to a decision about the need for gastrectomy when microscopic *foci* of signet ring cells are detected. However, patients should be aware that delaying surgery can be a hazardous decision.[57]

The management of individuals with a *CDH1* variant of uncertain significance and those in whom no mutation can be identified in the family is not straightforward. We would recommend that intensive endoscopic surveillance in an expert centre should be offered to these families who fulfil the HDGC criteria. Endoscopic screening has a valuable role in guiding clinical decision making and in one case series lesions were detected in 2/7 *CDH1* mutation-negative individuals (1/5 families).[57] Specifically, any malignant lesions detected endoscopically would prompt a referral for gastrectomy. However, all patients undergoing endoscopy for HDGC should be informed that, given the very focal and often endoscopically invisible nature of these lesions, it is quite possible that lesions will not be detected by random biopsies.

HDGC endoscopy protocol

Endoscopy should be performed in centres with an experienced MDT. However, it is appreciated that sometimes this is not practical for individuals who have to travel long distances. In this case, a local endoscopist in consultation with an expert centre on the endoscopy protocol and review of histology may be a helpful alternative.

As noted above, the optimal frequency of endoscopy is not known. Based on current experience, it is recommended that individuals should be offered annual endoscopy. The bleeding risk may be slightly higher than for other indications since more biopsies are taken. Therefore, it is recommended that the local high-risk endoscopy protocol is followed such that, if possible, anticoagulants (eg, warfarin and clopidogrel) are stopped prior to the procedure. The endoscopy should be performed using a white light high definition endoscope in a dedicated session of at least 30 min to allow for careful inspection of the mucosa on repeated inflation and deflation and for collection of biopsies. The mucosa should be thoroughly washed before examination with a combination of mucolytics (*N*-acetylcysteine) and antifoaming agent (such as simethicone) mixed with sterile water. This washing is ideally done via a pump operated by a foot pedal. The macroscopic appearances of the gastric mucosa and any focal visible lesions should be recorded using still images or video for future reference and specifically sampled for histology prior to the collection of random biopsies.

Prior to examination for small *foci*, the stomach should be adequately inflated and deflated to check distensibility. Poor distensibility should raise alarm for a submucosal infiltrative process like *linitis plastica*. When this is the case, biopsies should be taken and further imaging such as a high-resolution multidetector CT scan combined with endoscopic ultrasonography is suggested to visualise the gastric wall layers. No objective measures of distensibility are currently available, and this is an area that may warrant future research.

Although an association between *Helicobacter 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 when individuals are infected it should be eradicated, especially in those opting for surveillance. A rapid urease test is the preferred test at baseline, and additionally, it is recommended to take random biopsies from the antrum and the corpus due to patchy colonisation, especially in the presence of acid suppression.

Due to the tiny *foci* of signet ring cells, which can only be recognised by microscopy, multiple biopsies are required to maximise the likelihood of diagnosing them.[39] The anatomical gastric localisation in which *foci* are identified varies between studies; reasons for this remain to be clarified but may include environmental factors or differences in the molecular pathogenesis.[39 57–65] Therefore, it is recommended that any endoscopically visible lesions are biopsied including pale areas. Additionally, random sampling should be performed comprising five biopsies taken from each of the following anatomical zones: pre-pyloric area, antrum, transitional zone, body, fundus and cardia. A minimum of 30 biopsies is recommended as described in the Cambridge protocol (see online supplementary protocol 1).[22] Even though this will still lead to sampling bias due to the large gastric surface area, taking more biopsies is not feasible in practice.[65] The biopsies may be taken using a standard forceps, ideally with a spike as this will seize the lamina propria in which signet ring cell *foci* are present. In the case of a well-defined visible lesion, an endoscopic mucosal resection can be helpful to achieve a more reliable histopathological specimen to document the degree of invasion. However, this should be done for diagnostic rather than therapeutic purposes in view of the multifocal nature of the lesions.

Special mention should be given to pale areas since these are more likely to harbour microscopic *foci* of abnormal cells, although they lack specificity leading to false positives (figure 2).[66] Recent data also suggest that these areas are visible on careful examination by white light, but narrow band imaging may make them easier to visualise (A Cats, personal communication, 2014). As noted in the previous guidelines, chromoendoscopy with Congo-red and methylene blue is no longer recommended due to concerns over toxicity.[66] Virtual chromoendoscopy using autofluorescence and trimodal imaging does not seem to confer much additional benefit over white light.[57] In order to maximise the yield from endoscopy, specialist histopathology reporting is essential and the guidelines outlined in the pathology section below should be followed.

Endoscopic surveillance of colorectal cancer

Although there are case reports of colorectal and appendiceal signet ring cell carcinomas (SRCCs) in *CDH1* mutation carriers,[26 67–70] there is currently no evidence to suggest that the risk of colorectal cancer in *CDH1* mutation carriers is significantly elevated and there are insufficient data to give recommendations on colorectal cancer screening. In *CDH1* mutation families in which colon cancer is reported in mutation carriers, information should be collected concerning the age at diagnosis, whether the affected member(s) and first-degree or second-degree relatives are mutation carriers and whether the histopathology showed a mucinous component and/or signet ring cells. For such families, enhanced colonoscopy screening should be considered at age 40 or 10 years younger than the youngest diagnosis of colon cancer, whichever is younger, and repeated at intervals of 3–5 years. In the absence of a family history, the national guidelines for colon cancer screening should be followed. It is imperative that data on colonoscopic screening in these individuals are collected so that these guidelines can be based more on evidence than on specialist opinion in the future.

Breast cancer surveillance

Knowledge about breast cancer risk in HDGC has slowly advanced since first reported in 2000,[26] yet evidence is not sufficient such that recommendations can be made of comparable strength as in *BRCA1/2*. Genotype–phenotype correlations may eventually show some HDGC families do not have an increased LBC risk, but at present it should be assumed all women with a