Supplementary Text 1: Endoscopy Surveillance Protocol

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

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

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

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

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

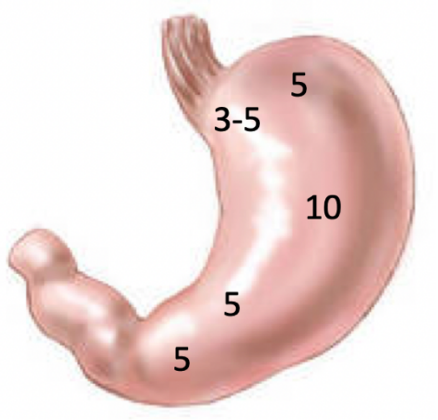
Distensibility
Prior to examination for visible mucosal abnormalities, the stomach should be assessed for distensibility. To assess for distensibility, the stomach should be maximally insufflated and then deflated using CO_2 or air. In cases of infiltrative disease, so-called '*linitis plastica*', the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

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

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

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

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



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

Expert centres

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