely to have an important impact

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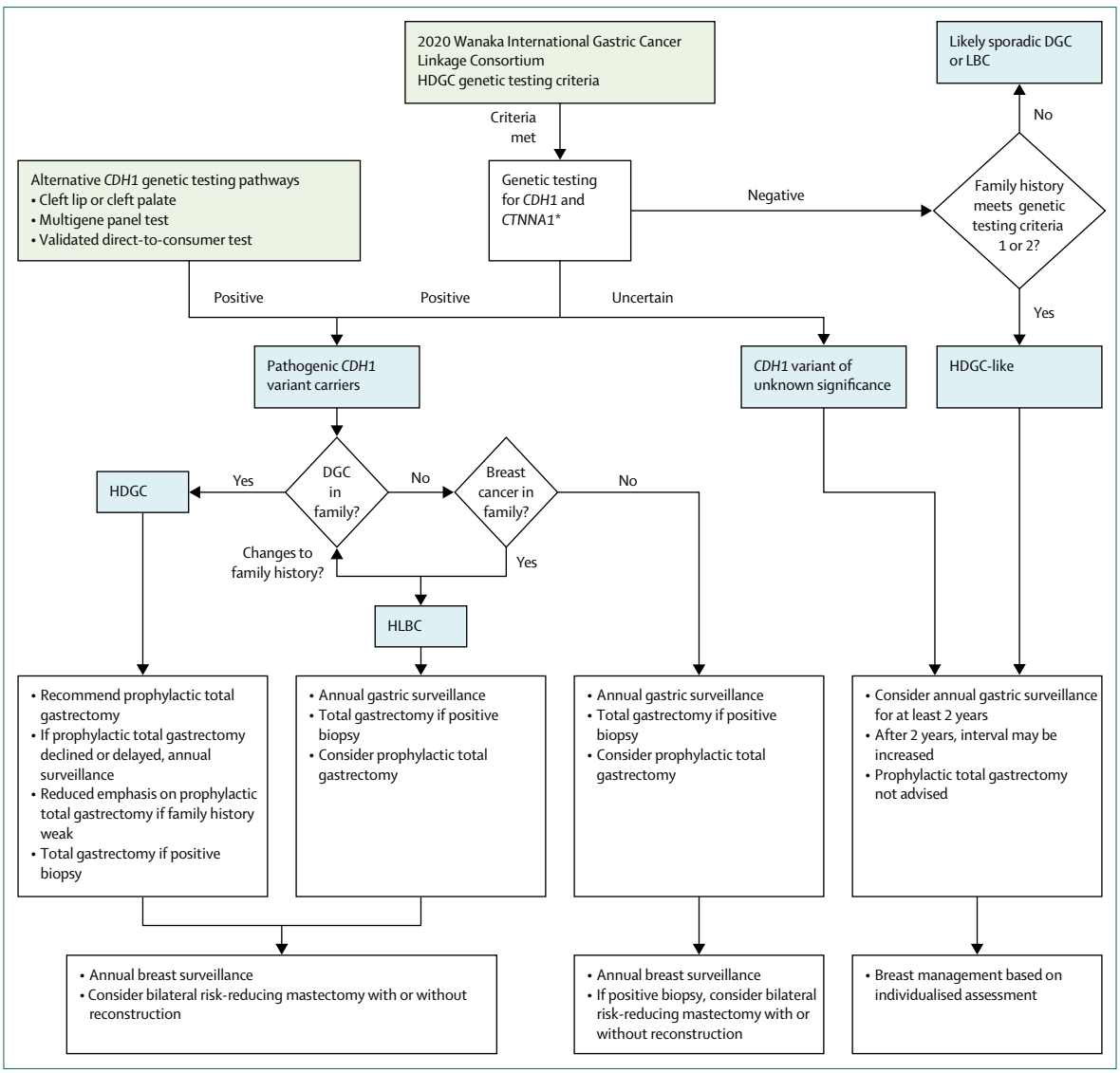

Figure 1: **Management of individuals and families who either meet the revised HDGC genetic testing criteria or have had a pathogenic *CDH1* variant identified through another route**

DGC=diffuse gastric cancer. HDGC=hereditary diffuse gastric cancer. LBC=lobular breast cancer. HLBC=hereditary lobular breast cancer. *See text for full description of *CTNNA1* pathway.

on our confidence in the estimate of the effect addressed by the recommendation.

Scope

These guidelines address the management of individuals and families who meet the revised genetic testing criteria for HDGC, and individuals with a pathogenic or likely pathogenic *CDH1* or *CTNNA1* variant[10] identified through other routes, including direct-to-consumer testing (figure 1). The management of sporadic DGC and LBC, familial intestinal gastric cancer,[11] gastric adenocarcinoma and proximal polyposis of the stomach, and familial gastric or breast cancer associated with other predisposition genes, is not covered in this update.

Definitions

In this Policy Review, the term pathogenic variant refers collectively to both likely pathogenic and pathogenic variants.[12] Rather than using a clinical definition, HDGC is now defined by the presence of a pathogenic germline *CDH1* or *CTNNA1* variant in either an isolated individual with DGC, or in a family with one or more DGC cases in first-degree or second-degree relatives. Similarly, hereditary lobular breast cancer (HLBC) is defined in this context by the presence of a pathogenic *CDH1* variant in either an isolated individual with LBC, or a family with one or more LBC cases in first-degree or second-degree relatives, but no known DGC in either situation. By definition, families with HLBC are recategorised as

having HDGC if DGC (or a precursor lesion of HDGC)[13] is identified in a family member at a later date. The distinction between HDGC and HLBC acknowledges the likelihood that not all families with pathogenic *CDH1* variants are equally at risk of DGC.[14,15] Families that are considered to be HDGC-like fulfil HDGC genetic testing family criteria 1 or 2 (panel 1), but have no identified pathogenic *CDH1* or *CTNNA1* variant. Thus, families must have at least one confirmed case of DGC, and another gastric cancer or LBC in first-degree or second-degree relatives, to be classified as being HDGC-like.

Genetic testing and penetrance

HDGC genetic testing criteria

Genetic testing criteria must balance health-care-related costs, public acceptance of the test, and the psychological burden imposed on the tested population, against the benefit of identifying more asymptomatic individuals at high risk. Accordingly, the 2020 HDGC genetic testing criteria have been relaxed, mainly through changes to age restrictions (panel 1). For example, the HDGC screening threshold age for isolated DGC cases is increased from younger than 40 years to younger than 50 years. Similarly, the threshold age for testing of women with bilateral LBC is increased from younger than 50 to younger than 70 years, with an expected yield of pathogenic *CDH1* variants of approximately 7%.[16] Furthermore, because approximately 13% of the New Zealand Māori population with advanced DGC have pathogenic germline *CDH1* variants,[17] all Māori with confirmed DGC are now recommended to undergo *CDH1* genetic testing. The 2015 criteria that recommended testing in individuals with a personal or family history of cleft lip or cleft palate and DGC,[18] or with HDGC precursor lesions, remain.[6] Individuals who meet the criteria for HDGC genetic testing should first have *CDH1* analysed and, if no variant is identified, be considered for *CTNNA1* analysis.

In Japan and South Korea, it is recommended that the Japanese Gastric Cancer Association classification[19] of signet ring cell carcinoma is used for DGC instead of the Lauren classification of DGC.[20] Index cases from families with newly identified HDGC who present with advanced gastric cancer can, however, display features of the non-solid type poorly differentiated adenocarcinoma subclass. Patients with multiple signet ring cell carcinoma lesions, identified either endoscopically or in the gastrectomy specimen, are also recommended to be offered *CDH1* genetic testing.

Genetic counselling

In individuals meeting genetic testing criteria, testing should be offered from the legal age of consent (generally 16–18 years). Testing of younger family members can also be considered based on family history.[21] Where possible, genetic counselling for HDGC and HLBC should include evaluation of a three-generation family history, any history of cleft lip or cleft palate, and histopathological confirmation of cancer diagnoses or any precursor lesions. Counselling should pay particular attention to the individual's psychosocial needs.[22] Counsellors should help patients to understand the importance of disclosing their diagnosis to family members at risk, and offer assistance to implement a communication plan. It can be helpful to meet with the wider family to discuss different perspectives and ensure consistent information is given to other family members.

Comprehensive, multidisciplinary discussion around the benefits and risks of gastric and breast cancer surveillance and risk-reducing surgery, including the long-term sequelae of prophylactic total gastrectomy, is required.[6] Most individuals who have undergone this surgery express little or no regret afterwards.[23–25] Both preimplantation genetic testing and prenatal diagnoses should be discussed during counselling and made available to *CDH1* pathogenic variant carriers, and adults of childbearing age should be offered reproductive genetic advice.

Multigene panel tests

With the widespread introduction of cancer gene panels, unexpected *CDH1* variants have been identified in individuals who do not have phenotypes suggestive of HDGC,[5] creating a substantial challenge for patients and clinicians.[5,26,27] Individuals undergoing panel tests that

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 person. 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.

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See Online for appendix

include *CDH1* and *CTNNA1* should receive genetic counselling, but with added emphasis on the uncertain risks that exist in families with no history of DGC. *CDH1* pathogenic variants appear to only be associated with LBC, and not invasive breast carcinoma of no special type (formerly designated as ductal breast cancer), nor other rare types of breast cancer; therefore, *CDH1* gene testing should only be contemplated in women with confirmed LBC.

Genetic testing

Genetic testing for germline variants of *CDH1* and *CTNNA1* should be performed in certified molecular diagnostic laboratories—eg, Clinical Laboratory Improvement Amendments (CLIA) approved, ISO 15189 accredited, or equivalent. Genetic analysis should include sequencing of the entire open reading frame, including intron–exon boundaries, and copy number analysis of individual exons to detect deletions or duplications. *CDH1* large deletions (including exons) are rare, accounting for fewer than 5% of pathogenic variants.[28] Any positive test results from direct-to-consumer testing must be validated in a certified laboratory. Variant interpretation should be performed using the American College of Medical Genetics and Genomics and Association for Molecular Pathology guidelines.[10] It is important to note that variants described as "likely pathogenic" have a 90% likelihood of pathogenicity;[12] therefore, a risk remains that the variant might be later reclassified as benign. There is no indication for presymptomatic testing in families carrying a variant of unknown significance, or a benign or likely benign variant. Particular care needs to be taken with the interpretation of missense variants; according to the *CDH1* variant curation guidelines, the currently published in vitro or in silico functional assays cannot be used to predict pathogenicity of *CDH1* missense variants,[10] and therefore these assays should not be used for *CDH1* variant classification until they are clinically validated. However, in-vitro assays that assess the effects of *CDH1* missense variants on E-cadherin levels, localisation, and function remain important research tools.[29]

Other than *CTNNA1*, additional genes that predispose specifically to DGC but not intestinal-type gastric cancer have not been identified, despite panel and whole-exome-sequencing efforts.[2,30,31] Increasing evidence suggests that germline pathogenic variants in *PALB2* might be the cause of increased gastric cancer risk in some families, although these variants are not confined to the diffuse subtype of gastric cancer.[31,32] *PALB2* testing could be considered in families where the increased risk remains unexplained, alongside testing for other genes associated with an increased risk of gastric cancer—eg, *ATM*, *BRCA2*,[2] the Lynch syndrome genes, *APC*, and *TP53*.

Cancer risk in carriers of *CDH1* pathogenic variants

Recent studies have shown that gastric cancer penetrance estimates for carriers of *CDH1* pathogenic variants are influenced by the clinical criteria used for the ascertainment of affected families (appendix p 1).[14,15] Hansford and colleagues[2] estimated the cumulative risk of gastric cancer by 80 years of age to be 70% in male carriers and 56% in female carriers, using data from families who all met the 2010 HDGC clinical criteria.[33] However, a recent report—in which only 37% of families with *CDH1* pathogenic variants met the less stringent 2015 HDGC clinical criteria—estimated the gastric cancer penetrance to be 42% for males and 33% for females.[14] Lower gastric cancer risk was also observed in a study in which 39% of families met the 2015 HDGC criteria.[15] Clearly, DGC risk varies between families and therefore family history should be considered when estimating an individual carrier's risk. Notably, estimates of female breast cancer risk, which have ranged from 39% to 55% have been more consistent between studies (appendix p 1). Since this variation in gastric cancer risk is likely to be strongly influenced by individual genetic background and lifestyle factors, it should not be assumed that the historical risk will equal the risk faced by younger generations.

Whether or not the penetrance of gastric cancer from pathogenic missense *CDH1* variants is substantially lower than that from truncating variants remains unknown, although considerable variability between different missense variants would be expected. Finally, no strong evidence exists to suggest that the risk of other cancer types is significantly increased in individuals with a *CDH1* pathogenic variant.[2,14,34] In particular, there is insufficient evidence to recommend additional colorectal cancer screening beyond adherence to national population screening guidelines.[6]

Clinical practice recommendations

HDGC

CDH1 variant carriers from families with confirmed HDGC should be advised to consider prophylactic total gastrectomy, irrespective of endoscopic findings (figure 1). Where possible, surgery is recommended in early adulthood, generally between 20 and 30 years of age.[6] Given the increased perioperative risks and prolonged recovery associated with older age, prophylactic total gastrectomy is not recommended in patients older than 70 years unless there are noteworthy mitigating circumstances. For individuals declining or wishing to postpone gastrectomy, yearly endoscopy by experienced endoscopists with knowledge of HDGC is recommended (appendix p 2). It is also recommended that *Helicobacter pylori* is eradicated if present.[35] LBC risk should be managed with either yearly surveillance or bilateral risk-reducing mastectomy.

Little is known about the penetrance of pathogenic *CTNNA1* variants.[36] However, intramucosal DGC foci have been observed in prophylactic total gastrectomy specimens from young asymptomatic carriers of these variants, suggesting that pathogenic variants in both *CDH1* and *CTNNA1* could have similar implications

regarding DGC risk.[4,37] Therefore, asymptomatic carriers of *CTNNA1* pathogenic variants are recommended to undergo yearly endoscopic surveillance in an expert centre, with prophylactic total gastrectomy being considered depending on the results of the biopsies and the penetrance of DGC in the family history. Breast cancer surveillance can be considered on a case-by-case basis.[36]

HLBC

The management of families with HLBC, and other individuals with a pathogenic *CDH1* variant but no family history of DGC, is not straightforward.[26] It is probable that DGC penetrance is significantly lower in these groups,[14,15] although more data are required for accurate estimates. Signet ring cell carcinomas have, however, been reported in prophylactic total gastrectomy specimens from carriers with no family history of DGC.[38] Therefore, yearly endoscopic surveillance should be offered to these groups, but prophylactic total gastrectomy should also be considered, giving careful attention to the uncertain gastric cancer risk. LBC risk in families with HLBC should be managed with either yearly surveillance or bilateral risk-reducing mastectomy. Yearly breast cancer surveillance is recommended in pathogenic *CDH1* variant carriers without a family history of DGC or breast cancer.

HDGC-like

Affected individuals from families that are HDGC-like, and their first degree relatives, may be considered for yearly endoscopic surveillance for at least 2 years (figure 1). Surveillance should begin at 40 years of age, or 10 years prior to the earliest case of gastric cancer within the family, with a minimum age of 18 years. Since a positive biopsy is most likely during the first endoscopy,[39,40] surveillance intervals can be prolonged at the discretion of the endoscopist after 2 years, based on individual findings in earlier endoscopies and on the family history.[39] Prophylactic total gastrectomy is not advised when endoscopies are negative, because of the uncertainty surrounding the level of individual risk of developing cancer. Individualised breast cancer risk assessment and surveillance are also recommended.

There are few data to support surveillance endoscopy in first-degree relatives of young individuals with DGC in the absence of any family history or pathogenic *CDH1* or *CTNNA1* variant.

CDH1 variant of unknown significance

Individuals who have a *CDH1* variant of unknown significance[10,12] (a genetic sequence with an unclear association to disease) and a family or personal history of DGC may be considered for annual endoscopic surveillance for at least 2 years as for those families that are HDGC-like. However, a paucity of data resulted in a lack of consensus regarding the clinical utility of surveillance in these groups. Accordingly, surveillance endoscopy should ideally be done as part of a research study. A prophylactic total gastrectomy is not advised for variant of unknown significance carriers when endoscopies are negative. Individualised breast cancer risk assessment and surveillance are recommended.

Breast surveillance and bilateral risk-reducing mastectomy

Hereditary breast cancer guidelines draw heavily on the evidence base from individuals with pathogenic *BRCA1* and *BRCA2* variants, most of whom will have had invasive breast carcinoma of no special type. Although these guidelines are useful, the hallmark of pathogenic *CDH1* variant-related breast cancer is LBC, a phenotype with specific clinical and radiological ramifications, as recently reviewed.[41] The recommendations outlined here (panel 2) are more specifically tailored to the risk and management of LBC, and are consistent with existing guidelines, including those from eviQ,[46] the National Institute for Health and Care Excellence,[47] the European Society for Medical Oncology,[48] and the National Comprehensive Cancer Network[49] (appendix p 4).

Breast surveillance for HDGC and HLBC should start at 30 years of age, with yearly MRI from 30–50 years of age, and potentially for longer. The benefit of adding mammography to MRI in young women, who generally have denser breasts, is uncertain, and limiting mammography until the age of 40–50 years has been suggested for *BRCA1* and *BRCA2* mutation carriers.[44] Although this approach could be considered on an individual basis, yearly mammography from 35 years of age is acceptable. Supplementary screening ultrasound in dense breasts is not without controversy,[50] but has a role,[51] especially when MRI is not available, or is contraindicated or declined.

When LBC is detected, treatment should follow standard practice.[41,52] A woman with a *CDH1* pathogenic variant could choose breast-conserving surgery, however bilateral risk-reducing mastectomy should also be considered, as for any woman at high risk for breast cancer. Skin and nipple-sparing mastectomy with immediate reconstruction is acceptable, provided adequate surgical margins are achievable.[47] A finding of lobular carcinoma in situ, which is typically a coincidental finding on biopsies being done for another reason, does not mandate risk-reducing mastectomy; however, this option should be discussed, alongside the option for ongoing surveillance and chemoprevention (panel 2).

In women with invasive breast carcinoma of no special type and no family history of LBC or DGC, who are found to carry a pathogenic *CDH1* variant from a panel test, management is challenging. If pathological review excludes misclassification, this is likely to be a sporadic cancer and breast-conserving surgery is acceptable, with ongoing surveillance.

Endoscopic surveillance

When endoscopic surveillance is offered (panel 3), the limitations of the procedure should be discussed—namely

Panel 2: **Breast cancer surveillance and risk-reducing mastectomy in hereditary diffuse gastric cancer (HDGC) and hereditary lobular breast cancer (HLBC)**

Discussions regarding the option for surveillance versus bilateral risk-reducing mastectomy need to cover key information to facilitate shared decision-making and informed consent, including the following points:

- The scant knowledge about breast cancer in HDGC and HLBC
- The paucity of prospective data on imaging for lobular breast cancer (LBC) in a screening setting[42]
- The individual's breast density on mammogram and background breast enhancement on MRI, and the potential impact of these on the sensitivity of detection of lobular breast cancer
- The individual's experience of breast surveillance, particularly tolerance of MRI
- What to expect if lobular breast cancer is detected during surveillance
- The option for chemoprevention
- Information about gadolinium contrast in line with recommendations from radiology societies[43]
- The potential harms of surveillance, in line with consent practices in breast screening programmes—eg, recall rate for further assessment after MRI

Breast cancer surveillance

- Surveillance should begin at age 30 years and include yearly clinical breast examination
- The concept of breast awareness should be explained, with education about the clinical features of lobular breast cancer—eg, indrawn nipple or skin tethering, thickening in breast tissue, or subtle change in breast contour, shape, or size
- Modifiable risk factors (eg, alcohol intake, exercise, and weight) should be discussed
- Yearly breast MRI with contrast is recommended:
  - Should begin at age 30 years, but the age when it should cease is not clear; there might be benefit to continuing beyond 50 years of age, even in non-dense breasts, because of the greater sensitivity of MRI in detection of lobular breast cancer
  - Should ideally be performed mid-cycle (days 10–14) when background breast enhancement is lowest
  - There is no evidence to support use of abbreviated MRI
- Yearly mammography from age 40 years is recommended but can be considered from 35 to 40 years on a case-by-case basis
  - Mammography alone is inadequate for screening in HDGC
  - Mammography is generally not recommended in those younger than 35 years unless there are clinically suspicious findings
  - The extra benefit of mammogram at the time of MRI is likely to be low, and the option to omit it can be considered on a case-by-case basis[44]
- Ultrasound has a role in women who are unable to have MRI or have no access to MRI
  - Should be combined with yearly mammography
  - Has a role in investigating symptoms between screening intervals

Bilateral risk-reducing mastectomy

- Can be considered in HLBC and HDGC
- Is not usually recommended in those younger than 30 years, nor generally in those older than 60 years of age

Chemoprevention

- In women at elevated risk of breast cancer, chemoprevention studies with selective oestrogen receptor modulators (pre-menopausal women) or aromatase inhibitors (post-menopausal women) show about a 50% risk reduction. Chemoprevention benefit is higher in some lobular carcinoma in situ studies,[45] although there have been no chemoprevention studies specifically for lobular breast cancer.
- Therapeutic levels of chemopreventative agents could be compromised after total gastrectomy
- The side-effects of endocrine therapy on quality of life can affect uptake and compliance, and discussion of these side-effects with a breast specialist is necessary

that DGC can be difficult to visualise on endoscopy, and it is unknown whether or not surveillance in this context positively affects life expectancy. The upper age limit for surveillance endoscopy depends on the patient's fitness for gastrectomy, but in general, surveillance in those older than the age of 70 years is probably not purposeful.

Although surveillance in expert centres suggests that superficial signet ring cell carcinoma lesions can be indolent for several years, the rate of progression is unpredictable.[39] If patients prefer to undergo surveillance, they must be informed that this could delay identification and treatment of gastric cancer. It is beneficial to build long-term relationships with patients to support them in their decision-making process. Yearly endoscopic surveillance should be performed in a centre with demonstrable expertise in recognition of signet ring cell carcinoma lesions. All surveillance programmes should be audited and ideally included in a prospective clinical trial.

Recent studies from expert centres in HDGC surveillance endoscopy report that signet ring cell carcinoma lesions are detected in gastric biopsies in 40–61% of these carriers of *CDH1* variants, most often at the baseline endoscopy (van Dieren J, Netherlands Cancer Institute, personal communication),[38,39] although older studies report a lower detection rate of 9–16%.[53–56] High-definition endoscopes, image-enhancing techniques (eg, narrow band imaging), and the experience of the endoscopist and pathologist are all factors likely to be related to the increase in signet ring cell carcinoma detection rates in more recent studies.

The a priori chance of having at least one signet ring cell carcinoma lesion in the total gastrectomy specimen from a carrier of a *CDH1* pathogenic variant is 95%.[57] Consequently, the clinical relevance of a few superficial (stage T1a) signet ring cell carcinoma lesions in endoscopic biopsies is questionable, especially since these superficial lesions can display a very indolent behaviour.[58] Therefore, the goal of surveillance is not to detect every single superficial lesion. However, for patients who wish to postpone surgery, the main goals are to exclude deeper infiltrating lesions; to detect large or numerous signet ring carcinoma T1a lesions, as these patients probably have a higher chance of developing higher stage lesions; and to assess changing histology and endoscopic appearance, which can signal more malignant behaviour (van Dieren J, personal communication).[21] A comparison between a superficial intramucosal pT1a lesion and a deeper intramucosal T1a lesion is shown in figures 2A–D, from both the endoscopic and histological perspectives.

Staging investigations are advised if erosive lesions, lesions with a disturbed vascular and pit pattern, or histopathological signs of invasion into or beyond the muscularis mucosae, are identified. If a signet ring cell carcinoma lesion with none of these risk indicators is identified, individual circumstances, such as age and comorbidity, might mean postponement of a prophylactic total gastrectomy is recommended after multidisciplinary team review. However, in this situation, intensified endoscopic monitoring for disease progression is advised, with endoscopy every 6 months.

***Panel 3:* Endoscopy key recommendations**

- Surveillance should be conducted in expert centres familiar with hereditary diffuse gastric cancer (HDGC)
- Surveillance instead of a prophylactic total gastrectomy can be considered depending on individual circumstances and wishes of pathogenic variant carriers (see definitions)
- Surveillance instead of a prophylactic total gastrectomy should be considered in pathogenic variant carriers with an unclear risk for diffuse gastric cancer (DGC), such as those who have not met HDGC genetic testing criteria or who carry pathogenic *CTNNA1* mutations
- Surveillance may be considered for individuals with a family history or personal history of DGC and a *CDH1* variant of unknown significance, and affected individuals from familes that are HDGC-like and their first degree relatives; after two negative endoscopies, surveillance intervals can be prolonged at the discretion of the endoscopist, based on individual findings in earlier endoscopies and on the family history
- Surveillance endoscopies should include both targeted and random biopsies
- The number of recommended random biopsies is 28–30 (three to five cardia, five fundus, ten body, five transition zone, and five antrum)
- We recommend gastric inlet patches in the oesophagus are registered, inspected, and biopsied
- All patients undergoing surveillance should be fully informed about the limitations of endoscopy

Prophylactic total gastrectomy

Patient selection and preparation

The decision to proceed to prophylactic total gastrectomy should be careful and deliberate. The patient, family, and care coordinators must be involved early in the decision-making process. Discussions should cover the risks of the operation, the long-term sequelae, and optimally include the individual surgeon's or institution's outcomes for this procedure. Patients should be offered preoperative psychological counselling to afford them an opportunity to express any concerns that might not have surfaced previously. The active engagement of patients who have recovered from prophylactic gastrectomy, to act as navigators, can help set realistic expectations about surgery and recovery, and provide a source of ongoing support throughout the process.

It is critical to assess and acknowledge an individual patient's competing risks (medical, oncological, and psychosocial) when the care plan is formulated. Untreated addictions (eg, food, drug, alcohol, or tobacco) will complicate recovery from gastrectomy and should be addressed preoperatively. If possible, gastrectomy should be avoided in patients with serious eating disorders (eg, anorexia or bulimia), or with other psychiatric diagnoses refractory to treatment that impair daily life (eg, bipolar disorder or severe depression) and could interfere with both the decision about surgery, and subsequent recovery.

Patients proceeding to gastrectomy should have a baseline endoscopy performed before surgery to ensure there is no endoscopically evident cancer, since this would require staging investigations. Endoscopy can also identify other coincidental pathology, such as Barrett's oesophagus, which might alter the proximal extent of the resection.

Surgery

Prophylactic total gastrectomy should only be offered by surgeons working in facilities with transparent outcome data and demonstrable capability in preventing, recognising, and managing the complications of total gastrectomy. Ideally, these facilities should be experienced in treating *CDH1* variant carriers. National guidelines for surgery provision differ across the world, but facilities undertaking prophylactic total gastrectomy should adhere to relevant local professional standards. The surgical approach is not as important as the experience of the surgeon, with minimally invasive approaches (laparoscopic and robotic) impacting more on short-term rather than long-term outcomes, when compared with open surgery.[59,60]

Gastrectomy should be total, with intraoperative confirmation of oesophageal squamous mucosa in

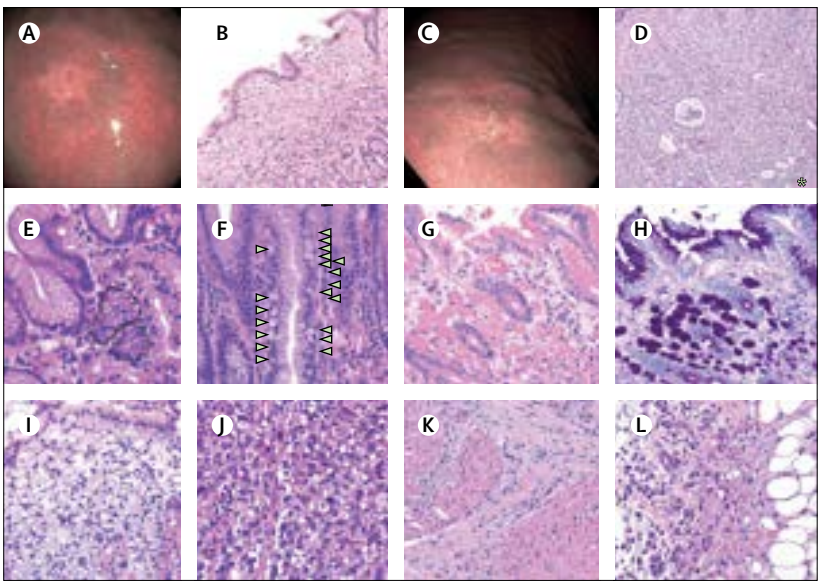

***Figure 2*: Endoscopic and histopathological images of HDGC gastric lesions**
(A, B) Superficial pT1a signet ring cell carcinoma focus, with (A) endoscopy of non-elevated pale lesion and (B) corresponding histology of signet ring cells with indolent phenotype superficially in the lamina propria. (C, D) Intramucosal pT1a signet ring cell carcinoma focus with invasion into the deeper lamina propria, with (C) endoscopy of 1 mm erosive lesion in middle of coarse pit pattern and (D) corresponding histology showing deeper invasion of signet ring cells almost reaching the muscularis mucosae (asterisk). (E, F) Precursor gastric lesions in HDGC, with (E) in situ signet ring cell carcinoma (dotted line) displaying signet ring cells within basal membrane and (F) pagetoid spread of signet ring cells (arrows) below the preserved epithelium. (G, H) Invasive HDGC gastric lesions within the lamina propria, with (G) intramucosal signet ring cell carcinoma focus (haematoxylin and eosin stain) and (H) periodic acid-schiff-diastase staining. (I, J) Intratumoural heterogeneity displayed in two biopsies from the same tumour, with (I) DGC with typical signet ring cells (indolent phenotype) and (J) DGC with pleomorphic, bizarre cells (aggressive phenotype). (K, L) Advanced DGC, with (K) invasion of gastric wall with prominent desmoplastic response and (L) peritoneal metastasis. HDGC=hereditary diffuse gastric cancer. DGC=diffuse gastric cancer.

the proximal margin and duodenal mucosa in the distal margin. Perigastric lymph node metastases are exceedingly uncommon in patients undergoing true prophylactic total gastrectomy (ie, in the absence of biopsy-proven DGC). As such, a deliberate extended D2 lymphadenectomy is not required and is generally discouraged to minimise postoperative morbidity. To avoid the potential of understaging the rare patient with a previously unappreciated T2 tumour, a reasonable compromise would be to perform a perigastric D1 lymph node dissection at the time of gastrectomy. Further detail on the surgical procedure and recovery are provided in appendix p 5.

Histopathology

Histopathology suggesting a diagnosis of HDGC

Two preinvasive or precursor lesions of signet ring cell carcinoma have been recognised exclusively in *CDH1* pathogenic variant carriers and are important clues to the diagnosis of HDGC. First, in situ signet ring cell carcinoma, corresponding to the presence of signet cells with hyperchromatic and depolarised nuclei within the basal membrane of a gland, replacing the normal cells of the gland; second, pagetoid spread of a row of signet cells below the preserved epithelium of glands and foveolae, and also within the basal membrane (figure 2E, F).[13] The predominant lesions in HDGC however are tiny foci of typical signet cells, usually confined to the superficial lamina propria, without infiltration beneath the muscularis mucosae. The neoplastic cells are usually small in the deep level at the neck gland zone, and enlarge towards the surface (figure 2G–I). Endoscopic biopsy specimens from *CDH1* pathogenic variant carriers can also have features of non-signet cell poorly cohesive (diffuse) gastric cancer with a so-called aggressive phenotype, represented by pleomorphic or bizarre, and diffusely infiltrative, cells (figure 2J). These features are highly suggestive of disease progression and should be described in the pathology report, to prompt staging and clinical intervention.[21] Criteria for the identification of signet ring cell lesions should be followed strictly to diminish the risk of over-diagnosing non-specific changes, and to distinguish them from mimickers of precursor lesions or signet ring cell carcinoma (appendix p 6).[61,62]

Histopathology of advanced HDGC

Similar to sporadic DGC, advanced HDGC predominantly presents as linitis plastica, with infiltration of the gastric wall by atypical cells with diffuse growth, and also cords, microglands, and small mucin lakes (figure 2K, L). A component of typical signet ring cells might also be seen.

Histopathology of prophylactic gastrectomies

The macroscopic examination of prophylactic total gastrectomy specimens should follow a specific protocol (appendix p 7), and a checklist is proposed for histological examination (appendix p 8). Both WHO (2019)[63] and Lauren[20] classifications should be used. Surgical margin analysis is mandatory to confirm that there is no residual gastric mucosa or tumour at the margins. The risk of developing signet ring cell carcinoma in oesophageal cardiac-type glands is unknown, and the risk is very low in heterotopic gastric mucosa in the duodenum.[64] To provide flexibility between routine clinical histopathology and research requirements, a three-level histopathology protocol is proposed, ranging from the minimum necessary for patient care, to total gastric embedding and mapping (appendix p 9).

Histopathology of *CDH1*-related breast cancer

In risk-reducing mastectomies from *CDH1* variant carriers, bilateral widespread foci of atypical lobular hyperplasia, lobular carcinoma in situ, and small foci of invasive LBC, have been detected (appendix p 10).[65] No unique histopathological or immunohistochemical findings distinguish *CDH1*-related LBC from sporadic LBC. Carriers of pathogenic *CDH1* variants have been diagnosed with invasive breast carcinoma of no special type,[5,34] although these are likely to be coincidental sporadic cancers. Since LBC can be misclassified, it is

	Recommendation
Early dumping (15–30 min postprandial)	Smaller meals, chewed well and eaten slowly; avoid drinking with meals
Late dumping (90 min to 3 h postprandial)	Meals with low sugar and high protein content; eat multiple small portions (six to eight a day); avoid drinking with meals
Lactose intolerance	Milk alternatives, lactase supplements
Fat malabsorption	Low-fat diet; consider addition of pancreatic enzymes; monitor blood levels of fat-soluble vitamins (A, D, E, and K); start vitamin D supplementation
Small bowel bacterial overgrowth or blind loop syndrome	Antibiotics with or without surgery
Dysphagia and anastomotic strictures	Smaller bites with deliberate mastication; upper endoscopy with balloon dilatation
Increased or decreased response to solid oral medication	Use alternate dosage forms (liquids; injections; or chewable, sublingual, dispersible tablets); open capsules and crush tablets if safe to do so; prescribe immediate release tablets (cf, controlled release preparations); avoid the oral contraceptive pill (use implant or intrauterine device); avoid gastrointestinal irritant drugs (eg, aspirin, non-steroidal anti-inflammatory drugs, oral bisphosphonates, and some antibiotics); avoid medication requiring acidic environment for absorption; lifelong monitoring of drug levels, markers, and metabolites, if possible, and assessment of desired outcomes by clinical observation and patient self-report
Increased effects of alcohol	Exert caution, avoid taking other CNS depressants, do not drive or operate heavy machinery; regular assessment of drinking patterns and behaviours; screening for alcohol use disorders
Nutritional deficiencies	High potency multivitamin with additional vitamin B12, iron, and calcium citrate supplements (iron and calcium separated by 4–5 h); correct dosing of vitamin B12 is essential;[69] for iron-deficiency anaemia, iron infusions (cf, oral supplements)
Osteopenia or osteoporosis	Regular bone density scans (baseline then every 2–5 years); ensure adequate supplementation of calcium citrate (in divided doses) and vitamin D; tailored, weight-bearing exercises; if osteoporosis present, intravenous bisphosphonate therapy
Gallstones	Low-fat diet; lead an active lifestyle; avoid medications known to cause gallstones (eg, gemfibrozil)
Bile reflux	Ensure appropriate length of Roux limb constructed at time of surgery; elevate head of bed >30 degrees (pillows or wedge); no oral intake 2–3 h before going to bed; avoid dietary triggers (spice; large, fatty, or sugary meals; large amounts of liquid at a time); ingesting appropriate food (eg, soft, dry cracker, or Greek yoghurt) may help soothe and carry bile downwards; consider bile acid sequestrants and sucralfate
Persistent nausea and vomiting	Assess thiamine levels, replace (oral or intravenous) when needed; avoid dairy; eat easy to digest, non-offensive foods; consider ondansetron wafers when necessary
Early satiety	Eat several small meals throughout the day; set a timer to ensure meals are not skipped
Weight loss	Weight loss (of around 15–20%)[55,64,70] is expected after a total gastrectomy but stabilises in 3–6 months; eat at least six to eight smaller meals per day and snack frequently; include protein-fortified or high-calorie (but low-fat) foods

Table: **Postgastrectomy complications and treatment recommendations**

important to review the original histology: β-catenin and p120-catenin can be used to confirm lobular phenotype; p120-catenin shows cytoplasmic staining (membranous in invasive breast carcinoma of no special type and ductal carcinoma in situ); and β-catenin is negative in lobular neoplasia.[66,67]

Long-term sequelae and follow-up

Optimally, patients undergoing prophylactic total gastrectomy should receive lifelong follow-up with an experienced multidisciplinary team to monitor for long-term sequelae including nutritional, hormonal, immune, neurocognitive, pharmacokinetic, and psychological effects.[6,68] Postgastrectomy symptoms and current treatment options are described in the table.[69,70] Patients should also be educated about symptoms of late internal herniation: an urgent, potentially life-threatening complication that can occur at any time after total gastrectomy.

Several HDGC and LBC advocacy organisations support affected families, including No Stomach For Cancer, Hereditary Diffuse Gastric Cancer Advocacy, DeGregorio Family Foundation, and The Lobular Breast Cancer Alliance.

Drug absorption

A total gastrectomy introduces a great deal of uncertainty surrounding the use of solid oral medicines. Patients often have to remind their health-care providers that medications need to be reconsidered after gastrectomy (panel 4).

The reconfiguration of the gastrointestinal tract allows for mixing of bile salts with ingested material, but the process is delayed, affecting solubility of medicines. Additionally, bypassing the stomach and proximal small intestine reduces the surface area available for drug absorption, alters onset of action and availability of intestinal drug transporters and enzymes, and impairs cycling of medications such as the oral contraceptive pill.

Poor tablet and capsule disintegration warrants substitution with liquids, or chewable or dispersible formulations. Caution needs to be exercised with liquids because the high sugar content can cause dumping syndrome, and dispersible tablets might cause abdominal discomfort. In some circumstances, crushing tablets or opening capsules is advisable. Delayed-release medication should be avoided, in view of the decreased functional length of the small intestine. Alternative

For more on **No Stomach For Cancer** see https://www.nostomachforcancer.org

For more on **Hereditary Diffuse Gastric Cancer Advocacy** see https://www.hereditarydiffusegastriccancer.org

For more on **DeGregorio Family Foundation** see https://www.degregorio.org

For more on **The Lobular Breast Cancer Alliance** see https://lobularbreastcancer.org

Panel 4: General pharmacological recommendations

- Inform all patients about altered absorption of medicines after total gastrectomy
- Substitute solid oral medication with chewable, dispersible, or liquid preparations
- Consider other routes of administration: sublingual, topical, vaginal, rectal, and parenteral
- Recommend patients crush tablets, or open capsules and ingest contents separately, when no other dosage forms exist and it is safe to do so
- Use alternative contraception rather than the oral contraceptive pill because of impaired absorption
- Where possible, avoid medicines that irritate the intestinal mucosa (eg, non-steroidal anti-inflammatory drugs, corticosteroids, oral bisphosphonates, aspirin, specific antibiotics, and potassium chloride)
- Avoid medication likely to cause gallstones (eg, gemfibrozil)
- Seek alternatives to medicines requiring an acidic environment for absorption (eg, carbamazepine, azole antifungal agents, phenytoin, and selegiline)
- Avoid extended and other delayed-release formulations
- Assess drug–nutrient interactions (eg, iron and calcium) as patients supplement post-surgery to avoid nutritional deficiencies
- Give special attention to the quantity and effects of alcohol
- Exert caution when prescribing medicines with a narrow therapeutic window

See Azran and colleagues[69] for further details.

Search strategy and selection criteria

We searched PubMed using the search terms "hereditary diffuse gastric cancer", "hereditary lobular breast cancer", "germline *CDH1*", and "germline *CTNNA1*" for non-review articles published from the date the previous International Gastric Cancer Linkage Consortium Hereditary Diffuse Gastric Cancer guidelines were accepted for publication (March 18, 2015) until Jan 1, 2020. Only English language manuscripts were assessed for inclusion in the manuscript.

medicines to those requiring an acidic environment for sufficient absorption (eg, azole antifungal agents) should also be sought. Conversely, the increased pH of the intestinal tract will increase exposure to a small number of medications (weak acids), including non-steroidal anti-inflammatory drugs. Other analgesics should be prescribed where possible, and drugs that irritate the intestinal wall should be avoided (eg, aspirin, oral bisphosphonates, and doxycycline).[71]

The variability in absorption and effectiveness of oral medicines necessitates regular clinical assessment and review of medicines (table). Favourable administration routes should be explored, including sublingual, transdermal, vaginal or rectal, and injectable preparations.

Sexuality and fertility

Both total gastrectomy and bilateral mastectomy can have substantial effect on sexuality for patients.[72] For example, changes to the digestive system affect eating, drinking, and bowel habits, which might interfere with intimate relationships and self-confidence. Postprandial fullness, bloating, diarrhoea, dumping syndrome, and altered alcohol tolerance can all affect sexuality. It is helpful to include an obstetrician or gynaecologist, and a specialist in maternal medicine, in the care of women with HDGC.

Women who do not wish to achieve pregnancy can be offered an intrauterine device or other form of contraception that does not require gastrointestinal absorption. Those who do wish to achieve pregnancy should be counselled about preimplantation genetic diagnosis and provided with nutritional counselling before and during pregnancy. An interval of at least 6–12 months after surgery is recommended to allow for weight stabilisation and nutritional recovery. Pregnancies after total gastrectomy appear to be normal,[73] although caution is nevertheless warranted because pregnancies after bariatric surgery show an increased risk of adverse perinatal outcomes, such as preterm births, small-for-gestational-age babies, and babies being admitted to the intensive care unit.[74]

Future research

Numerous questions remain about the early molecular and cellular events that lead to progressive disease in *CDH1* pathogenic mutation carriers, in particular the genetic and epigenetic triggers that shift signet ring cells from indolent to invasive behaviour. Other priority areas for future research include individual risk assessment and disease modifiers, *CDH1* and *CTNNA1* variant of unknown significance pathogenicity determination, genotype–phenotype correlations, chemoprevention methods,[75] and improved methods of endoscopic surveillance (appendix p 11–12).

Conclusion

HDGC risk reduction is a multidisciplinary process that requires shared decision-making with patients at each stage of the process in order to achieve optimal long-term results. Prophylactic total gastrectomy is still the cornerstone of HDGC management. However, knowledge surrounding endoscopic abnormalities and signet ring cell carcinoma detection rates in families with HDGC is improving. Therefore, confidence is increasing that endoscopic surveillance in expert centres could be safely offered to patients who wish to postpone surgery, or to those whose risk is not well defined, for example, when pathogenic *CDH1* variants are found in the absence of a family history of DGC.[76]

Contributors

VRB, FC, DGC, CO, JLDA, JMvD, and NH led an expert writing group; CO, DGC, JLDA, DGH, NH, RSvdP, and FC chaired focus group meetings; KLH led the pharmacology section; KLH, RSvdP, JA, PRB, TMB, AB, ACa, ACh, KECS, JLD, DDP, RCF, JMF, KG, IG, RHH, PK, SSK, AL, PFM, TN, SP, JR, HS, MS, MT, TU, HY, H-KY, and JW were members of a writing group. DGC, JLDA, JMvD, KLH, CO, RSvdP, PRB, TMB, ACa, KECS, JLD, MdP, JMF, IG, DGH, PK, SK, PFM, SP, JR, HS, TU, HKY, ACa, JF, PG, KP, and RS presented at the Wānaka meeting. RSVDP, MML, KP, and AER made special contributions to meeting

design. All other authors contributed to the focus groups at the consensus meeting. PG compiled and integrated the manuscript drafts and is the lead author. The final manuscript was reviewed by all authors.

Declaration of interests

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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.

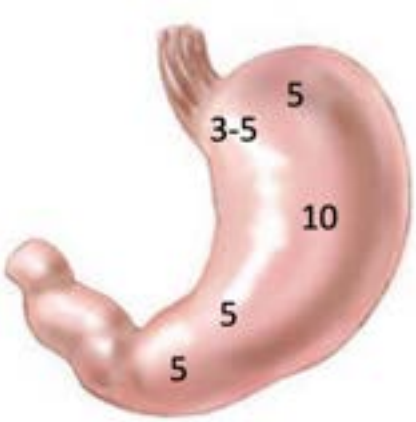
Distensibility
Prior to examination for visible mucosal abnormalities, the stomach should be assessed for distensibility. To assess for distensibility, the stomach should be maximally insufflated and then deflated using CO_2 or air. In cases of infiltrative disease, so-called '*linitis plastica*', the 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.

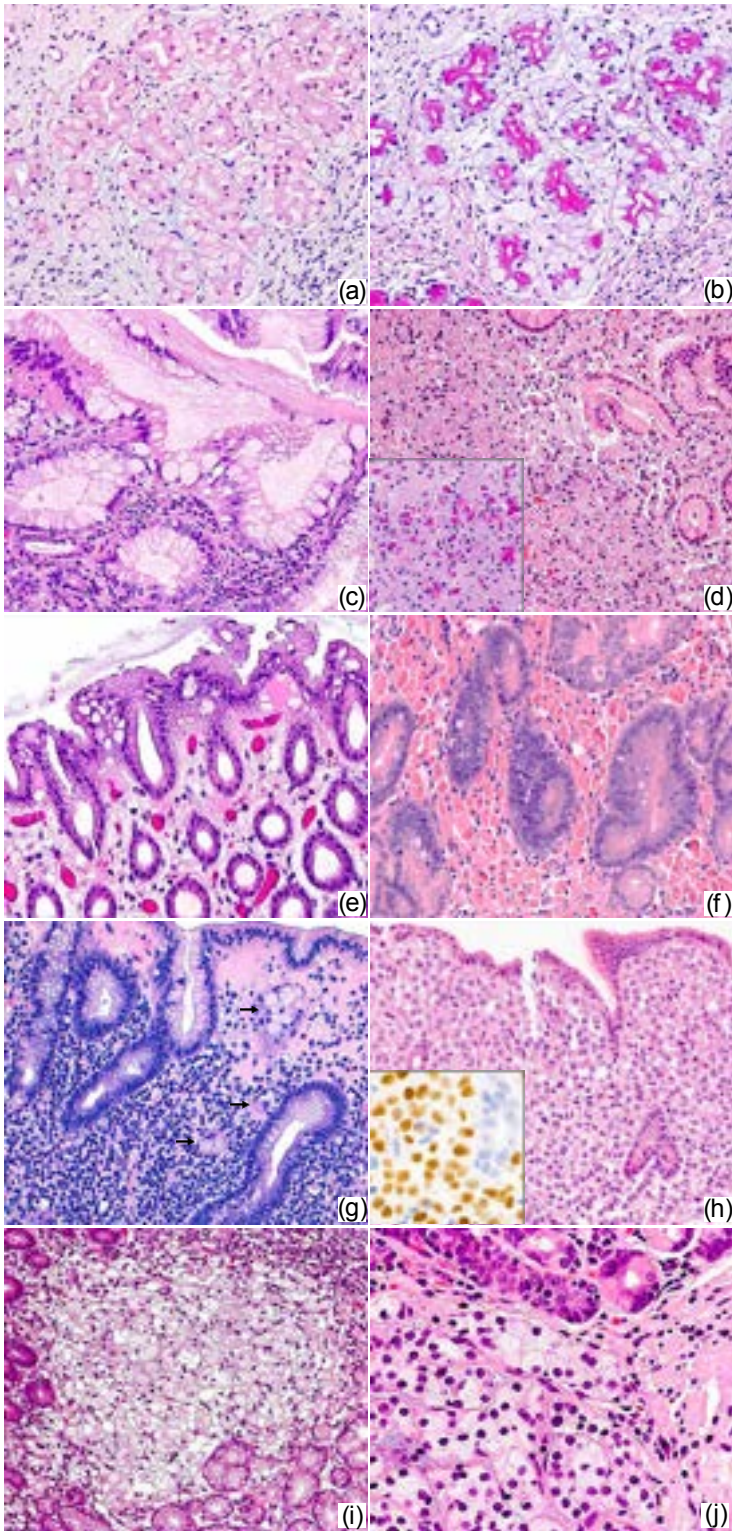
Supplementary Text 2: Surgery and recovery

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.

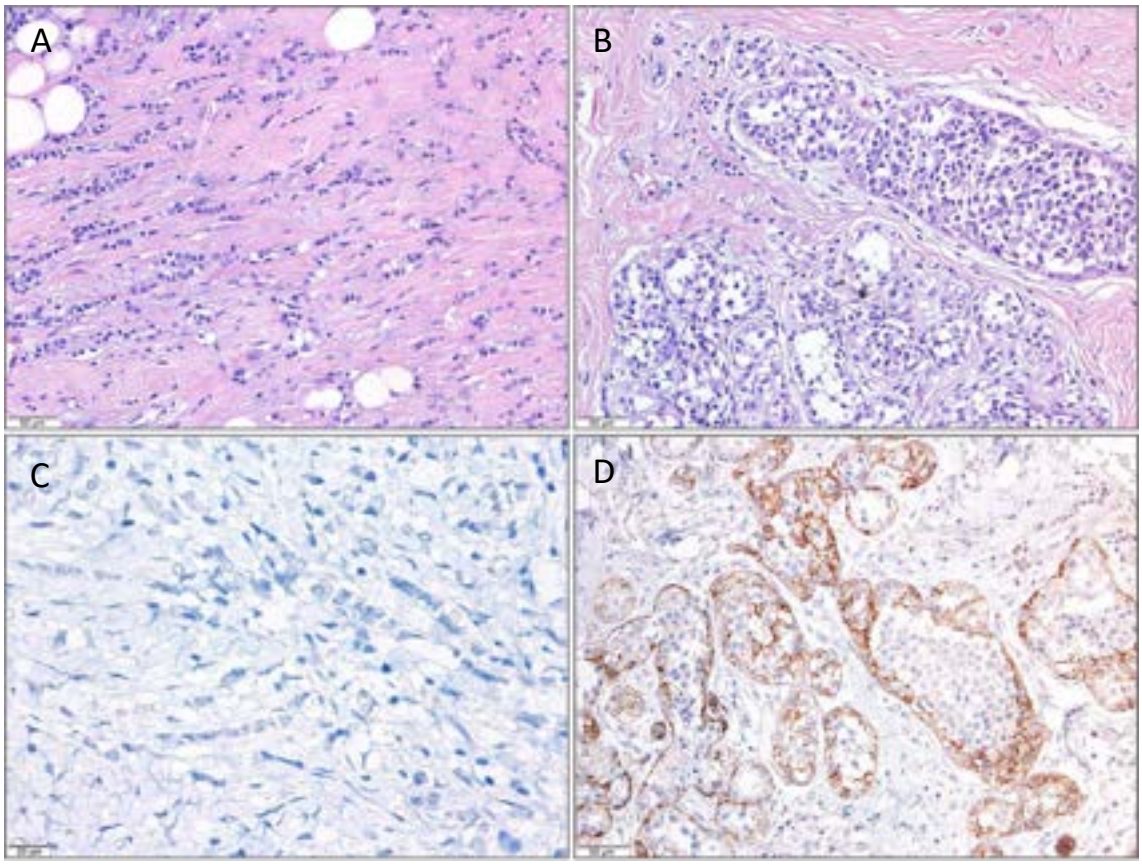
Supplementary Table 3: Checklist for reporting of prophylactic gastrectomy specimens

(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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