Hereditary Gastric Cancer: A New Syndrome

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5.1 Introduction

The first description of *CDH1* germline mutation was reported in Maori kindred and families with diffuse gastric cancer (DGC) and lobular breast cancer (LBC) aggregation [1]. In 1999, the International Gastric Cancer Linkage Consortium (IGCLC) defined the hereditary diffuse gastric cancer (HDGC) syndrome and established clinical criteria for *CDH1* genetic screening of individuals and families at risk [2]. Using those first guidelines, the detection rate of *CDH1* mutations was approximately 40% [3]. However, the guidelines were subsequently revised given that *CDH1* germline mutations were also identified in individuals who did not meet

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testing criteria [4–6]. Hansford et al. reported that in individuals meeting the IGCLC 2010 criteria [5], the cumulative lifetime risk of gastric cancer at 80 years of age was 70% (95% CI, 59–80%) for males and 56% (95% CI, 44–69%) for females, whereas the breast cancer lifetime risk for females was 42% (95% CI, 23–68%) [7].

To date, several *CDH1* mutations affecting the entire coding sequence and functional domains have been identified in the context of HDGC [7, 8]. Whereas the majority of HDGC patients display *CDH1* truncating mutations that induce a deleterious effect and are thus a *bona fide* cause of DGC, around 20% harbor mutations of the missense type, which represent a major clinical challenge.

It has been estimated that HDGC accounts for only 1% of all diagnosed gastric cancers, but this small proportion represents a very complex syndrome, due to its difficult clinical and molecular management. In this chapter we will address these different aspects to improve understanding and translation in clinical practice.

5.2 *CDH1* Gene and E-Cadherin Protein

The *CDH1* gene (OMIM no. 192090) is located on chromosome 16q22.1 and encodes for the E-cadherin protein [9]. This macromolecule is a transmembrane glycoprotein expressed on epithelial tissue and is responsible for calcium-dependent, cell-to-cell adhesion [10]. E-cadherin is critical for establishing and maintaining polarized and differentiated epithelia through intercellular adhesion complexes. The human E-cadherin function is to suppress cell invasion; in fact its deregulation is correlated with the infiltrative and metastatic ability of the tumor [11], with the consequent loss of cell adhesion and concomitant increase in cell motility [12]. In human samples, somatic *CDH1* alterations are associated with poor survival and worse prognosis in gastric cancer patients [13].

5.3 Updated Clinical Criteria

Clinical criteria for the definition of HDGC syndrome were established in the last IGCLC meeting [14] and, in particular, *CDH1* testing is recommended when one of the following criteria have been met and following confirmation of cancer diagnoses:

Family Criteria

(a) ≥2 cases of gastric cancer in family regardless of age, with at least one DGC;
(b) ≥1 case of DGC at any age and ≥1 case of LBC at age <70 years in different family members;
(c) ≥2 cases of LBC in family members <50 years of age.

Table 5.1 Mutation types identified within study groups

Mutation type	Series study	Family study	Unknown study	Total	*p*-Value*
Deletion	46 (24.6%)	77 (21.6%)	4 (20.0%)	127 (22.6%)	0.05
Insertion	9 (4.8%)	46 (12.9%)	3 (15.0%)	58 (10.3%)	–
Non-sense	36 (19.3%)	85 (23.9%)	4 (20.0%)	125 (22.2%)	–
Missense	54 (28.9%)	71 (19.9%)	6 (30.0%)	131 (23.3%)	–
Splice-site	41 (21.9%)	77 (21.6%)	3 (15.0%)	121 (21.5%)	–
Imbalance	1 (0.5%)	0 (0.0%)	0 (0.0%)	1 (0.2%)	–
Total	187 (33.2%)	356 (63.2%)	20 (3.6%)	563	–

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*p-Value from Chi-square excluding imbalance mutation type

Individual Criteria

(d) DGC at age <50 years;
(e) DGC at any age in individuals of Maori ethnicity;
(f) DGC at any age in individuals with a personal or family history (first-degree relative) of cleft lip or cleft palate;
(g) history of DGC and LBC, both diagnosed at age <70 years;
(h) bilateral LBC, diagnosed at age <70 years;
(i) gastric in situ signet ring cells or pagetoid spread of signet ring cells in individuals <50 years of age.

5.4 *CDH1* Mutation Frequency

Recently we conducted a systematic study to assess the overall *CDH1* germline mutations reported worldwide. We classified the published studies as "series study", "family study", or "unknown study", according to whether or not the *CDH1* testing criteria were adopted.

A total of 563 *CDH1* germline mutations were identified: 33.2% in the series study group, 63.2% in the family study group, and 3.6% in the unknown study group [15]. The mutation types identified within each study group are shown in Table 5.1.

5.5 Pathology

DGC with signet-ring cells is the predominant histologic type in carriers of *CDH1* germline mutations. In advanced stages, HDGC is indistinguishable from sporadic DGC; conversely, "early" stage HDGC is characterized by the presence of multiple foci of diffuse-type, signet-ring cell carcinoma (SRCC) confined to the superficial gastric mucosa [16].

Carneiro et al. proposed a histologic model for gastric cancer development in E-cadherin mutation carriers: at the beginning, histopathologic analysis shows a pattern of *in situ* SRCC with early pagetoid spread. Subsequently, early invasion is followed by overt pagetoid proliferation of signet-ring cells, and lastly, invasive SRCC is evident [17].

Macroscopic examination and sampling of prophylactic gastrectomies should follow specific protocols, and the histological examination should be made using a checklist [5].

Gross examination of prophylactic total gastrectomy samples revealed HDGC lesions in only a minority of cases, encompassing pale patches, nodules, and tiny ulcers/scars. The majority of total gastrectomies from *CDH1* carriers exhibit tiny mucosal foci of SRCC or *in situ* SRCC, although sometimes these were only discovered after careful review by an expert pathologist [18].

The application of the total-embedding protocol considerably increased the number of HDGC lesions identified. These findings argue in favor of the use of the total-embedding protocol and the thorough histopathological examination of the entire gastric mucosa, as the gold standard practice for the evaluation of total gastrectomy specimens from *CDH1* carriers.

5.6 Singularities of *CDH1* Missense Variants

Missense variants are subtle alterations in genetic terms, still they yield clinical phenotypes similar to those caused by truncating mutations, including familial aggregation of gastric cancer, LBC and cleft lip/palate abnormalities [6, 7, 19]. In light of current knowledge, no genotype-phenotype correlations can be established based on mutation type, domain affected or amino acid substituted [19].

The consequences of missense variants arise through distinct mechanistic effects encompassing protein misfolding and premature degradation, trafficking deregulation, aberrant glycosylation, and activation of oncogenic signaling pathways [20–24]. The multiplicity of these effects may underlie cancer cell plasticity and, consequently, different severity grades.

In the last two decades, several attempts have been made to improve variant interpretation and management of germline carriers [21, 25–30]. Accordingly, Lee et al. have described *CDH1* specifications for the variant curation guidelines proposed by the American College of Medical Genetics and Genomics, and the Association for Molecular Pathology (ACMG/AMP) [31, 32]. The recommendations were developed and validated following a systematic evaluation of variants obtained from a large cohort of clinical laboratory data [31]. Nevertheless, most of the rule specifications are not recommended for use in missense changes and a large proportion of variants remain unclassified. A comprehensive approach combining multiple lines of evidence is thus crucial to estimate the clinical relevance of novel missense alterations. In this sense, familial and population data, as well as *in silico* and *in vitro* evidence should be collected and further explored [5, 33] (Fig. 5.1).

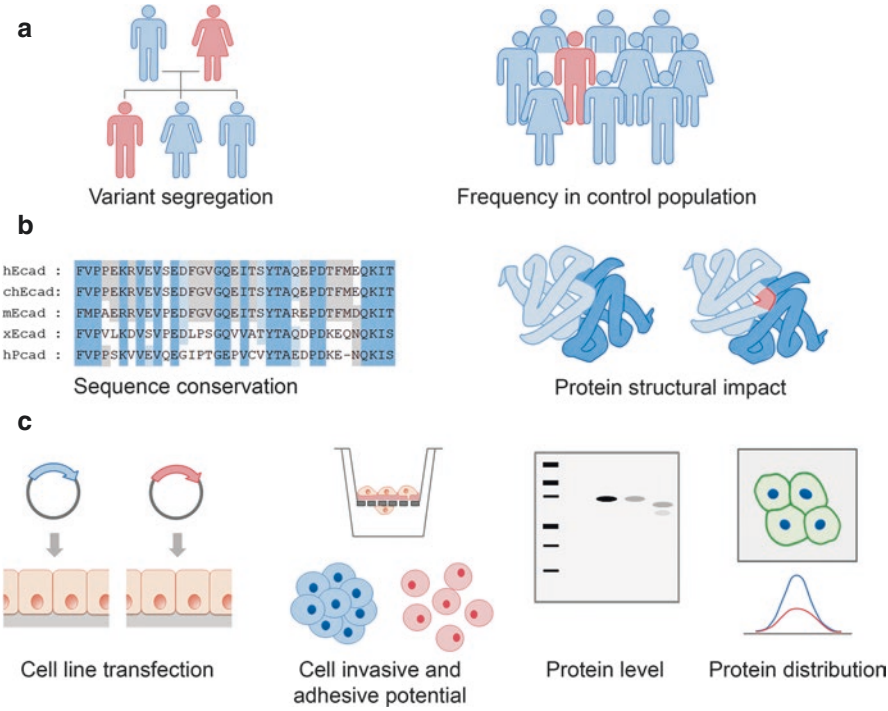

Fig. 5.1 Proposed approach for missense variant classification. (**a**) Variant frequency in control populations and its segregation within pedigrees are important genetic parameters to determine the significance of missense variants. (**b**) *In silico* analyses evaluate sequence conservation across species and can estimate putative effects on protein structure. (**c**) Functional studies include the transfection of cell lines with the variant and the wild-type E-cadherin form and thereafter the assessment of protein levels, distribution patterns, as well as invasive and cell-cell adhesive capacities

Mutation frequency in healthy control populations, co-segregation of mutation with the disease within pedigrees, and mutation recurrence in unrelated families are important genetic parameters to evaluate disease risk [26]. Regarding variant frequency in different ethnic groups, one should be aware that databases can be poorly curated and have limitations including low-quality data, or lack of details on study origin and context [32]. *In silico* tools are advantageous to predict the degree of conservation of mutated amino acids within species, impact on splicing, and putative effects on protein structure [21, 26]. For this approach, several programs should be tested as different outputs can be achieved, depending on the selected algorithm [21, 26]. Likewise, current structural models were built using *Xenopus* and mouse data and do not cover the juxtamembrane region, which affects prediction performance [21]. In contrast, experimental strategies can determine the functional impact of missense alterations in up to 85% of the cases [8]. Despite the low throughput and associated technical limitations, *in vitro* assays using cell lines transfected with vectors encoding the variant and the wild-type protein allow investigation at the protein expression level, intracellular localization and main E-cadherin functions—cell-cell

adhesion and invasion suppression [28–30, 34]. Exceptionally, analysis of migratory patterns and of the cadherin-catenin interplay can also be applied [28, 34, 35]. Demonstrative of the urge to solve this issue, efforts have been made to develop *in vivo* models that better mimic the disease context (personal communication Seruca's Lab).

Overall, the classification of *CDH1* missense variants remains a challenge for future research. In this context, the establishment of an accurate analytical pipeline and its subsequent validation, based upon clinical and pathological evidence, will have a major impact on patient monitoring and treatment.

5.7 Prophylactic Total Gastrectomy

Prophylactic total gastrectomy (PTG) has been suggested as the treatment of choice for carriers of *CDH1* mutations, because of the lack of effective endoscopic screening and surveillance programs.

PTG can be performed either laparoscopically or open, based on the experience of the surgeon. Intraoperative frozen section of the resection margins is recommended to ensure that no gastric mucosa has been left behind. An extended D2 lymphadenectomy is not required and is generally discouraged to minimize postoperative morbidity. Instead, a D1 lymph node dissection is usually recommended. Regarding the reconstruction technique, a jejunal pouch reconstruction has been suggested by some surgeons but there are no clear data indicating advantages of this more complex technique over a standard direct Roux-en-Y, which is generally preferred [18].

Finally, the IGCLC recommended gastric surveillance instead of a PTG in pathogenic variant carriers with an unclear risk for DGC, and in individuals with a family or personal history of DGC and a *CDH1* variant of uncertain significance (VUS), and affected family members from HDGC-like families and their first-degree relatives [14].

To date, we identified 224 surgical procedures classified as PTG, with an age range of 18–71 years old. The majority of PTGs were performed in the USA (111; 49.6%) followed by the Netherlands (40; 17.8%), Canada (28; 12.5%), Belgium (8; 3.6%), Spain (8; 3.6%), Denmark (7; 3.1%), Portugal (6; 2.7%), Austria (6; 2.7%), Mexico (4; 1.8%), Iran (2; 0.9%), Australia (1; 0.4%), Chile (1; 0.4%), Germany (1; 0.4%), Hawaii (1; 0.4%), and Italy (1; 0.4%) (unpublished data).

5.8 Endoscopy

The primary goal of surveillance endoscopy is to assess for gastric mucosal changes that may signal progression of early cancer foci and exclude more infiltrative (>T1a) lesions. In addition, results of surveillance endoscopy can provide patients the opportunity to make more informed decisions about gastrectomy. Unfortunately, endoscopic detection of SRCC in *CDH1* carriers is poor, and histological evaluation

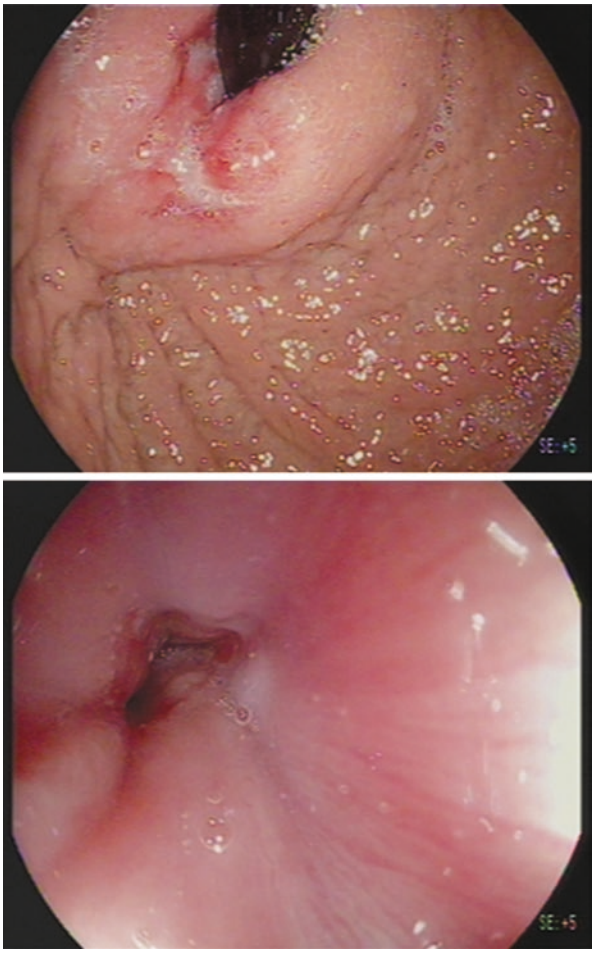

Fig. 5.2 Patient *CDH1* germline mutation carriers presenting pT3N1 stage cardias gastric cancer. Cardias of modestly padded appearance where the known ulcerated neoplasm is observed with fine irregularities involving the mucosa up to the Z line

of surgical specimens demonstrates cancer foci in up to 45–60% of cases with a negative endoscopic evaluation [36, 37].

The main factor that hinders the endoscopic diagnosis of early DGC is that the tumor cells begin infiltrating the mucosa, while preserving a normal surface epithelium. Thus, endoscopy findings can remain normal until late stages of the disease leading to a delay in the diagnosis and a very poor prognosis (Fig. 5.2). Moreover, SRCC foci can be sparse (less than 2% of the gastric mucosa) and each focus is very often less than 1 mm in greatest diameter [38].

According to consensus guidelines, individuals who tested positive for a *CDH1* mutation should be advised to consider prophylactic gastrectomy regardless of any endoscopic findings [5]. However, some patients, despite carrying a pathogenic variant, elect to delay or not pursue the surgical intervention due to personal and psychological preferences. In that case and for those carrying a VUS or fulfilling the HDGC criteria without having a germline *CDH1* mutation, annual endoscopy

surveillance starting at age 20 or at the cut-off of 5 years prior to the family's earliest cancer diagnosis, following the Cambridge protocol and in experienced centers, is recommended even if the endoscopic approach is suboptimal [5, 39].

According to the IGCLC endoscopy surveillance protocol (Cambridge method), a careful examination in a dedicated session of at least 30 min with high-definition white light is recommended. Extensive washing of the mucosa with the assistance of mucolytic and anti-foaming agents is advised in order to allow for careful evaluation of the entire gastric mucosa. Since the lack of distensibility is a sign of an infiltrative process such as linitis plastica, repeated insufflation and deflation to maximize visualization of the entire gastric mucosa, and a check for distensibility is suggested.

Prior to obtaining random gastric biopsies, targeted biopsies of all suspicious lesions, in particular pale areas (considered more likely to have abnormal signet-ring cells), erythema, erosion, or other gastric abnormalities should be taken. After sampling of all visible lesions, five random biopsies should then be taken from each of the six anatomic regions (prepyloric, antrum, transitional zone, body, fundus, and cardia), with these groups of biopsies each being sent separately for pathological analysis [5]. Given the large number of biopsies performed, it is recommended to stop anticoagulation, if possible, prior to the procedure.

However, the Cambridge protocol of surveillance carries a high false-negative rate. A model developed by Fujita et al. estimated that for a 90% detection rate, the theoretical number of biopsies necessary is 1768 per patient, but this is not clinically feasible [40]. The main disadvantage of taking an extensive number of biopsies is the formation of scar tissue, which can then mimic the superficial pale appearance of SRCC lesions. Mi et al. showed that targeted biopsies (of typical pale lesions) can result in detection of SRCC foci in more than 40% of patients, yielding a sensitivity of 28% [41]. However, we have to consider other studies demonstrating that pale areas are very non-specific for SRCC [39, 42, 43]. In a recent paper, in a cohort of *CDH1* mutation carriers, SRCC lesions were identified by an extensive endoscopic surveillance protocol in 69% of SRCC-positive patients who underwent a gastric resection. In this paper the yield of targeted biopsies (11%) was much higher for identification of SRCC lesions than the yield of random biopsies (0.9%). The low number of SRCC detected through random sampling demands a critical reappraisal of random biopsy sampling in the IGCLC guideline [44].

Given its poor reproducibility and high false-negative rates, techniques of early gastric cancer surveillance other than the Cambridge method have been explored. Chromoendoscopy, which aids in identifying mucosal pale areas, was reported to improve SRCC detection rates; however, this technique is limited to detecting only larger cancer lesions. Moreover, due to concerns about dye toxicity, chromoendoscopic examination is currently not recommended as a standard of care for HDGC [5, 43, 45]. Autofluorescence and narrow-band imaging as adjuncts to white-light endoscopy and random biopsy do not appear to improve occult cancer detection. Endoscopic ultrasonography combined with the Cambridge method failed to demonstrate an improvement in the sensitivity of detection [46].

Further development of endoscopic techniques, such as electronic enhanced imaging techniques, confocal endomicroscopy, magnification and artificial intelligence, is warranted to improve the detection rate of SRCC foci.

Confocal endomicroscopy (CEM) is indicated for microscopic visualization of the mucosa during endoscopy at an approximately 1000-fold magnification, and might limit the sampling error of untargeted biopsies [47, 48]. A phase II clinical trial is currently underway to compare CEM to standard endoscopic gastric mapping in an effort to reduce the false-negative detection rate of SRCC in patients diagnosed with HDGC [49].

Despite no known association between *Helicobacter pylori* (*H. pylori*) and HDGC, baseline *H. pylori* testing on the gastric biopsy specimens is recommended given that *H. pylori* is considered a class I carcinogen by the World Health Organization. Subsequent treatment and confirmation of eradication in individuals who are *H. pylori*-positive is advised [50].

5.9 Lobular Breast Cancer

LBC is a morphological typology of breast cancer, comprising up to 15% of all cases of this cancer [51]. It represents a good prognostic phenotype, with low histological grade, hormone receptor positivity, and with a generally favorable response to endocrine therapy [51]. However, when it is associated with the E-cadherin dysfunction, it shows a cellular discohesive pattern and a loss in tissue basic structure, resulting in cellular unregulated growth, metastases and worse prognosis [52].

Several genetic studies have identified novel germline *CDH1* mutations in LBCs correlated with the HDGC syndrome [53, 54]; indeed, LBC is associated with HDGC, and E-cadherin constitutional mutations have been described in both gastric and breast cancers [55]. Thus, women with pathogenic *CDH1* variants present an elevated lifetime risk of invasive LBC, in addition to an increased risk of gastric cancer [56]: female *CDH1* mutation carriers meeting the IGCLC 2010 criteria [5] have in fact a risk of breast cancer of 42% (95% CI, 23–68%), mostly of them LBC [3, 7, 57].

Clinical management of heritable *CDH1* gene mutation carriers is challenging and the subject of extensive scientific debates and studies. The latest IGCLC clinical criteria established as mandatory for *CDH1* genetic screening include a personal or family history of HDGC and LBC, one diagnosed <50 years [5, 6]. Testing is also suggested in families with bilateral LBC or a family history of two or more cases of LBC <50 years [5, 6].

The IGCLC approved that E-cadherin genetic screening associated with LBC can be reconsidered in two different cancer inherited predispositions, both LBC in the setting of the HDGC syndrome, and hereditary lobular breast cancer (HLBC) not associated with gastric tumors [6].

Hence, *CDH1* germline mutations have been identified in cases of LBC not associated with the classical HDGC syndrome [58]. Therefore, a novel working group dedicated to the clinical and genetic management of HLBC has proposed new

criteria to identify patients at risk of HLBC: (a) bilateral LBC with or without a family history of LBC, with age at onset <50 years; and (b) unilateral LBC with a family history of LBC, with age at onset <45 years [6, 58].

At present, there is no shared or defined protocol for breast surveillance in *CDH1* mutation carriers: indeed, the literature does not document many cases of identified *CDH1* germline mutations and data concerning the breast cancer risk in these subjects are not substantial [58]. Meanwhile, the clinical genetic trial "Understanding how *CDH1* germline mutations affect HLBC" [59] is ongoing and aims to identify the role of *CDH1* in HLBC without DGC aggregation.

In mutated *CDH1* women, careful breast radiological monitoring is nonetheless recommended, due to the significant risk of LBC developing [54], even if there are no international guidelines on breast radiological surveillance in these individuals, unlike for ascertained *BRCA1/2* genetic mutation carriers [54]. Histopathological non-cohesive features of LBC make radiological diagnosis not easy on mammography [60, 61], with a reported sensitivity ranging between 57% and 81% [62–64]. Ultrasound and breast magnetic resonance imaging (MRI) play instead a more significant role in LBC detection, presenting a reported overall diagnostic sensitivity of between 68% and 98% [65], and 93% [66], respectively. Corso et al. recommended the use of annual breast MRI followed by mammography and ultrasound at six-month intervals, similar to the program established for *BRCA1/2* carriers [58]. Furthermore, updated clinical practice guidelines recommend starting breast surveillance for HDGC and HLBC at 30 years of age, with yearly MRI from 30 to 50 years of age, underlining the uncertain advantage of adding mammography in young women and the role of supplementary screening ultrasound in dense breasts, when MRI is not feasible [14].

When considering the risk management of *CDH1* mutation carriers, distinguishing between never-affected individuals and patients diagnosed with breast cancer should be a priority [18].

The recent American Society of Clinical Oncology (ASCO) 2020 guidelines revealed a de-escalation in breast surgery recommendations when LBC is detected, as both *BRCA* and moderate-penetrance gene mutations should be treated with breast-conserving therapy, when this is clinically appropriate [58, 67]. Insufficient data exist to recommend contralateral breast cancer risk-reducing surgery to affected *CDH1* mutation carriers [6] and prophylactic surgery to healthy individuals with *CDH1* mutation, even if also family history, ability to undergo high-risk screening procedures, and patient preference are major factors to be taken into account in the decision-making process [68]. Indeed, discussion on prophylactic surgery should be set up after genetic counselling, in a multidisciplinary context [6].

As there are currently no specific indications for prophylactic mastectomy, the chance of risk-reducing surgery should be discussed in relation to the potential presence of LBC in the personal clinical history of *CDH1* mutation carriers. A precise scheme on surgical management for *CDH1* carriers has been recently delineated: information on risk-reducing surgery should be provided to *CDH1* positive patients with a diagnosis of LBC, who have a clinical indication for mastectomy or already had a mastectomy as part of their cancer treatment [58, 69]. Likewise, prophylactic

surgery should be provided to individuals with a positive family history for LBC and a well-documented *CDH1* pathogenic alteration in a first-degree relative [58, 69].

The aim of prophylactic mastectomy is to achieve maximum risk reduction, removing completely all the breast gland. Skin- and nipple-sparing mastectomy with immediate reconstruction is deemed adequate [14]. On the basis of current evidence [58], as defined for *BRCA* mutation carriers, nipple-sparing mastectomy with immediate reconstruction represents the surgical procedure of choice, which preserves both the skin and nipple-areola complex, obtaining pleasant aesthetic results and psychological well-being, with excellent oncological safety and a low complication rate [70–73].

5.10 Conclusion

HDGC syndrome is likely a much more complex disease than what was initially thought. PTG remains the only life-saving approach for individuals carrying deleterious germline mutations and fulfilling the HDGC criteria. However, great caution is needed in the absence of a family history of gastric cancer. Prophylactic mastectomy should be discussed in *CDH1* carriers with a strong aggregation for LBC, fulfilling the established clinical criteria. In asymptomatic *CDH1* carriers who do not fulfill the clinical criteria, surveillance is preferred. Given the complexity and the rarity of this syndrome, *CDH1* carriers should always be treated in a multidisciplinary fashion and in highly specialized cancer centers.

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