Hereditary Diffuse Gastric Cancer: Updated Clinical Practice Guidelines


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Abstract

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 \textit{CDH1}, although pathogenic variants in \textit{CTNNA1} occur in a minority of HDGC families. Here, the International Gastric Cancer Linkage Consortium (IGCLC) has updated practice guidelines for HDGC, recognising the emerging evidence of variability in gastric cancer risk between HDGC families, the growing capability of endoscopic and histological surveillance in HDGC and greater experience managing long-term sequelae post total gastrectomy in young patients. To redress the balance between the accessibility, cost and acceptance of genetic testing and greater 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 \textit{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 is not well defined.
**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). First described in an extended New Zealand Māori family in 1998, HDGC is now estimated to have a population incidence of approximately 5-10/100,000 births. The majority of 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 cell-cell adhesion, tension sensing, and signal transduction functions.\(^3\) 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 has led to the increased identification of variants in individuals with a family history of breast cancer but little or no 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 post-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 16-18\(^{th}\) 2019 a group of genetic researchers (19), pathologists (seven), gastroenterologists (ten), breast and gastric surgeons (seven), clinical geneticists and genetic counsellors (seven), pharmacists (one) and HDGC advocates/family members (13) met in Wānaka, Aotearoa New Zealand to update the IGCLC guidelines and identify areas of emerging research. The shared vision was to build a consensus for HDGC management that was tightly connected to the experience of HDGC families. 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 and research priorities. After the Wānaka meeting, expert writing panels (genetics, gastroenterology, pathology, surgery, and advocacy) achieved consensus within their specialty and drafted the manuscript. Because of the relatively low incidence of HDGC, randomised clinical trial data specific to HDGC is lacking. Instead, as for other rare diseases, the recommendations in these guidelines have relied on consensus expert opinion, expert evidence and observational studies.\(^7, 8\) Therefore, the evidence level for our recommendations is categorised as ‘low’ to ‘moderate’ according to the GRADE definitions.\(^9\) That is, further research is ‘likely to very likely’ to have an important impact on our confidence in the estimate of the effect addressed by the recommendation.

**Scope**

These guidelines address the management of (i) individuals and families who meet revised genetic testing criteria for HDGC and (ii) individuals with a pathogenic or likely pathogenic CDH1/CTNNA1 variant\(^10\) identified through other routes, including direct-to-consumer testing (Fig. 1). The management of sporadic DGC and LBC, Familial Intestinal Gastric Cancer,\(^11\) GAPPS and familial gastric or breast cancer associated with other predisposition genes is not covered in this update.

**Definitions**

In this document, the term ‘pathogenic variant’ refers collectively to both ‘likely pathogenic’ and ‘pathogenic’ variants as defined previously.\(^12\) 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 (see the Histopathology section for description) or in a family with one or more DGC cases in first 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 or second degree relatives, but no known DGC in either situation. By definition, HLBC families are re-categorised as HDGC if DGC (or precursor lesions 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.\(^14, 15\) ’HDGC-like’ families are defined as those that fulfil HDGC genetic testing family criteria 1 or 2 (panel 1), but have no identified pathogenic CDH1/CTNNA1 variant. Thus, ‘HDGC-like’ families must have at least one confirmed DGC and another gastric cancer or LBC in 1\(^{st}\) or 2\(^{nd}\) degree relatives.
Genetic testing and penetrance

HDGC genetic testing criteria

Genetic testing criteria must balance healthcare-related costs, public acceptance, 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 threshold age for isolated DGC cases is increased from <40yrs to <50yrs. Similarly, testing of women with bilateral LBC is increased from <50yrs to <70yrs, with an expected yield of pathogenic CDH1 variants of approximately 7%. Further, because approximately 13% of New Zealand Māori with advanced DGC have pathogenic germline CDH1 variants, it is now recommended that all Māori with confirmed DGC undergo CDH1 genetic testing. The 2015 criteria that recommended testing in individuals with a personal or family history of cleft lip/cleft palate and DGC, or with HDGC precursor lesions, remain. Individuals who fulfill criteria for HDGC genetic testing should first have CDH1 analysed and, if no variant identified, considered for CTNNA1 analysis.

In Japan and South Korea, it is recommended that the Japanese Gastric Cancer Association classification of signet-ring cell carcinoma is used instead of the Laurén classification of DGC. Index cases from new HDGC families 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 be considered based on family history. Where possible, genetic counselling for HDGC and HLBC should include evaluation of a three-generation family pedigree, 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. Counsellors should help patients 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 received.

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 (PTG), is required. Most individuals who have undergone a PTG express little or no regret after surgery. Both pre-implantation genetic testing and prenatal diagnoses should be discussed during counselling and made available to CDH1 and CTNNA1 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, creating a significant challenge for patients and clinicians. Individuals undergoing panel tests that include CDH1 and CTNNA1 should undergo genetic counselling as described above, 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’ (IC-NST; formerly designated as ductal breast cancer) or 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, e.g., 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 less than 5% of pathogenic variants. Any positive test results from direct-to-consumer testing must be validated in a certified laboratory. Variant interpretation should be performed using the ACMG/AMP guidelines. It is important to note that ‘likely pathogenic’ variants have a 90% likelihood of pathogenicity, therefore a risk remains that the variant might be later reclassified as benign. There is no indication for pre-symptomatic testing in
families carrying a variant of unknown significance (VUS) or a ‘likely benign’ or ‘benign’ variant. Particular care needs to be taken with the interpretation of missense variants; according to the CDH1 ACMG/AMP 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.\(^{2,30,31}\) There is increasing evidence that germline pathogenic variants in PALB2 may explain gastric cancer risk in some families, although these variants are not confined to the diffuse subtype.\(^{31,32}\) PALB2 testing could be considered in unexplained families alongside other genes associated with an increased risk of gastric cancer, e.g., 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 CDH1 pathogenic variants are influenced by the clinical criteria used for ascertainment (page 1, Supplementary Material).\(^{14,15}\) Hansford et al.\(^{2}\) estimated the cumulative risk of gastric cancer by age 80yrs in male and female carriers to be 70% and 56% respectively using families who all met the 2010 HDGC clinical criteria.\(^{33}\) However, a recent report in which only 37% of CDH1 families 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 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 39-55%, have been more consistent between studies (page 1, Supplementary Material). 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.

It is unknown if the penetrance of pathogenic missense CDH1 variants is substantially lower than truncating variants, although considerable variability between different missense variants would be expected. Finally, there is no strong evidence 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 confirmed HDGC families should be advised to consider PTG, regardless of endoscopic surveillance (Fig. 1). Where possible, surgery is recommended in early adulthood, generally between 20 and 30yrs of age.\(^{5}\) Given the increased perioperative risks and prolonged recovery with age, PTG is not recommended in patients over 70yrs unless there are significant mitigating circumstances. For those declining or wishing to postpone PTG, it is recommended that annual endoscopy is carried out by experienced endoscopists with knowledge of HDGC (see page 2 of Supplementary Material for protocol). It is also recommended that Helicobacter pylori is eradicated if present.\(^{35}\) LBC risk should be managed with either annual surveillance or bilateral risk-reducing mastectomy (BRRM).

Little is known about the penetrance of pathogenic CTNNA1 variants.\(^{36}\) However, intramucosal DGC foci have been observed in PTG specimens from young asymptomatic carriers, suggesting that pathogenic variants in CDH1 and CTNNA1 may have similar implications regarding DGC risk.\(^{4,37}\)

Therefore, it is recommended that asymptomatic carriers of CTNNA1 pathogenic variants undergo annual endoscopic surveillance in an expert centre with a PTG being considered, depending on the results of the biopsies and the penetrance of DGC in the pedigree. Breast surveillance can be considered on a case-by-case basis.\(^{36}\)

**HLBC:** The management of HLBC family members and other individuals with a pathogenic CDH1 variant but no family history of DGC is not straightforward.\(^{28}\) 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 (SRCC) have, however, been reported in PTG specimens from carriers
with no family history of DGC. Therefore, annual endoscopic surveillance should be offered to these groups but PTG should also be considered, giving careful attention to the uncertain gastric cancer risk. LBC risk in HLBC families should be managed with either annual surveillance or BRRM. Annual breast surveillance is recommended in pathogenic CDH1 variant carriers without a family history of DGC or breast cancer.

‘HDGC-like’: Affected family members from ‘HDGC-like’ families and their first degree relatives may be considered for annual endoscopic surveillance for at least two years (Fig. 1). It should begin at 40yrs of age or ten years prior to the earliest case of gastric cancer, with a minimum age of 18yrs. Since a positive biopsy is most likely during an initial endoscopy, surveillance intervals can be prolonged at the discretion of the endoscopist after two years, based on individual findings in earlier endoscopies and on the family history. PTG is not advised when endoscopies are negative due to the uncertainty surrounding the level of individual risk of developing cancer. Individualised breast cancer risk assessment and surveillance are also recommended.

CDH1 VUS: Individuals who have a CDH1 VUS (a genetic sequence with an unclear association to disease) and a family or personal history of DGC may also be considered for annual endoscopic surveillance for at least two years as described above. 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 conducted as part of a research study. A PTG is not advised for VUS carriers when endoscopies are negative. Individualised breast cancer risk assessment and surveillance are recommended.

There is little 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.

Lobular breast cancer surveillance and surgery

Hereditary breast cancer guidelines draw heavily on the evidence base from individuals with pathogenic BRCA1/2 variants, most of whom will have had IC-NST. Whilst 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. The recommendations outlined here (Panel 2) are more specifically tailored to the risk and management of LBC and are consistent with existing guidelines including eviQ, NICE, ESMO, and NCCN (page 4, Supplementary Material).

Breast surveillance for HDGC and HLBC should start at age 30yrs, with annual MRI between 30-50yrs and potentially longer. The benefit of adding mammography to MRI in young women who generally have denser breasts is uncertain, and limiting mammography until 40-50yrs has been suggested for BRCA1/2 mutation carriers. Whilst this could be considered on an individualised basis, annual mammogram from 35yrs is acceptable. Supplementary screening ultrasound in dense breasts is not without controversy, but has a role, particularly when MRI is not available, contraindicated or declined.

When LBC is detected, treatment should follow standard practice. A woman with a CDH1 pathogenic variant may choose breast-conserving surgery, however BRRM should also be considered, as for any woman at high risk of developing breast cancer. Skin and nipple sparing mastectomy with immediate reconstruction is acceptable, provided adequate surgical margins are achievable. A finding of lobular carcinoma in situ (LCIS), typically a coincidental finding on biopsy 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 IC-NST 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 as described above.

Endoscopic surveillance

When endoscopic surveillance is offered (Panel 3), the limitations should be discussed, namely that DGC can be difficult to visualise and it is unknown if surveillance in this context positively affects life expectancy. The upper age limit for surveillance endoscopy depends on the fitness for gastrectomy, but in general surveillance over the age of 70yrs is probably not purposeful.
Although surveillance in expert centres suggests that superficial SRCC lesions can be indolent for a period of years, the rate of progression is unpredictable. 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. Annual endoscopic surveillance should be performed in a centre with demonstrable expertise in recognition of SRCC lesions. It is recommended that all surveillance programmes are audited and ideally included in a prospective clinical trial.

Recent studies from expert centres on HDGC surveillance endoscopy report that SRCC lesions are detected in gastric biopsies in 40-61% of these carriers, most often at the baseline endoscopy (J. Van Dieren, pers. comm), although older studies report a lower yield of 9-16%. High-definition endoscopes, image enhancing techniques (e.g., narrow band imaging) and the experience of the endoscopist and pathologist are all factors likely to be related to the increase in SRCC detection rates.

The a priori chance of having at least one SRCC lesion in the total gastrectomy specimen from a CDH1 mutation carrier is 95%. Consequently, the clinical relevance of a few superficial (stage T1a) SRCC lesions in endoscopic biopsies is questionable, especially since these superficial SRCC foci can display a very indolent behaviour. Therefore, the goal of surveillance is not to detect every single superficial SRCC focus. But, in patients wishing to postpone surgery, the main goals are to (i) exclude deeper infiltrating lesions, (ii) detect large or numerous SRCC T1a lesions, as these patients probably have a higher chance of developing higher T-stage lesions, and (iii) assess changing histology and endoscopic appearance which can signal more malignant behaviour (J. Van Dieren, pers. comm). A comparison between a superficial intramucosal pT1a SRCC focus and a deeper intramucosal T1a lesion is shown in Fig. 2A-D from both the endoscopic and histologic perspectives.

Staging investigations are advised if erosive lesions, lesions with a disturbed vascular and pit pattern or histopathologic signs of invasion into or beyond the muscularis mucosae are identified. If a SRCC lesion with none of the above risk indicators is identified, individual circumstances, such as age and comorbidity, may mean postponement of a PTG remains a better option after multidisciplinary team review. However, in this situation, intensified six-monthly endoscopic monitoring for disease progression is advised.

**Prophylactic total gastrectomy**

**Patient selection and preparation**

The decision to proceed to PTG should be careful and deliberate. It is imperative to involve the patient, family and care coordinators early in the decision-making process. Discussions should cover the risks of PTG, 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 concerns that might not have surfaced previously. The active engagement of patients who have recovered from PTG 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, psychosocial) when the care plan is formulated. Untreated addictions (food, drug, alcohol, tobacco) will complicate recovery from PTG and should be addressed preoperatively. If possible, PTG should be avoided in patients with serious eating disorders (anorexia, bulimia) or with other psychiatric diagnoses refractory to treatment that impair daily life (eg, bipolar disorder and severe depression), and could interfere with both the decision about surgery and subsequent recovery.

Patients proceeding to gastrectomy should have a baseline endoscopy performed prior to surgery to ensure there is no endoscopically-evident cancer, as this would require staging investigations. It will also identify other coincidental pathology, such as Barrett's esophagus, which may alter the proximal extent of the resection.
Surgery
PTGs should only be offered by surgeons working in facilities with transparent outcome data and demonstrable capability in preventing, recognising and managing the complications of a total gastrectomy. Ideally, these facilities should be experienced in treating CDH1 variant carriers. National guidelines for surgery provision may differ across the world, but units undertaking PTG should adhere to relevant local professional standards. The surgical approach is not as important as experience, with minimally invasive approaches (laparoscopic and robotic) impacting more on short-term than long-term outcomes.59, 60

Gastrectomy should be total, with intraoperative confirmation of esophageal squamous mucosa in the proximal margin and duodenal mucosa in the distal margin. Perigastric lymph node metastases are exceedingly uncommon in patients undergoing true PTGs, i.e. 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 peri-gastric D1 lymph node dissection at the time of PTG. Further detail on the surgical procedure and recovery are provided (page 5, Supplementary Material).

Histopathology
Histopathology of biopsies from individuals suspected for HDGC
Two pre-invasive/precursor lesions of SRCC have been recognised exclusively in CDH1 carriers and are important clues to the diagnosis of HDGC: (i) in situ SRCC, corresponding to the presence of SRC with hyperchromatic and depolarised nuclei within the basal membrane of a gland replacing the normal cells of the gland, and (ii) pagetoid spread of a row of SRCs below the preserved epithelium of glands and foveolae, and also within the basal membrane (Fig. 2E-F).13 The predominant lesions in HDGC however are tiny foci of typical SRCs, 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 (Fig. 2G-I). Endoscopic biopsy specimens from CDH1 carriers may also contain features of non-SRC poorly cohesive (diffuse) gastric cancer with an 'aggressive' phenotype, represented by pleomorphic/bizarre, and diffusely infiltrative cells (Fig. 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 SRC lesions should be strictly followed to diminish the risk of over diagnosing non-specific changes and to distinguish them from mimickers of precursor lesions or SRCC (page 6, Supplementary Material).61, 62

Histopathology of advanced HDGC
Like sporadic DGC, advanced HDGC predominantly presents as linitis plastica with infiltration of the gastric wall by atypical cells with diffuse growth, and also cords, (micro)glands, and small mucin lakes (Fig. 2K-L). A component of typical SRCs may be seen.

Histopathology of prophylactic gastrectomies
The macroscopic examination of PTG specimens should follow a specific protocol (page 7, Supplementary Material) and a checklist is proposed for histological examination (page 8, Supplementary Material). Both WHO 201963 and Laurén classifications20 should be used. Surgical margin analysis is mandatory to confirm that there is no residual gastric mucosa and tumour at the margins. The risk of developing SRCC in esophageal cardiac-type glands is unknown and 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 (page 9, Supplementary Material).

Histopathology of CDH1-related breast cancer
In risk-reducing mastectomies from CDH1 variant carriers, bilateral widespread foci of atypical lobular hyperplasia, LCIS and small foci of invasive LBC have been detected (page 10, Supplementary Material).65 There are no unique histopathological or immunohistochemical findings that distinguish CDH1-related LBC from sporadic LBC. Carriers of pathogenic CDH1 variants have been diagnosed with IC-NST,5, 34 although these are likely to be coincidental sporadic cancers. Since LBC can be misclassified, it is important to review the original histology; β-catenin and p120-catenin may be used to confirm lobular phenotype; p120-catenin shows cytoplasmic staining (membranous in IC-NST and ductal carcinoma in situ) and β-catenin is negative in lobular neoplasia.66, 67
**Long term sequelae and follow-up**

Optimally, patients undergoing PTG should be followed for life by an experienced multidisciplinary team for long-term sequelae including nutritional, hormonal, immune, neurocognitive, pharmacokinetic and psychological effects. Several HDGC and LBC advocacy organisations support affected families, including No Stomach For Cancer (www.nostomachforcancer.org), Hereditary Diffuse Gastric Cancer Advocacy (www.HereditaryDiffuseGastricCancer.org), DeGregorio Family Foundation (www.degregorio.org) and The Lobular Breast Cancer Alliance (https://lobularbreastcancer.org).

**Drug absorption**

A total gastrectomy introduces a great deal of uncertainty surrounding the use of solid oral medicines. Patients often have to remind their healthcare providers that medications need to be reconsidered post-gastrectomy (see 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 drug transporters/enzymes, and impairs cycling of medications such as the oral contraceptive pill.

Poor tablet and capsule disintegration warrants substitution with liquids, or chewable/dispersible formulations. Caution need to be exercised with liquids as the sugar content may precede dumping syndrome and dispersible tablets may cause abdominal discomfort. In some circumstances, crushing tablets or opening capsules may be advisable. It is recommended to avoid delayed release medication, attributable to the decreased functional length of the small intestine.

Alternative medicines to those requiring an acidic environment for sufficient absorption (e.g., 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 (NSAIDs). Other analgesics should be prescribed where possible and drugs irritant to the intestinal wall should be avoided (e.g., aspirin, oral bisphosphonates, doxycycline).

The variability in absorption and efficacy of oral medicines necessitates regular clinical assessment and review of medicines (Table 1). Favourable administration routes should be explored including sublingual, transdermal, vaginal/rectal, and injectable preparations.

**Sexuality and fertility**

Both a total gastrectomy and bilateral mastectomy can have significant impact on sexuality for patients. For example, changes to the digestive system affect eating, drinking and bowel habits, which may 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/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 pre-implantation 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 post-PTG appear to be normal, although caution is nevertheless warranted as pregnancies after bariatric surgery show an increased risk of adverse perinatal outcomes, such as preterm births, small for gestational age babies, and intensive care unit admissions.
Future research
Numerous questions remain on the early molecular and cellular events that lead to progressive disease in CDH1 pathogenic mutation carriers, in particular the genetic and epigenetic triggers which shift SRCs from indolent to invasive behaviour. Other priority areas include individual risk assessment and disease modifiers, CDH1 and CTNNA1 VUS pathogenicity determination, genotype-phenotype correlations, chemoprevention methods, and improved methods of endoscopic surveillance (page 11, Supplementary Material).

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. PTG is still the cornerstone of HDGC management. However, knowledge surrounding endoscopic abnormalities and SRCC detection rates in HDGC families is increasing. Therefore, there is increasing confidence 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.

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 January 1st 2020 to the date the previous IGCLC HDGC guidelines were accepted for publication (18th March 2015). Only English language manuscripts were assessed for inclusion in the search.

Contributions
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, AC, ACh, KECS, JLD, DDP, RF, JMF, KG, IG, RHH, PK, SK, AL, PFM, TN, SP, JR, HS, MS, MT, TU, HY, HKY AND JW were members of a writing group. DGC, JLDA, JMVD, KLH, CO, RSVDP, PRB, TMB, AC, KECS, JLD, MDP, JMF, IG, DGH, PK, SK, PFM, SP, JR, HS, TU, HKY, AC, JF, PG, KP, and RS presented at the Wānaka meeting. RSVDP, MMcL, 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.

Conflicts of interest
PRB reports personal fees from AstraZeneca, Janssen and Roche Diagnostics and non-financial support from GENETICANCER, outside the submitted work. DGH is founder and CMO of Contextual Genomics. The work of Contextual Genomics in no way overlaps with the topics of this review. LZ received other support from Future Technology Research LLC, Roche Diagnostics Asia Pacific, BGI, and Illumina, outside the submitted work. A family member of LZ has a leadership position and ownership interest in the Shanghai Genome Center. All other authors declare no competing interests.

Acknowledgements
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**Abbreviations**

- GC - Gastric cancer
- DGC - Diffuse gastric cancer
- HDGC - Hereditary diffuse gastric cancer
- LBC - Lobular breast cancer
- HLBC - Hereditary lobular breast cancer
- PTG - Prophylactic total gastrectomy
- TG - Total gastrectomy
- BRRM - Bilateral risk-reducing mastectomy

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**2020 Wanaka IGCLC HDGC Genetic Testing Criteria**

- Criteria met
- Positive
- Positive
- Negative
- Likely sporadic DGC or LBC
- Family history meets genetic testing criteria 1 or 2?

**Alternative CDH1 genetic testing pathways**

- Cleft lip/palate
- Multigene panel test
- Validated direct-to-consumer test

**Genetic testing for CDH1 & CTNNA1**

**Pathogenic CDH1 variant carriers**

- HDGC
  - Changes to family history?
  - YES
  - NO
  - Breast cancer in family?
  - NO
  - YES
  - HLBC

- Options:
  - Recommend PTG
  - Annual gastric surveillance
  - If declined or delayed, annual surveillance
  - Reduced emphasis on PTG if family history weak
  - TG on positive biopsy
  - Consider PTG

**CDH1 variant of unknown significance**

- Options:
  - Consider annual gastric surveillance for at least 2 years
  - After 2 years, interval may be increased
  - PTG not advised

**'HDGC-like'**

- Options:
  - Breast management based on individualised assessment

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**Fig. 1.** Flow chart for the 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.

*See text for description of CTNNA1 pathway.*
Fig. 2. Endoscopic and histopathological images of HDGC gastric lesions. A-B: Superficial pT1a SRCC focus. A) Endoscopy of non-elevated pale lesion. B) Corresponding histology showing SRCs with “indolent” phenotype superficially in the lamina propria. C-D: Intramucosal pT1a SRCC focus with invasion into the deeper lamina propria. C) Endoscopy of 1mm erosive lesion in middle of coarse pit pattern. D) Corresponding histology showing deeper invasion of SRCs almost reaching the muscularis musosae (asterisk). E-F: Precursor gastric lesions in hereditary diffuse gastric cancer (HDGC) E) In situ SRC carcinoma (dotted line) displaying SRCs within basal membrane. F) Pagetoid spread of SRCs (arrows) below the preserved epithelium. G-H: Invasive HDGC gastric lesions within the lamina propria. G) Intramucosal SRCC focus (H&E) and H) PAS-D staining. I-J: Intratumoral heterogeneity displayed in two biopsies from the same tumour. I) DGC with typical SRCs (indolent phenotype). J) DGC with pleomorphic, bizarre cells (aggressive phenotype). K-L: Advanced DGC. K) Invasion of gastric wall with prominent desmoplastic response. L) Peritoneal metastasis.
**Panel 1: 2020 HDGC genetic testing criteria**

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

**Family criteria**
1. ≥2 cases of gastric cancer in family regardless of age, with at least one DGC
2. ≥1 case of DGC at any age and ≥1 case of LBC <70yrs in different family members
3. ≥2 cases of LBC in family members <50yrs

**Individual criteria**
4. DGC <50yrs
5. DGC at any age in individuals of Māori ethnicity
6. DGC at any age in individuals with a personal or family history (1st degree) of cleft lip/cleft palate
7. History of DGC and LBC, both diagnosed <70yrs
8. Bilateral LBC, diagnosed <70yrs
9. Gastric *in situ* signet ring cells and/or pagetoid spread of signet ring cells in individuals <50yrs

*Family members must be 1st or 2nd degree blood relatives of each other. Where possible test an affected person. If there are no living affected relatives, consider tissue testing (tumour or normal) from an affected deceased relative. If these options are not possible, consider indirect testing in unaffected family members.*
**Panel 2: Breast surveillance and risk reducing mastectomy in HDGC and HLBC**

Discussions weighing up the option for surveillance versus bilateral risk-reducing mastectomy (BRRM) need to cover key information to facilitate shared-decision making and informed consent, including:

- The limited knowledge on breast cancer in HDGC and HLBC
- The lack of prospective data on imaging for LBC in a screening setting
- An individual’s breast density on mammogram and background breast enhancement on MRI, and the potential impact of these on the sensitivity of detection of LBC
- The woman’s experience of breast surveillance, particularly tolerance of MRI
- What to expect if LBC is detected at surveillance
- The option for chemoprevention (see below)
- Information about gadolinium contrast in line with recommendations from Radiology Societies
- The potential ‘harms of surveillance’, in line with consent practices in breast screening programmes e.g., recall rate for further assessment after MRI

**Breast surveillance**

- Surveillance should begin at age 30yrs and include 12 monthly clinical breast examination
- The concept of ‘breast awareness’ should be explained, with education about the clinical features of LBC e.g., thickening, indrawn nipple or a change in breast skin
- Modifiable risk factors (e.g., alcohol, exercise, weight) should be discussed
- Annual breast MRI with contrast is recommended:
  - Breast MRI should begin at age 30yrs, but the age when it should cease is not clear.
  - There may be benefit to continuing beyond 50yrs, even in non-dense breasts, because of the greater sensitivity of MRI in detection of LBC
  - Breast MRI should ideally be performed mid-cycle (10-14 days) when background breast enhancement is lowest
  - There is no evidence to support use of abbreviated MRI
- Annual mammography from age 40yrs is recommended but may be considered from 35-40yrs on a case-by-case basis
  - Mammography alone is inadequate for screening in HDGC
  - Mammography is generally not recommended under age 35yrs 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
- Ultrasound has a role in women who are unable to have MRI or have no access to MRI
  - Ultrasound should be combined with annual mammography
  - Ultrasound has a role in investigating symptoms between screening intervals

**Bilateral risk-reducing mastectomy**

- BRRM can be considered in HLBC and HDGC
- BRRM is not usually recommended under age 30yrs nor generally after 60yrs

**Chemoprevention**

- In women at elevated risk of breast cancer, chemoprevention studies with selective estrogen receptor modulators (premenopausal women) or aromatase inhibitors (post menopausal women) show about a 50% risk reduction. Chemoprevention benefit is higher in some LCIS studies, although there are no LBC-specific chemoprevention studies.
- Therapeutic levels of chemopreventative agents may be compromised post-total gastrectomy
- The side effects of endocrine therapy on quality of life can affect uptake and compliance and discussion of these is necessary with a breast specialist.
**Panel 3: Endoscopy-key recommendations**

- Surveillance should be conducted in expert centres familiar with HDGC
- Surveillance instead of a PTG can be considered depending on individual circumstances and wishes of pathogenic variant carriers (see definitions).
- Surveillance instead of a PTG should be considered in pathogenic variant carriers with an unclear risk for 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 or personal history of DGC and a \( CDH1 \) VUS, and affected family members from ‘HDGC-like’ families 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 pedigree
- Surveillance endoscopies should include both targeted and random biopsies
- The number of recommended random biopsies is 28-30 (three-five cardia, five fundus, ten body, five transition zone and five antrum)
- We recommend gastric inlet patches in the esophagus are registered, inspected and biopsied
- All patients undergoing surveillance should be fully informed about the limitations
Panel 4: General pharmacological recommendations

- Inform all patients about altered absorption of medicines post-total gastrectomy
- Substitute solid oral medication with chewable, dispersible or liquid preparations
- Consider other routes of administration: sublingual, topical, vaginal, rectal and parenteral
- Recommend to 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 than the oral contraceptive pill due to impaired absorption.
- Avoid medicines irritant to the intestinal mucosa where possible e.g., NSAIDs, corticosteroids, oral bisphosphonates, aspirin, specific antibiotics and potassium chloride
- Avoid medication likely to cause gallstones e.g., gemfibrozil
- Seek alternatives to medicines requiring an acidic environment for absorption e.g., carbamazepine, azole antifungal agents, phenytoin and selegiline
- Avoid extended and other delayed-release formulations
- Assess drug-nutrient interactions (e.g., 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 et al\textsuperscript{71} for further detail.
<table>
<thead>
<tr>
<th>Complications</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early dumping (15-30min postprandial)</td>
<td>Smaller meal, chewed well and eaten slowly. Avoid drinking with meals.</td>
</tr>
<tr>
<td>Late dumping (1.5-3hr postprandial)</td>
<td>Meals with low sugar, high protein content. Eat multiple small portions (6-8 a day). Avoid drinking with meals.</td>
</tr>
<tr>
<td>Lactose intolerance</td>
<td>Milk alternatives, lactase supplements.</td>
</tr>
<tr>
<td>Small bowel bacterial overgrowth/blind loop syndrome</td>
<td>Antibiotics +/- surgery.</td>
</tr>
<tr>
<td>Dysphagia and anastomotic strictures</td>
<td>Smaller bites with deliberate mastication. Upper endoscopy with balloon dilatation.</td>
</tr>
<tr>
<td>Increased/decreased response to solid oral medication</td>
<td>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 (c.f. controlled release preparations). Avoid the oral contraceptive pill (use implant/IUD). Avoid GI irritant drugs (e.g. aspirin, NSAIDs, oral bisphosphonates, some antibiotics). Avoid medication requiring acidic environment for absorption. Lifelong monitoring of drug levels/markers/metabolites, if possible, and assessment of desired outcomes by clinical observation and patient self-report.</td>
</tr>
<tr>
<td>Increased effects of alcohol</td>
<td>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.</td>
</tr>
<tr>
<td>Nutritional deficiencies</td>
<td>High potency multivitamin with additional vitamin B12, iron and calcium citrate supplements (iron &amp; calcium separated by 4-5hrs). Correct dosing of vitamin B12 is essential. For iron deficiency anaemia, iron infusions (c.f. oral supplements).</td>
</tr>
<tr>
<td>Osteopenia/Osteoporosis</td>
<td>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, IV bisphosphonate therapy.</td>
</tr>
<tr>
<td>Gallstones</td>
<td>Low-fat diet. Lead an active lifestyle. Avoid medications known to cause gallstones e.g., gemfibrozil.</td>
</tr>
<tr>
<td>Bile reflux</td>
<td>Ensure appropriate length of Roux limb constructed at time of surgery. Elevate head of bed &gt;30 degrees (pillows or wedge). No oral intake 2-3 hours prior to bed. Avoid dietary triggers (spice, large/fatty/sugary meals, large amounts of liquids at a time). Ingest appropriate food (soft, dry cracker or Greek yoghurt) may help soothe and carry bile downwards. Consider bile acid sequestrants and sucralfate.</td>
</tr>
<tr>
<td>Persistent Nausea &amp; Vomiting</td>
<td>Assess thiamine levels, replace (oral/IV) when needed. Avoid dairy. Have easy to digest, non-offensive foods. Consider ondansetron wafers when necessary.</td>
</tr>
<tr>
<td>Early Satiety</td>
<td>Eat multiple small meals throughout the day. Set a timer to ensure meals are not skipped.</td>
</tr>
<tr>
<td>Weight loss</td>
<td>Weight loss (~15-20%) is expected after a total gastrectomy but stabilises in 3-6 months. Eat at least 6-8 smaller meals per day and snack frequently. Include protein-fortified/high-caloric (but low-fat) foods.</td>
</tr>
</tbody>
</table>

Table 1: Post-gastrectomy complications and treatment recommendations
References


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

<table>
<thead>
<tr>
<th>Study</th>
<th>% families meeting genetic testing criteria</th>
<th>Subsets</th>
<th>Cumulative risk</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Gastric cancer (males)</td>
</tr>
<tr>
<td>Pharoah et al.²</td>
<td>11/11 (100%)*</td>
<td>-</td>
<td>67% (95% CI, 39-99%)</td>
</tr>
<tr>
<td>Pharoah et al.²</td>
<td>75/75 (100%)**</td>
<td>-</td>
<td>70% (95% CI, 59-80%)</td>
</tr>
<tr>
<td>Xicola et al.³</td>
<td>15/38 (39%)#</td>
<td>-</td>
<td>37.2% (95% CI, 8.7-89.5%)</td>
</tr>
<tr>
<td>Roberts et al.⁴</td>
<td>14/41 (37%)#</td>
<td>-</td>
<td>42% (95% CI, 30-56%)</td>
</tr>
<tr>
<td></td>
<td>4/9 (44%)#</td>
<td>families with ≥3 gastric cancers</td>
<td>64% (95% CI, 43-87%)</td>
</tr>
<tr>
<td></td>
<td>11/32 (34%)</td>
<td>families with ≤2 gastric cancers</td>
<td>27% (95% CI 15-41%)</td>
</tr>
</tbody>
</table>

*Families with ≥3 cases of DGC. **2010 IGCLC genetic testing criteria. #2015 IGCLC genetic testing criteria. vRemaining 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. 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 CO2 or air. In cases of infiltrative disease, so-called ‘limitis 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 limitis 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. Two recent reports show that targeted biopsies can result in detection of SRCC foci in 28%-43% (and Van Dieren, pers. comm) of patients, although smaller series have also reported no visible lesions. 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. 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. 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). 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. 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.\textsuperscript{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](image)

**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 \textit{CDH1} carriers are managed. We would recommend that patients are surveilled and treated in an expert centre.\textsuperscript{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

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

*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. 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. 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. 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 mucopolietic 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 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 studies23), 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 $\geq$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 Laurën’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 |
### Levels of pathological examination depending on availability of resources

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

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 immunoeexpression 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

<table>
<thead>
<tr>
<th>Main Topic</th>
<th>Sub-topics</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Emerging Research Areas</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Carriers of likely pathogenic and pathogenic variants in CDH1 or CTNNA1</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Main Topic</strong></td>
<td><strong>Sub-topics</strong></td>
</tr>
</tbody>
</table>
| 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-inflammatory |

**Carriers of variants of unknown significance (VUS)**

<table>
<thead>
<tr>
<th>Main Topic</th>
<th>Sub-topics</th>
</tr>
</thead>
</table>
### 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

<table>
<thead>
<tr>
<th>Main Topic</th>
<th>Sub-topics</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Novel disease causative events</strong></td>
<td>- Alternative loss of function mechanisms affecting CDH1 and CTNNA1, such as epimutations or defects in regulatory regions</td>
</tr>
<tr>
<td></td>
<td>- Alternative genes to CDH1 and CTNNA1</td>
</tr>
<tr>
<td></td>
<td>- Somatic mosaicism associated with CDH1 and CTNNA1 loss of function</td>
</tr>
<tr>
<td><strong>Surveillance endoscopy</strong></td>
<td>- Risk estimation and benefit of endoscopic surveillance</td>
</tr>
</tbody>
</table>

**All patient groups**

<table>
<thead>
<tr>
<th>Main Topic</th>
<th>Sub-topics</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Improved endoscopic methods</strong></td>
<td>- Confocal endoscopy</td>
</tr>
<tr>
<td></td>
<td>- Artificial intelligence</td>
</tr>
<tr>
<td></td>
<td>- Measurements of resistance of the gastric wall for detection of (larger) submucosal infiltrative lesions</td>
</tr>
<tr>
<td><strong>Model systems</strong></td>
<td>- Development of pre-clinical and clinical models to better estimate risk and inform surveillance strategies</td>
</tr>
</tbody>
</table>
References


5. Meining A, Bajbouj M. Gastric inlet patches in the cervical esophagus: what they are, what they cause, and how they can be treated. *Gastrointest Endosc* 2016; **84**: 1027-29.


