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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 *CDH1*, although pathogenic variants in *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 *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,[1] 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

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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

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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, a-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 16-18th 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.

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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 1st or 2nd 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%.[16] Further, because approximately 13% of New Zealand Māori with advanced DGC have pathogenic germline *CDH1* variants,[17] 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,[18] or with HDGC precursor lesions, remain.[6] 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[19] of signet-ring cell carcinoma is used instead of the Laurén classification of DGC.[20] 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

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based on family history.[21] 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.[22] 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.[6] Most individuals who have undergone a PTG express little or no regret after surgery.[23–25] 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,[5] creating a significant challenge for patients and clinicians.[5, 26, 27] 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) 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, *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.[28] 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.[10] It is important to note that 'likely pathogenic' variants 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 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*

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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 findings (Fig. 1). Where possible, surgery is recommended in early adulthood, generally between 20 and 30yrs of age.[6] 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

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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.[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 (SRCC) have, however, been reported in PTG specimens from carriers with no family history of DGC.[38] 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,[39, 40] 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.[39] 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[10,12] (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.

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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.[41] The recommendations outlined here (Panel 2)[42–45] are more specifically tailored to the risk and management of LBC and are consistent with existing guidelines including eviQ,[46] NICE,[47] ESMO,[48] and NCCN[49] (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.[44] 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,[50] but has a role,[51] particularly when MRI is not available, contraindicated or declined.

When LBC is detected, treatment should follow standard practice.[41, 52] 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.[47] 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).[45]

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 mis-classification, 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.[39] If patients prefer to undergo surveillance, they must be informed that this could delay identification and

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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),[38, 39] although older studies report a lower yield of 9-16%.[53–56] 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%.[57] 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.[58] 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).[21] 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,

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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

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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 2019[63] and Laurén classifications[20] 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.[6, 68] Post-gastrectomy symptoms and current treatment options are described in Table 1.[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 (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).[71]

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).[71]

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.[72] 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,[73] although caution is nevertheless

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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.[74]

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,[75] 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,[76] 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 manuscript.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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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.

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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[42]
- 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[43]
- 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

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- 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[44]

- 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,[45] 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.

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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

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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[71] for further detail.

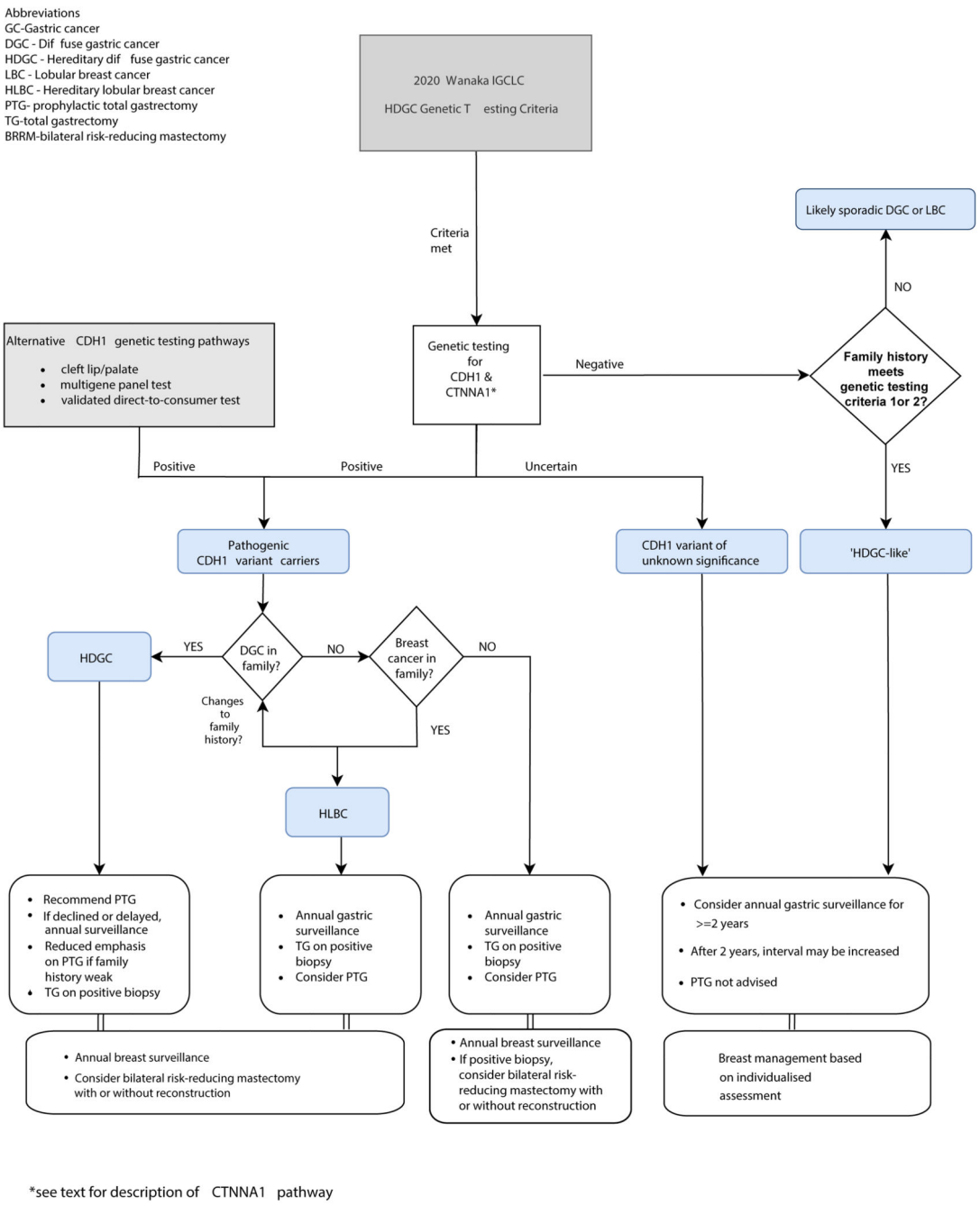

Fig. 1.

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.

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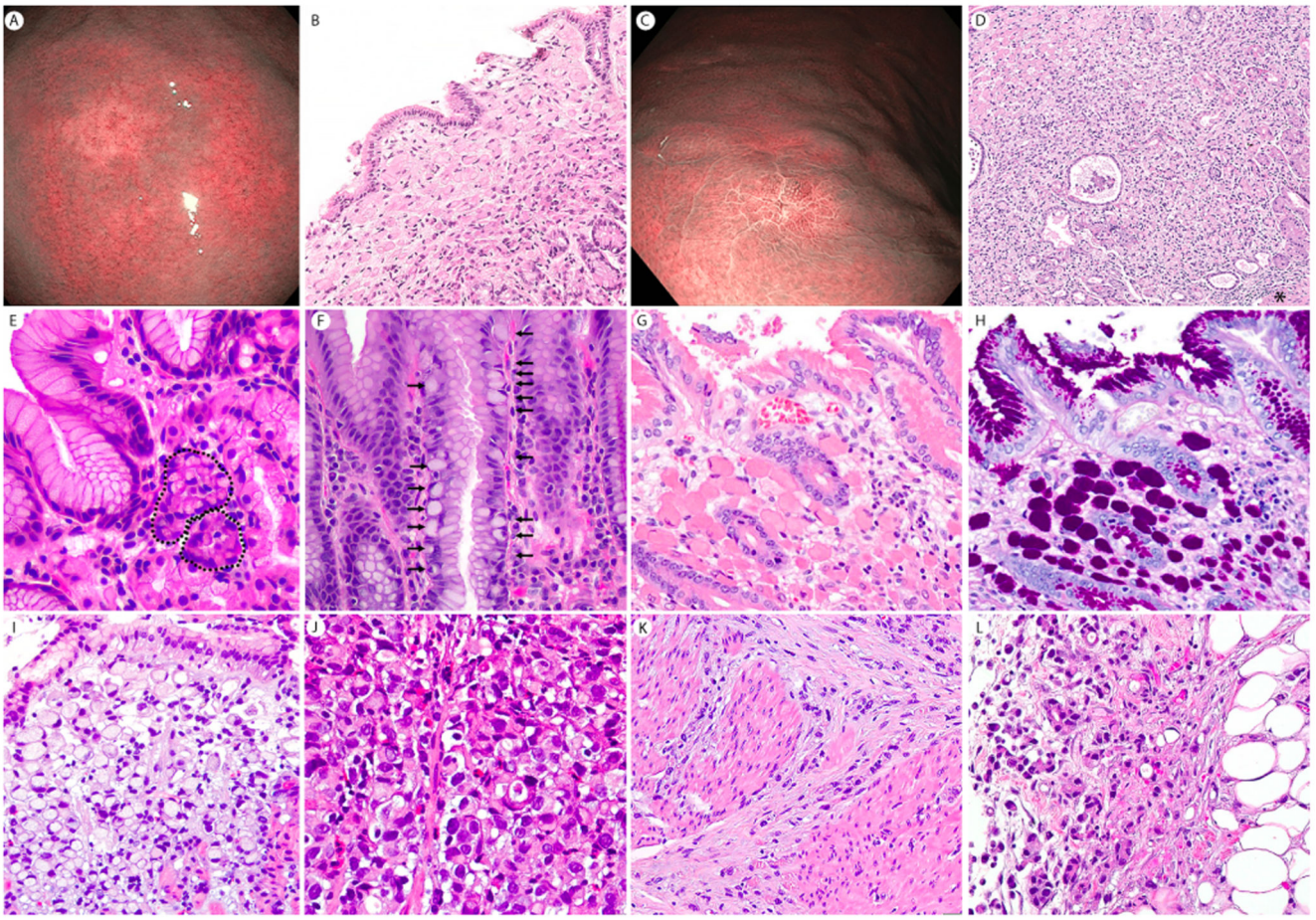

Fig. 2. Endoscopic and histopathological images of HDGC gastric lesions. A-B

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.

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Table 1
Post-gastrectomy complications and treatment recommendations

Complications	Recommendation
Early dumping (15-30min postprandial)	Smaller meal, chewed well and eaten slowly. Avoid drinking with meals.
Late dumping (1.5-3hr postprandial)	Meals with low sugar, high protein content. Eat multiple small portions (6-8 a day). Avoid drinking with meals.
Lactose intolerance	Milk alternatives, lactase supplements.
Fat malabsorption	Diet low in fat. Consider addition of pancreatic enzymes. Monitor blood levels of fat-soluble vitamins (ADEK). Start vitamin D supplementation.
Small bowel bacterial overgrowth/blind loop syndrome	Antibiotics +/- surgery.
Dysphagia and anastomotic strictures	Smaller bites with deliberate mastication. Upper endoscopy with balloon dilatation.
Increased/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 (*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.
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 & calcium separated by 4-5hrs). Correct dosing of vitamin B12 is essential.[69] For iron deficiency anaemia, iron infusions (*c.f.* oral supplements).
Osteopenia/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, IV bisphosphonate therapy.
Gallstones	Low-fat diet. Lead an active lifestyle. Avoid medications known to cause gallstones *e.g.,* gemfribrozil.
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 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.
Persistent Nausea & Vomiting	Assess thiamine levels, replace (oral/IV) when needed. Avoid dairy. Have easy to digest, non-offensive foods. Consider ondansetron wafers when necessary.
Early Satiety	Eat multiple small meals throughout the day. Set a timer to ensure meals are not skipped.
Weight loss	Weight loss (~15-20%)[55, 64, 70] 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.