Familial gastric cancer: overview and guidelines for management*


Abstract
Families with autosomal dominant inherited predisposition to gastric cancer have been described. More recently, germline E-cadherin/CDH1 mutations have been identified in hereditary diffuse gastric cancer kindred. The need to have protocols to manage and counsel these families in the clinic led a group of geneticists, gastroenterologists, surgeons, oncologists, pathologists, and molecular biologists to convene a workshop to produce consensus statements and guidelines for familial gastric cancer. Review of the available cancer pathology from people belonging to families with documented germline E-cadherin/CDH1 mutations confirmed that the gastric cancers were all of the diffuse type. Criteria to define the different types of familial gastric cancer syndromes were agreed. Foremost among these criteria was that review of histopathology should be part of the evaluation of any family with aggregation of gastric cancer cases. Guidelines for genetic testing and counselling in hereditary diffuse gastric cancer were produced. Finally, a proposed strategy for clinical management in families with high penetrance autosomal dominant predisposition to gastric cancer was defined.

Keywords: gastric cancer; familial; hereditary; E-cadherin

Gastric cancer ranks second in terms of global cancer burden world wide. A decreasing incidence has been noted but gastric cancer remains a main public health concern. Diet and infection with *H pylori* are probably the prominent environmental risk factors for gastric cancer, but familial aggregation in a variable but significant proportion of cases suggests the importance of genetic predisposition. This has been supported by reports of dominantly inherited predisposition to gastric cancer, and subsequently the description of germline mutations in the E-cadherin/CDH1 gene in Maori kindreds with hereditary, early onset, diffuse type gastric cancer.

The identification of this new dominantly inherited familial cancer syndrome, designated hereditary diffuse gastric cancer (HDGC), and the subsequent realisation that similar families existed in other ethnic groups, led a group of clinical geneticists, gastroenterologists, surgeons, oncologists, pathologists, and molecular biologists from seven different countries to convene a workshop to produce consensus statements and guidelines for familial gastric cancer. In the first part of this paper we present an overview of gastric cancer which summarises formal presentations and communications from workshop participants. This overview constituted the background for discussions in working groups that resulted in the formulation of proposals for consensus statements and guidelines that were then agreed by all the Workshop participants. The working groups held their discussions around four major topics: (1) a review of the available cancer pathology from subjects belonging to families with documented germline E-cadherin/CDH1 mutations; (2) criteria to define the types of familial gastric cancer syndromes that have been described to date; (3) guidelines for genetic testing and counselling in hereditary diffuse gastric cancer; and (4) a proposed strategy for clinical management in families with high penetrance autosomal dominant predisposition to gastric cancer, including screening and the eventual role of prophylactic gastrectomy.

Overview of gastric cancer in the context of inherited predisposition

**PATHOLOGY OF GASTRIC CANCER**
Carcinomas of the stomach are morphologically heterogeneous. This heterogeneity is reflected in the diversity of histopathological classifications available which are based on different approaches, such as histological profile, degree of differentiation, pattern of growth, and histogenesis. The morphological heterogeneity of gastric carcinomas is also
reflected by the frequent occurrence of two or more distinct components in individual cases. The classification of Lauren is one of the most useful classifications, distinguishing two main types of gastric carcinoma, intestinal and diffuse, which display different clinicopathological profiles and often occur in distinct epidemiological settings. Lauren's classification has, nevertheless, several drawbacks. The first concerns the existence of a fairly large group of tumours which do not fit within the two major types. This group of "unclassified" or "indeterminate" gastric cancer includes undifferentiated (solid) carcinomas, as well as carcinomas exhibiting a dual pattern of differentiation (mixed intestinal and diffuse). The solid carcinomas display a clinicopathological profile similar to that of glandular (intestinal) carcinomas, thus supporting the assumption that they could be considered as a solid variant of intestinal carcinoma. Another drawback to Lauren's classification concerns the confusion linked to the term "intestinal". This led to the proposal of a modification of Lauren's classification which recognises four main types of gastric cancer: glandular, isolated cell type, solid, and mixed carcinoma.

The importance of distinguishing two main histopathological types of gastric cancer, one with a diffuse component (isolated cell and mixed types) and one without a diffuse component (glandular/intestinal and solid types), is highlighted by finding somatic E-cadherin mutations exclusively in the first group.

Features of gastric mucosa at the periphery of sporadic gastric carcinomas are in keeping with these two histogenetic pathways. Chronic atrophic gastritis and intestinal metaplasia are significantly more frequent at the periphery of glandular (intestinal) carcinomas and there is a higher prevalence of foveolar hyperplasia at the mucosa overlying or at the periphery of isolated cell type (diffuse) carcinomas. Systematic studies of the non-neoplastic gastric mucosa of members of families with hereditary gastric cancer are necessary to elucidate the nature of premalignant lesions in this context. This information will be of the utmost importance for the surveillance of people carrying germline mutations.

GENETIC PREDISPOSITION TO Gastric CANCER

Earlier studies described a familial component only for diffuse gastric carcinoma, but more recently similar proportions of intestinal gastric cancer patients with a positive family history have been found. The first description of a clear molecular basis for familial gastric cancer was the report of germline inactivating (truncating) E-cadherin/CDH1 mutations in three Maori kindred with early onset diffuse gastric cancer. Shortly afterwards it was shown that E-cadherin/CDH1 inactivating germine mutations also accounted for a proportion of European ancestry kindred with familial diffuse gastric cancer (three mutations in 10 families), but were absent in eight families with intestinal gastric cancer. Subsequently, a further six inactivating germine mutations in families of European origin have been reported. Germine inactivating mutations of E-cadherin have also been found in one family of African American origin, another Maori family, and one family of Pakistani origin (CO, NG, and CC, unpublished data). All these families have diffuse type gastric cancer. Germine missense E-cadherin/CDH1 “mutations” have been identified in index cases from one Japanese family, two Korean families, and two other families (CO, DGH, and CC, unpublished data). Again, all families have diffuse type gastric cancer. However, the pathogenic significance of these genetic variants remains to be elucidated.

Gastric cancer might also be seen as part of the tumour spectrum in other inherited cancer predisposition syndromes. In particular, gastric cancer has been identified as part of the spectrum of cancers in hereditary non-polyposis colorectal cancer (HNPCC), Li-Fraumeni syndrome (LFS), familial adenomatous polyposis (FAP), and Peutz-Jeghers syndrome. The first report describing familial clustering of gastric cancer in a kindred subsequently shown to have HNPCC was that of family G reported by Warthin in 1913. However, in a follow up report of this family, the risk of gastric cancer was found to have decreased significantly, consistent with this cancer's decline in the United States and other industrial nations. The first report of a specific excess risk of gastric carcinoma in HNPCC was by Vasan et al., but limited data on the histopathological subtypes of gastric cancers were presented. The most detailed study on gastric cancer in HNPCC is based upon clinical data and tumour samples recorded in the Finnish HNPCC registry, which included 51 families with a mutation in hMSH2 or hMLH1 or that met the Amsterdam criteria. A total of 570 members of these 51 families were affected by malignancy, 62 of which were gastric carcinoma. Clinical information was obtained on 45 of these patients and tumour samples were examined in 24. The mean age of diagnosis of gastric cancer was 56 years, and the average percentage of gastric cancers within a family was 11, with a range of 0-40%. Nineteen of the gastric cancers were of the intestinal type and three were of the diffuse type. H pylori infection was found in only three of 15 cases. Replication error (RER) was detected “clearly” in seven tumours and “fairly clearly” in 11. These data support the view that gastric cancer belongs to the tumour spectrum of HNPCC, the intestinal type of histology is characteristic, as is the RER+ phenotype, but H pylori infection appears to be uncommon.

Very few studies have addressed the population attributable risk of familial aggregation in gastric cancer. One such study from Italy suggests a risk of around 8%. In Japan the molecular epidemiological features of families with aggregation of gastric cancer were studied in a hospital based series. Families were recruited by reviewing the genealogical trees of 3632 patients with gastric cancer. The criteria for recruiting such families were the following:
at least three relatives should have gastric cancer and one of them should be a first degree relative of the other two, at least two successive generations should be affected, and in one of the relatives gastric cancer should be diagnosed before the age of 50. Thirty-one cases (0.9%) fitted into all three of these criteria. In 18 of the 31 families gastric carcinoma was the only reported cancer, and there were no families that fitted the clinical criteria of HNPCC or LFS. Paraffin embedded tissues were available in 29 probands. Slight dominance of the intestinal type (17/29) was observed. Interestingly, this sharply contrasts with data from familial gastric cancer registry databases in the UK where analysis of 26 families fitting the three criteria defined by Yokota’s group showed that 17 of these were of diffuse type, only three were of the intestinal type, and in six pathology information was not available or specified (NG, FMR, ERM, and CC, unpublished data). There is a need for large population based studies of genetic predisposition to gastric cancer to determine the attributable risk of germ-line mutations. To date, a single E-cadherin germ-line mutation in a case of apparently sporadic diffuse gastric cancer in a young person has been reported.21

E-CADHERIN MUTATIONS AND GASTRIC CANCER
The E-cadherin gene coding sequence gives rise to a 27 amino acid signal peptide (exons 1-2), a 154 amino acid precursor peptide (exons 2-4), and a 728 amino acid mature protein.32 The mature protein consists of three major domains, a large extracellular domain (exons 4-13), and smaller transmembrane (exons 13-14) and cytoplasmic domains (exons 14-16).32 As in other autosomal dominant cancer predisposing genes only one E-cadherin allele is mutated in the germine and the vast majority of genetic changes lead to truncation of the protein. The 14 truncating producing mutations described so far are distributed throughout the gene (table 1). In sporadic gastric cancers, truncating mutations are uncommon and sequence changes usually result in either missense mutations (most commonly in exons 8 and 9) or exon skipping, especially of exons 6-9.22 The mechanism whereby these alterations in cadherin structure results in cancer is at present not elucidated but is probably complex. For example the “wild type” E-cadherin allele does not appear to be silenced, since in the limited familial gastric cancer cases studied there is still residual E-cadherin immunoreactivity.20 22

Putative missense mutations have been reported in families with diffuse gastric cancer, but their functional significance has not been tested.

Table 1  E-cadherin germ-line truncating mutations reported to date

<table>
<thead>
<tr>
<th>Exon</th>
<th>Mutation (effect)</th>
<th>Reference</th>
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<tbody>
<tr>
<td>2</td>
<td>A(49-2)G (splice site)</td>
<td>20</td>
</tr>
<tr>
<td>2</td>
<td>G59A (W20X)</td>
<td>20</td>
</tr>
<tr>
<td>2</td>
<td>G707T (E24X)</td>
<td>21</td>
</tr>
<tr>
<td>3</td>
<td>C187T (R65X)</td>
<td>19</td>
</tr>
<tr>
<td>3</td>
<td>C190T (Q64X)</td>
<td>21</td>
</tr>
<tr>
<td>3</td>
<td>372-377 delC (frameshift)</td>
<td>22</td>
</tr>
<tr>
<td>5</td>
<td>G586T (G196X)</td>
<td>21</td>
</tr>
<tr>
<td>7</td>
<td>G1008T (splice site)</td>
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</tr>
<tr>
<td>8</td>
<td>G(1137+1)A (splice site)</td>
<td>21</td>
</tr>
<tr>
<td>9</td>
<td>1711 insG (frameshift)</td>
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<td>11</td>
<td>1588insC (frameshift)</td>
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<td>19</td>
</tr>
<tr>
<td>13</td>
<td>C2190T (Q699X)</td>
<td>19</td>
</tr>
<tr>
<td>15</td>
<td>2382-2386 insC (frameshift)</td>
<td>8</td>
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non-endemic regions. In endemic regions such as Japan, which uses mass screening protocols, a higher rate of diagnosis of early stage gastric cancers has been observed.24 The survival of early gastric cancer (for example, not beyond the mucosa or submucosa) is much better than advanced lesions, so identifying these lesions at the earliest of stages is imperative for optimal survival. There are several lesions of the stomach generally recognised as precancerous with varying degrees of risk but, excluding dysplasia, routine interval surveillance examinations such as endoscopy are not routinely performed in these conditions.35

Endoscopy is generally considered to be the best method to diagnose gastric cancer but its cost is a major limitation for its use in mass screening protocols. Diagnosing diffuse gastric carcinoma is most difficult, as these lesions tend not to form a grossly visible exophytic mass, but rather spread submucosally as single cells or clustered islands of cells. Improved methods to diagnose these early diffuse lesions is a pressing issue especially to those with germline E-cadherin mutations. New technologies available or emerging but not in current routine use which might potentially aid our ability to diagnose early diffuse gastric cancer lesions include chromoendoscopy (that is, methylene blue or indigo carmine staining) or endogenous fluorescence detection methods.36 37 Endoscopic ultrasound is at present available in many centres and, although mainly used to stage previously diagnosed tumours further, it might be helpful in identifying early diffuse type gastric carcinoma lesions. Future studies of these and other methods of examining the stomach in predisposed subjects are needed to draw conclusions on their use in diagnosing early gastric lesions. For now, in the surveillance of those predisposed to gastric cancer development not desiring prophylactic gastrectomy, clinicians are urged to undertake the most detailed endoscopic mucosal examination with multiple biopsies of even the most subtle of lesions.

DIAGNOSIS AND SCREENING OF GASTRIC CANCER
Diagnosing gastric cancer in its early stages is a difficult task. Symptoms do not appear until the lesion reaches late stages of development and are generally non-specific.31 When the diagnosis of gastric carcinoma is established, it is at an incurable advanced stage (stage III or IV) in over two thirds of the cases in
and FRL, unpublished data). There are therefore no publications or large experience in addressing the morbidity and mortality of this procedure. The reports that exists in regard to total gastrectomy for gastric cancer are extensive. The consensus regarding the different reconstruction methods and the nutritional consequences should be equally applicable to prophylactic gastrectomy for hereditary gastric cancer. The complications and quality of life data, however, could be expected to differ because prophylactic gastrectomy is performed in a young, healthy population without malignant disease. An accurate definition of the risks and outcome of prophylactic gastrectomy will therefore not be available for some years.

The principal controversies in reconstruction of the GI tract after total gastrectomy are (1) reconstruction via a Roux-en-Y direct limb versus use of an interposed jejunal graft to allow oesophago-jejuno-duodenal reconstruction, and (2) construction of a pouch to increase reservoir volume distal to the oesophageal anastomosis versus direct connection of the isoperistaltic jejunum. Several groups have studied these issues and from what they published it appears that jejunal interposition between the oesophagus and duodenum may have a slight advantage in maintenance of weight, but at the cost of significantly increased bile reflux and an additional anastomosis, which increases risk of technical complications. One therefore concludes that direct Roux-en-Y reconstruction is probably preferable.

Many authors have examined the complications of total gastrectomy and they revolve mainly around the oesophageal anastomosis. A recent paper which examines complications in detail identifies mortality of 4%, abdominal abscess in 8%, wound infection in 8%, pneumonia in 11%, myocardial complications in 9%, and reoperation in 5%, with an average hospital stay of 23 days. As noted at the outset, the complications in a young, healthy population could be expected to be less than this, but to what extent is not known. In general, authors have identified 30 day mortality after total gastrectomy in the 3-6% range, oesophageal anastomotic leakage rates in the 10-12% range, and wound and intra-abdominal septic complications in the 5-10% range. Oesophageal anastomotic strictures rates of 10-15% are also usually identified. The principal long term morbidity after total gastrectomy is in the alteration of eating habits, dumping syndrome, diarrhoea, and weight loss, which are universally present. Several recent papers have examined these in detail, particularly that by Leidman and weight loss, which are universally present.

Consensus statements and guidelines

Pathology in HDGC: The panel of pathologists present at the workshop reviewed haematoxylin and eosin stained slides available from 23 pathological samples obtained from 22 subjects belonging to eight different families with inactivating germline E-cadherin/CDH1 mutations. Thirteen slides contained primary gastric cancer: 11 were of the diffuse type and two were of the mixed type (with both diffuse and intestinal/glandular components). Pathology from seven intra-abdominal metastases, including one Krukenberg ovarian metastasis, showed diffuse type carcinoma. One breast cancer from a gene carrier (who also had diffuse gastric cancer) was invasive lobular carcinoma. There was also one colorectal cancer (moderately differentiated adenocarcinoma) from another gene carrier. In one person, first cousin of an identified germline E-cadherin mutation carrier, there was a moderately differentiated gastro-oesophageal junction adenocarcinoma, but it has not yet been determined if he is a mutant gene carrier. In summary, all the gastric carcinomas from documented germline mutant E-cadherin carriers have been of the diffuse type and two of these had a glandular/intestinal component. To determine whether the diffuse gastric carcinomas from germline mutation carriers have any distinctive features among all diffuse carcinomas will require a controlled and blinded analysis of a larger number of such carcinomas. Interestingly, one case of lobular breast carcinoma in a mutant gene carrier was available for review and other cases have been reported, which, together with the previous description of somatic E-cadherin mutations in sporadic lobular breast cancer, suggest that this tumour might be a part of the tumour spectrum in HDGC. The finding of a Krukenberg ovarian metastasis in a mutant gene carrier suggests that any case of “ovarian carcinoma” in a family with aggregation of diffuse gastric cancer should have pathology carefully reviewed to determine its origin.

Definition of familial gastric cancer syndromes: In formulating a definition of familial gastric cancer syndromes, a distinction must be made between the histopathological subtypes (diffuse or diffuse with glandular component/mixed versus intestinal) which segregate within families. It is therefore proposed that review of histopathology should be part of the evaluation of any family with aggregation of gastric cancer cases. This is the first instance in which distinctive histopathology can be used as a phenotypic criterion.
to identify gene carriers in a familial epithelial cancer syndrome. This will reduce the number of phenocopies and consequently allow for a broader set of clinical criteria without running into the problem of very low yield of mutation detection.

**Familial diffuse gastric cancer**

Hereditary diffuse gastric cancer (HDGC) was defined as any family that fits the following criteria: (1) two or more documented cases of diffuse gastric cancer in first/second degree relatives, with at least one diagnosed before the age of 50, or (2) three or more cases of documented diffuse gastric cancer in first/second degree relatives, independently of age of onset. On the very limited data available, we predict that up to 25% of families that fit these criteria will have inactivating germline E-cadherin/CDH1 mutations. Lobular breast carcinomas, colorectal carcinomas, and prostate carcinomas have been documented in mutant gene carriers, but the inclusion of these tumours as diagnostic criteria seems premature at this stage.

A syndrome of autosomal dominant gastric polyps and diffuse gastric cancer has been described and shown not to be linked to E-cadherin/CDH1.5-11 This syndrome should be suspected in any family with aggregation of hyperplastic gastric polyps and diffuse gastric cancer, since it may be distinct from HDGC.

**Familial intestinal gastric cancer**

The workshop participants decided to adjust the criteria used to define familial intestinal gastric cancer (FIGC) depending upon the incidence of gastric cancer in the population. Thus countries with high incidence (Japan, Portugal) should use the diagnostic criteria analogous to the Amsterdam criteria for HNPCC: (1) at least three relatives should have intestinal gastric cancer and one of them should be a first degree relative of the other two; (2) at least two successive generations should be affected; (3) in one of the relatives, gastric cancer should be diagnosed before the age of 50. In countries with low incidence (USA, UK) FIGC was defined as: (1) at least two first/second degree relatives affected by intestinal gastric cancer, one diagnosed before the age of 50; or (2) three or more relatives with intestinal gastric cancer at any age.

**Gastric cancer in other familial cancer syndromes**

Gastric cancer is part of the HNPPC tumour phenotype and the current criteria to identify HNPPC should be used for these families. Gastric cancer should be recognised as a component of other hereditary cancer syndromes, such as LFS, FAP, and Peutz-Jeghers syndrome.

GENETIC TESTING AND COUNSELLING FOR HDGC

The workshop participants felt strongly that testing guidelines should be developed in parallel with ongoing scientific discovery of the genes responsible for HDGC rather than after the disorder is fully delineated and understood at some distant time in the future. These guidelines will be important for clinicians who are currently caring for families with known E-cadherin mutations, as well as providing assistance to clinicians and HDGC families in the near future. The guidelines should be regarded as provisional; they are based on our current understanding of the clinical, pathological and molecular information from known HDGC kindreds. Subsequent workshops will update and revise the guidelines as issues such as heterogeneity, penetrance, age of onset, test specificity and sensitivity, as well as the role of screening and prophylactic gastrectomy, are further clarified.

**Guidelines for genetic counselling and testing for HDGC**

Genetic counselling and testing for germline E-cadherin mutations should be considered for subjects whose family pedigrees meet or exceed the minimum requirements for HDGC.

This workshop encouraged all genetic counselling centres, cancer centres, surgeons, and general practitioners to review the family history of patients with diffuse gastric cancer to determine eligibility for testing. The workshop participants were unable to estimate the prevalence of mutations in patients who present without a family history of gastric cancer. It is therefore premature to offer E-cadherin genetic testing for apparently sporadic cases of diffuse gastric cancer, even if those subjects are affected at a young age. Work in various laboratories world wide is currently investigating this issue, so that this recommendation may be altered in the near future. Families with gastric cancer with intestinal subtype histology should not be referred for germline E-cadherin mutation analysis, since all evidence to date shows the absence of E-cadherin mutations in both sporadic and familial intestinal type gastric cancers. The workshop participants recognise that offering E-cadherin mutation testing to HDGC families involves uncertainty about clinical management, disease outcome, and psychosocial burden for the family member. However, in light of the highly lethal nature of diffuse gastric cancer, autosomal dominant inheritance pattern, and high penetrance for heterozygotes, withholding such information may do more harm for at risk family members. This situation is analogous to other high risk cancer family syndromes, where delay in diagnosis could have disastrous consequences.

Pre- and post-test genetic counselling must be provided to subjects from HDGC kindreds who are undergoing genetic testing for germline E-cadherin mutations.

The complexities and uncertainties surrounding the clinical impact of E-cadherin mutations necessitate that genetic testing be provided within the counselling framework established for other family cancer syndromes. These protocols divide testing into separate diagnostic and predictive phases. For HDGC kindreds, diagnostic testing would be initiated on a sample from an affected subject in order to identify pathological germline E-cadherin mutations. A test looking for the specific family...
mutation could be offered to healthy at risk family members on a predictive basis. Since most mutations will be unique to a specific family, it is very important that genetic testing not be offered to at risk subjects without proceeding through the diagnostic phase. Each family member who is interested in testing should be provided with counselling before and after the test is performed. We suggest that this process be undertaken by a multidisciplinary group of clinicians who can explain and support the family member as they decide which options to follow in the future.

The pre-test counselling should review and discuss the natural history of gastric cancer, provisional definition of HDGC, risk owing to autosomal dominant inheritance, the possible outcomes of the test and their implications, and the courses of action which can follow different results. The concept of penetrance, or the chance of a heterozygous carrier developing gastric cancer over his or her lifetime, should be fully explained. An approximation of 70% for the penetrance of the susceptibility gene was reported for the first large Maori kindred with a germline E-cadherin mutation. A similar penetrance estimate was determined in an additional seven families (35 gastric cancer cases in total) contributed by workshop participants (PP and CC, unpublished observations). A note of caution should be introduced here, since these preliminary penetrance estimates are still based on limited numbers and might be refined once more families are studied. The impact of genetic testing on health and life insurability, as well as other psychosocial issues, should be discussed. If family members wish to proceed with testing, informed consent documents should be signed and submitted with the sample.

The benefits of diagnostic testing for the family will be an opportunity to identify the underlying cause of the cancer in the family and to provide for predictive testing and intensive clinical management for at risk family members.

Once a mutation has been identified, the primary benefit of predictive testing for an at risk family member would be to clarify their risk for developing diffuse gastric cancer in the future. A negative test result implies that the subject will be at the general population risk for gastric cancer rather than the higher risk based on family history without genetic testing. These subjects would not require further gastric screening or need to consider prophylactic gastrectomy. On the other hand, those family members who do inherit the abnormal allele may face up to a 70% lifetime chance of developing gastric cancer. Inherent in these guidelines for testing is the hope that early identification of gene carriers will improve clinical outcome through the use of intensive screening or prophylactic surgery.

Predictive testing of minors in HDGC, as well as other family cancer syndromes, is controversial. Since at least five subjects have been reported to develop this lethal cancer under the age of 18 years, the workshop participants suggested that HDGC is now part of the small set of hereditary cancer syndromes, such as MEN2A (multiple endocrine neoplasia type 2A) or medullary thyroid cancer, LFS, and FAP, in which genetic testing is potentially clinically useful in children. Until further is known about gene penetrance in youngsters, great caution will have to be exercised when testing minors. If a clinical group is faced with such a family situation, intensive and structured counselling sessions should be provided for the family and child, in which the child indicates his/her understanding and assent for the test. While testing minor children may appear to be a radical option, successful programmes have been developed for other cancer syndromes that are acceptable to the family and child.

Genetic counselling and testing for E-cadherin mutations should be provided by health professionals with experience in cancer genetic counselling. The workshop members anticipate that kindreds that meet the minimal criteria for HDGC will require intensive counselling and evaluation, including pedigree analysis and risk assessment, as decisions are reached about testing, screening, and prophylactic surgery.

Families undergoing germline E-cadherin testing should be entered in research protocols for the initial mutational analysis. Positive test results must be confirmed in a separate clinical laboratory before disclosure by the health professional caring for the family.

Since our understanding of the molecular genetics of HDGC is in its infancy, all mutational testing for E-cadherin mutations should only be provided on an investigational basis until more is known about the disease. Whenever possible, the families that choose to undergo testing should be entered into a cooperative registry for ongoing research and discovery (the IGCLC is running one such registry in Cambridge, UK: Department of Oncology, Box 193, Addenbrooke’s Hospital, Cambridge CB2 2QQ, UK). A multidisciplinary study focused on HDGC and E-cadherin would ultimately benefit both the families with identified E-cadherin mutations and the research community as a whole. For genetic counselling purposes, the patients and families will be provided with information on current research developments in a timely manner while learning more about the management recommendations as they are refined in the future. It is anticipated that each participating research laboratory will develop specific and informed consent documents in accordance with the requirements of each institution’s Institutional Review Board (IRB) or Ethics Committee. The informed consent process will be included in the genetic counselling sessions before sample collection. Samples from affected family members should be submitted directly to the research laboratory for initial mutational analysis. At present, samples may be in the form of whole blood, banked DNA, or paraffin tissue. If paraffin samples are the only available option owing to the death of the affected cases in the family, paraffin blocks on two separate cases should be analysed (to avoid the problem of artefactual “mutations” in
DNA isolated from this type of material). This recommendation may be altered by specific laboratory protocols on a case by case basis.

Once a pathological mutation is identified, the test result must be confirmed in a laboratory approved for clinical molecular testing before disclosure to the counselling professional and, ultimately, to the patient and family. A second sample from an affected subject will then be submitted. In this way, critical genetic test results can be accurately transferred from the research environment to the clinical setting for management and follow up decisions.

Participating research laboratories in the Linkage Consortium (IGCLC) will facilitate the transfer of methodology to clinical laboratories.

The workshop participants strongly felt that the research laboratory had no role in providing specific testing information directly to patients and family. Rather, researchers will assist all tested families by providing the necessary assistance to the clinical laboratory. The genetic counselling or health professional group will provide the active link between the research and clinical groups caring for each family.

SURVEILLANCE FOR AT RISK SUBJECTS FROM FAMILIAL GASTRIC CANCER KINDRED

Patients with familial gastric cancer syndrome resulting from mutation in the E-cadherin gene face up to a 70% likelihood of developing gastric cancer during their lifetime. This risk is similar to MEN2 and BRCAl. The average age of onset in both males and females is 38 years, though cases of onset at ages 15 and 16 have been documented in the reported world experience, and several cases between 20-30 years of age. All cases of gastric cancer arising in the E-cadherin familial syndrome are of the diffuse type, frequently resulting in ulcers in the gastric mucosa. As a result mucosal abnormalities tend to occur late and delay the endoscopic diagnostic (CEJ and PML, unpublished observations). Surveillance endoscopy might therefore only identify relatively advanced disease and more effective surveillance techniques need to be explored in this population (see above).

Prophylactic gastrectomy is effective in preventing gastric carcinoma, but has a high morbidity. The workshop participants estimated that the morbidity in the young, healthy population for prophylactic gastrectomy would be 1-2% mortality, 10-20% major acute morbidity, principally related to oesophageal anastomotic problems, and 100% long term morbidity related to weight loss, rapid intestinal transit, dumping syndrome, and diarrhoea. The participants emphasised that when a total gastrectomy is performed in this population it is essential to document the complete removal of gastric mucosa by pathologically identifying rims of oesophageal and duodenal mucosa at the two ends of the surgical specimen. This recommendation was based on the consensus view that once a person decides to undertake such a major prophylactic operation it would make little sense to retain any “at risk” gastric mucosa, and on the anecdotal evidence of a case of gastric cancer developing after prophylactic partial gastrectomy in one gene carrier.10

The high surgical risk of the procedure should be minimised by performance at centres with extensive experience in gastric surgery. The decision to perform prophylactic gastrectomy should be balanced with age based risk, based on age specific penetrance data. Other factors, for example, the decision to have children, may affect the decision regarding timing of prophylactic gastrectomy, and it is essential that patients carrying the gene have the opportunity for extensive counselling, discussion, and reflection with knowledgeable clinicians, geneticists, and counsellors before making the decision to proceed. If a decision is made by an E-cadherin mutation carrier not to have prophylactic gastrectomy, that patient should be offered intensive surveillance by the most sensitive methods available at the time (endoscopy every six to 12 months). The risk of other cancers (breast, colon) should also be targets of screening, as they may also be increased in this population, and the patient should be counselled regarding these.

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21 Richards FM, McKee SA, Rajpar MH, et al. Germline E-cadherin gene (CDH1) mutations predispose to familial


