Aetiology of colorectal cancer and relevance of monogenic inheritance


Background and aims: Although diet and lifestyle are associated with the development of colorectal malignancies, the only clearly identified aetiological factors in colorectal cancer are inheritance (hereditary non-polyposis colorectal cancer (HNPCC) and familial polyposis), inflammatory bowel diseases, papillomavirus, and acquired immunodeficiency syndrome (AIDS). Our aim was to determine what proportion of colorectal neoplasms could be attributed to these specific factors.

Patients and methods: Data from a colorectal cancer registry were analysed over a 15 year period, during which nearly 2500 cases were recorded. In patients with suspected HNPCC, microsatellite instability and immunohistochemical expression of proteins encoded by the main DNA mismatch repair genes were assessed. In families with unstable neoplasms, constitutional mutations of the mismatch repair genes hMSH2, hMLH1, and hMSH6 were evaluated by single strand conformation polymorphism analysis and sequencing.

Results: Inflammatory bowel diseases, familial polyposis, and AIDS were rare causes of colorectal cancer (three, three, and one case, respectively). Anal squamous carcinoma developed in 27 patients (1.0%) and could be attributed to papillomavirus infection. In 58 patients (from 34 families) a clinical diagnosis of HNPCC was established (2.4%). In total, cases with a known aetiology were 92 (3.7% of all patients). Microsatellite instability was detected in 15 cancers from HNPCC families, and germline mutations in six families (12 patients, 0.5% of the total). Families with unstable tumours, with or without mutations, were clinically similar, suggesting the involvement of the mismatch repair system even when mutations were not detected.

Conclusions: The study suggests that the aetiology of colorectal malignancies remains elusive in the large majority of cases. Among specific causes, HNPCC represents the most frequent. However, with a population based approach, constitutional mutations of the main genes involved in HNPCC can be detected in only 20% of cases.
area covered by the registry includes Modena and 10 surrounding communities, for a total of 265 227 residents (128 228 men and 136 939 women) at census 1991 (mid-revision). Modena is in Northern Italy, between Milan and Bologna. The area is highly industrialised (in particular motorcars, textiles, and pottery), entirely flat, almost exclusively urban, and with one of the highest income per person in Italy. The population density is 450 km² (average population density in Italy 192 km²).

Tumours of the large bowel were classified according to the International Classification of Diseases for Oncology (ninth revision). Clinical diagnoses such as “carcinoma in situ”, “neoplastic foci”, “superficial cancerisation”, or “severe dysplasia” were not considered as cancer unless there was clear infiltration of the neoplastic tissue through the muscularis mucosae. Colorectal malignancies were staged using the TNM system, which closely corresponds to Dukes’ classification, into four main categories. This procedure follows simple physiopathological considerations and eliminates ambiguities and confusion consequent to the numerous revisions of Dukes’ staging system.

Definition of the known causes of cancer

IBD (ulcerative colitis and Crohn’s disease affecting the large bowel) were defined by a combination of clinical and morphological investigations. In each case in whom cancer developed, the diagnosis of IBD was confirmed by repeated intestinal biopsies, and the disease lasted for more than five years.

In the only patient with human immunodeficiency virus (HIV) infection who developed a neoplasm of the large bowel, AIDS was diagnosed by clinical findings, HIV testing, and plasma HIV RNA.

It is now widely accepted that the large majority if not all cases of squamous anal carcinoma are caused by HPV. Thus for the purposes of the present study, we considered all 27 cases of anal carcinoma as caused by HPV infection. No attempt was made to confirm the presence of HPV related proteins by immunohistochemistry or other techniques in tumour samples.

FAP was defined as the presence of at least 10 polyps scattered throughout the large bowel and by the existence of extracolonic manifestations, such as dental abnormalities, polypos in the stomach and duodenum, desmoid tumours, supernumerary teeth, and congenital hypertrophy of the retinal pigmented epithelium. The adenomatous nature of the colorectal lesions was documented by histological analysis.

HNPCC was identified following the guidelines of the International Study Group on HNPCC (Amsterdam criteria II) as follows: (1) a family should have at least three first degree relatives affected by cancer of the HNPCC spectrum (colorectum, endometrium, urothelium, small bowel); (2) in one (or more) of the affected relatives, cancer should be diagnosed before the age of 50 years; (3) two consecutive generations (or more) should be affected; (4) tumours need to be histologically verified; and (5) FAP should be excluded. Most HNPCC families (30/34, 88.2%) were further analysed for microsatellite instability (MSI) and for constitutional mutations of the main mismatch repair genes (see below). According to this molecular characterisation, HNPCC families were subdivided into three main groups: in group A, families showed MSI+ and germline mutations in either hMLH1, hMSH2, or hMSH6 genes; in group B, MSI was present in the majority of tumours tested although constitutional mutations were not detected; and group C included families without mutations and with microsatellite stable tumours.

Analysis of microsatellite instability

MSI was evaluated as previously reported in detail. Briefly, 5 µm thick sections were cut from paraffin blocks of colorectal carcinomas and the corresponding normal mucosa. Neoplastic tissue was microdissected with sterile scalpels into polypropylene tubes, and DNA was extracted. Polymerase chain reactions (PCRs) were carried out to amplify DNA from colorectal lesions and normal mucosa at four simple repeated sequences. The loci examined were BAT26, BAT40, D2S123, and D18S57. The reaction volume for PCR was 10 µl, which contained 50–100 µg of DNA. After PCR, DNA from colorectal lesions and normal mucosa of the same patient were loaded in adjacent lanes on a standard 6% denaturating polyacrylamide gel and visualised by autoradiography. Lesions were scored as positive (MSI+) when instability was detected in at least two microsatellite loci (50%). A family was considered MSI+ when 50% or more of the investigated patients showed MSI in the resected neoplasms.

Mutation analysis

Constitutional mutations in the main mismatch repair genes (hMSH2, hMLH1, and hMSH6, from homologous bacterial genes) were evaluated under conditions previously reported. Blood samples were drawn from the probands and other affected family members. Genomic DNA isolated from peripheral mononuclear cells was subjected to single strand conformation polymorphism analysis of the hMSH2, hMSH6, and hMLH1 genes. Samples showing mobility shift compared with controls were subsequently amplified and directly sequenced with the Sequenase (USB, Cleveland, Ohio, USA) enzyme using the PCR product sequencing kit (Amersham, UK) in the presence of α-35S-d-ATP.

Analysis of MSH2, MLH1, and MSH6 protein expression

In HNPCC families with MSI+ tumours, immunohistochemical expression of the proteins encoded by the main DNA mismatch repair genes were evaluated. Paraffin embedded samples of colorectal carcinoma, resected from HNPCC patients, were sectioned at 6 µm. After dewaxing and rehydration, slides were submitted to microwave antigen retrieval (30 minutes at 350 W in 10 mM citrate buffer, pH 6.0). Mouse monoclonal antibodies to full length MSH2 and MLH1 (clones 129–1129 and clones 168–15, respectively; Pharmingen, San Diego, California, USA) were used at a 1:40 dilution. Monoclonal antibodies to MSH6 protein (clone 44; Transduction Laboratories, Kentucky, USA) were used at a 1:2000 dilution. Immunoperoxidase staining was carried out using dianaminobenzidine as chromogen with the Nexes 1:2000 dilution. Monoclonal antibodies to MSH6 protein (clone 44; Transduction Laboratories, Kentucky, USA) were used at a 1:2000 dilution. Immunoperoxidase staining was carried out using dianaminobenzidine as chromogen with the Nexes Automatic Staining System (Ventana, Strasbourg, France).

Tumours were considered positive for protein inactivation when complete absence of nuclear staining was evident in epithelial cells of the lesions, over a background of definite nuclear staining of adjacent non-neoplastic epithelial and stromal cells.

Statistical analysis and survival

Crude indices, age adjusted (world population) incidence rates, and cumulative risks were calculated following the guidelines of the International Agency for Research on Cancer (IARC). The χ² and ANOVA tests were used (when appropriate) to assess the statistical significance of differences among groups. For survival analysis, categorical variables were created for all parameters evaluating colorectal cancer specific survival using the method of Kaplan-Meier, and estimating differences with the log rank test. Statistical significance was set at p<0.05, and all analyses were carried out using the Statistical Package for Social Sciences (SPSS) software.

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RESULTS

Table 1 shows the main features of colorectal cancer registration during the 15 year period from 1984 to 1998. Incidence rates were similar to those usually observed in Western countries, and crude rates tended to rise in the 1990s due to a sharp increase in localised lesions (Dukes’ A and B).30

Table 2 illustrates the main clinical findings of patients in whom a causative factor for colorectal malignancy could be identified, or strongly suspected, compared with individuals in whom the aetiology remained undefined. Rather surprisingly, IBD and FAP—both clinical conditions rendering affected individuals particularly susceptible to colorectal malignancy—accounted for only three tumours each. Similarly, although the registration period was entirely within the HIV epidemic, AIDS was associated with colorectal cancer in only one patient. Squamous carcinomas of the anal region developed in 27 patients; according to the most recent views,18 these lesions are closely related to long lasting HPV infection. Finally, in 58 individuals—and in 34 families—a clinical diagnosis of HNPCC was established.21 In total, cases with a known aetiology were 92, and accounted for 3.7% of all registered patients. These findings are further illustrated in fig 1, clearly indicating that Lynch syndrome represents by far the most frequent among the known causes of colorectal malignancies.

Representative extended pedigrees of families showing the distinctive clinical features of HNPCC are shown in fig 2. In the family in fig 2A, a constitutional mutation of the hMSH2 gene was detected whereas the family shown in fig 2B was characterised by diffuse MSI but no germline mutations. Of note is the close similarities of the two kindreds in terms of age of onset of tumours, vertical transmission, aggregation, and tumour spectrum.

In Lynch syndrome, affected individuals frequently show an early age of cancer onset and improved clinical outcome5 compared with other colorectal cancer patients. Thus the age distribution of the 58 patients with HNPCC was compared with those of patients with anal carcinoma and sporadic colorectal neoplasms. As shown in fig 3, individuals with Lynch syndrome tended to be younger than those in the two

![Figure 1](https://example.com/fig1.png)  
**Figure 1** Frequency (number of cases) of the main known causes of colorectal cancer. HNPCC, hereditary non-polyposis colorectal cancer; Virus, human papillomavirus; IBD, inflammatory bowel disease; FAP, familial adenomatous polyposis; AIDS, acquired immunodeficiency syndrome.

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**Table 1** Main data for cancer registration during the whole 15 year period (1984–1998)

<table>
<thead>
<tr>
<th>ICD-O</th>
<th>Crude incidence rate</th>
<th>Age standardised incidence (World population)</th>
<th>Cumulative risk 0–74 (&lt;1000)</th>
<th>Affected individuals</th>
</tr>
</thead>
<tbody>
<tr>
<td>153 Colon</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>45.7</td>
<td>24.1</td>
<td>30.3</td>
<td>850</td>
</tr>
<tr>
<td>Female</td>
<td>40.6</td>
<td>12.9</td>
<td>20.6</td>
<td>814</td>
</tr>
<tr>
<td>154 Rectum</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>23.8</td>
<td>16.9</td>
<td>17.2</td>
<td>448</td>
</tr>
<tr>
<td>Female</td>
<td>17.3</td>
<td>7.4</td>
<td>9.0</td>
<td>350</td>
</tr>
<tr>
<td>Total</td>
<td>69.5</td>
<td>37.0</td>
<td>47.5</td>
<td>1298</td>
</tr>
</tbody>
</table>

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**Table 2** Clinical features of patients with known aetiological factors compared with patients with no apparent causative agent

<table>
<thead>
<tr>
<th>Aetiology</th>
<th>n</th>
<th>Sex (M/F)</th>
<th>Age at diagnosis (y)</th>
<th>Tumour site(s) (% R/L/Rec)</th>
<th>Staging (% I–II/III–IV)</th>
<th>Five year survival (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AIDS</td>
<td>1</td>
<td>1/–</td>
<td>25</td>
<td>100/-/-</td>
<td>–</td>
<td>0</td>
</tr>
<tr>
<td>IBD</td>
<td>3</td>
<td>1/2</td>
<td>61 (11)</td>
<td>67/–/33</td>
<td>67/33</td>
<td>66.7</td>
</tr>
<tr>
<td>FAP</td>
<td>3</td>
<td>3/–</td>
<td>37 (8)</td>
<td>100/-/-</td>
<td>100/-</td>
<td>66.7</td>
</tr>
<tr>
<td>HPV</td>
<td>27</td>
<td>6/21</td>
<td>66 (13)</td>
<td>–/-/-100</td>
<td>–</td>
<td>34.4</td>
</tr>
<tr>
<td>HNPCC</td>
<td>58</td>
<td>33/25</td>
<td>58 (12)</td>
<td>51/33/16</td>
<td>54/46</td>
<td>58.6</td>
</tr>
<tr>
<td>No apparent cause</td>
<td>2370</td>
<td>1254/1116</td>
<td>69 (11)</td>
<td>32/36/23</td>
<td>51/49</td>
<td>48.6</td>
</tr>
</tbody>
</table>

*R, right colon (from caecum to splenic flexure); L, left colon (descending–sigmoid colon); Rec, rectum.
†Only referred to adenocarcinoma; HNPCC versus no apparent cause, p = 0.8 (NS).
‡Values are mean (SD). Age differences among groups were assessed by analysis of variance (ANOVA); HNPCC versus no apparent cause, p < 0.001 (F = 47.9).
§HPV versus no apparent cause, p = 0.14 (F = 2.1); HNPCC versus HPV, p = 0.01 (F = 6.1).
¶HNPCC versus no apparent cause, p = 0.04 (y² = 11.1).
AIDS, acquired immunodeficiency syndrome; IBD, inflammatory bowel disease; FAP, familial adenomatous polyposis; HPV, human papillomavirus; HNPCC, hereditary non-polyposis colorectal cancer.

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other groups, with a mean age of cancer onset of 58 (12) years versus 66 (13) years \( (p, 0.01) \) and 69 (11) years, respectively \( (p, 0.001) \). Five year specific survival (table 2, fig 4) did not show significant differences between HNPCC and the other groups (log rank 0.71, \( p, 0.5 \)).

Although clinical features of HNPCC were established in 34 kindreds, in only six families and 12 individuals (0.5%) were constitutional mutation of \( hMSH2 \), \( hMLH1 \), and \( hMSH6 \) genes detected (together with MSI). Nine additional families showed the MSI+ phenotype although germline mutations were not found; 15 families were MSI− (and, consequently, constitutional mutations were not searched for), while five additional families could not be tested. Thus constitutional mutations in one of the mismatch repair genes were found in only 20% of the HNPCC families which could be tested, and MSI in 50%. Table 3 shows the main clinical features of the HNPCC patients and families divided into four main groups: families positive for constitutional mutations (and MSI+), families with MSI+ tumours but no detectable germline mutations, families with stable tumours, and families which could not be tested. A close similarity was found between the two groups featured by MSI which showed a similar mean age at cancer diagnosis (51 (9.0) and 51 (11) years) and overall five year survival (63% and 56%), suggesting involvement of the mismatch repair system even when constitutional mutations cannot be detected with the most...
Aetiology of colorectal cancer and relevance of monogenic inheritance

Sporadic colorectal cancer (C). ANOVA tests showed that the colorectal cancer (HNPCC) (A), anal carcinoma (B), and apparently sporadic colorectal cancer (CRC) (C), although the clinical outcome tended to be better in HNPCC, no significant difference was detected (log rank 0.71; p<0.5).

Figure 3  Age distribution of patients with hereditary non-polyposis colorectal cancer (HNPCC) (A), anal carcinoma (B), and apparently sporadic colorectal cancer (C). ANOVA tests showed that the distribution was significantly different for HNPCC compared with the two other groups (see text).

DISCUSSION

Our study has shown that the aetiology of colorectal cancer remains elusive in the large majority (96.3%) of cases from a population based cancer registry. These cases can only be related to Western diet, low physical activity, and other lifestyle related factors. Among specific causative agents, there was a very limited role for FAP, AIDS, and IBD, whereas HNPCC (Lynch syndrome) was by far the main factor responsible for colorectal malignancies although in a population based approach constitutional mutations of the main genes involved in the DNA repair mechanism (hMLH1, hMSH2, and hMSH6) were detected in only 20% of the investigated families. Anal carcinomas represent a subset of tumours easily recognizable by the squamous histological type and in which specific causative agents have been demonstrated.

As specific causative factors were detected in only 3.7% of all colorectal tumours, this implies that in most cases we have no clear idea of the aetiology. Diet and lifestyle can be invoked but this leaves researchers unsatisfied, for at least two main reasons. Firstly, studies on diet and colorectal malignancies are highly controversial and usually show very low relative risks. Secondly, recent studies indicate that obesity is becoming more and more frequent in the USA as well as in Europe; moreover, there is a tendency to a more sedentary life in most Western countries. These trends are unlikely to revert—at least in the short term—and, consequently, it is difficult to foresee easy control of the main environmental risk factors for colorectal tumours.

We were surprised to observe so few cases of colorectal cancer associated with IBD, in spite of the great emphasis given to the risk of malignancy, especially in long lasting ulcerative colitis. It is possible that the availability of efficacious treatments in inducing long remissions in IBD reduced the risk of cancer development; moreover, this risk might appear greater when highly selected series of patients with extensive colitis are followed up for many years. Finally, the low cancer rate observed in this population based approach has no direct implication on the risk of cancer in individual patients with IBD, in whom close surveillance should be recommended. Similarly, FAP and AIDS were rare causes of colorectal cancer. In the case of FAP, this can be attributed to the close endoscopic surveillance of segregating families—especially at present when molecular tests are available for the identification of predisposed individuals—and to the efficacy of preventive surgery. Indeed, there is common techniques. The profound clinical differences of the group with MSI—tumours suggest that in these families other mechanisms may be invoked to explain cancer aggregation and segregation. The constitutional molecular changes detected in HNPCC families are reported in table 4.
evidence that extracolonic malignancies and desmoid tumours represent a more likely cause of death in these patients. Although cancer risk is high in AIDS, this shows an unusual spectrum; in a recent study, Goedert et al showed that individuals with AIDS had a 310-fold increased risk for Kaposi sarcoma, a 113-fold increased risk for non-Hodgkin lymphoma, and increased risks for several other malignancies, although no excess risk for colorectal cancer could be detected. These findings are in accordance with the results of the present study. The close relation between cervical and vaginal cancer is well known. Even though the association of anal cancer with HPV has been reinforced by the frequent detection of HPV DNA in tissue samples, this correlation has not been established yet.

The present study showed that individuals with HNPCC and germline mutations in the corresponding genes had a 310-fold increased risk for Kaposi sarcoma, a 113-fold increased risk for non-Hodgkin lymphoma, and increased risks for several other malignancies, although no excess risk for colorectal cancer could be detected. These findings are in accordance with the results of the present study. The close relation between cervical and vaginal cancer is well known. Even though the association of anal cancer with HPV has been reinforced by the frequent detection of HPV DNA in tissue samples, this correlation has not been established yet.

### Table 3: Clinical features of registered HNPCC patients and families subdivided into four main groups (families positive for constitutional mutations (and MSI+), families with MSI+ tumours but no detectable germline mutations, families with stable tumours, and families which could not be tested)

<table>
<thead>
<tr>
<th></th>
<th>Mut+ MSI+</th>
<th>Mut− MSI+</th>
<th>Mut− MSI−</th>
<th>Not tested</th>
</tr>
</thead>
<tbody>
<tr>
<td>No of families</td>
<td>6</td>
<td>9</td>
<td>15</td>
<td>4</td>
</tr>
<tr>
<td>No of subjects</td>
<td>190</td>
<td>171</td>
<td>510</td>
<td>77</td>
</tr>
<tr>
<td>Family size (mean (SD))</td>
<td>31 (10)</td>
<td>19 (4)</td>
<td>34 (6)</td>
<td>19 (4)</td>
</tr>
<tr>
<td>Members affected</td>
<td>69</td>
<td>45</td>
<td>138</td>
<td>19</td>
</tr>
<tr>
<td>Total tumours</td>
<td>85</td>
<td>58</td>
<td>158</td>
<td>20</td>
</tr>
<tr>
<td>Colorectal tumours</td>
<td>43</td>
<td>41</td>
<td>95</td>
<td>13</td>
</tr>
<tr>
<td>Extracolonic tumours*</td>
<td>21</td>
<td>11</td>
<td>10</td>
<td>1</td>
</tr>
<tr>
<td>Age at diagnosis (y)†</td>
<td>51 (9)</td>
<td>51 (11)</td>
<td>63 (11)</td>
<td>63 (5)</td>
</tr>
<tr>
<td>Colorectal cancer site</td>
<td>Right colon</td>
<td>19</td>
<td>19</td>
<td>23</td>
</tr>
<tr>
<td></td>
<td>Left colon+rectum</td>
<td>12</td>
<td>15</td>
<td>44</td>
</tr>
<tr>
<td></td>
<td>Not assessable</td>
<td>12</td>
<td>7</td>
<td>28</td>
</tr>
<tr>
<td>5 y CRC survival (%)</td>
<td>63</td>
<td>56</td>
<td>31</td>
<td>46</td>
</tr>
</tbody>
</table>

*Including only extracolonic HNPCC related tumours (that is, endometrium, small bowel, renal pelvis and ureters, ovary, stomach).
†Considering colorectal cancer only (values are mean (SD)).
‡Mut+, individuals (and families) with constitutional mutations of hMSH2, hMLH1, or hMSH6 gene; MSI+, individuals (and families) with microsatellite instability in resected neoplasms.

1. HNPCC, hereditary non-polyposis colorectal cancer; MSI, microsatellite instability; CRC, colorectal carcinoma.

### Table 4: Constitutional mutations detected in HNPCC families registered between 1984 and 1998

<table>
<thead>
<tr>
<th>Family ID</th>
<th>Gene</th>
<th>DNA change</th>
<th>Effect</th>
<th>Immunohistochemistry</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>hMSH2</td>
<td>4 bp del exon 7</td>
<td>Truncated protein</td>
<td>No MSH2 protein expression</td>
</tr>
<tr>
<td>10</td>
<td>hMSH2</td>
<td>AT intron 6</td>
<td>Truncated protein</td>
<td>No MSH2 protein expression</td>
</tr>
<tr>
<td>39</td>
<td>hMSH2</td>
<td>del A exon 16</td>
<td>Truncated protein</td>
<td>Normal expression</td>
</tr>
<tr>
<td>41</td>
<td>hMSH6</td>
<td>del A exon 19</td>
<td>Truncated protein</td>
<td>No MSH6 protein expression</td>
</tr>
<tr>
<td>1</td>
<td>hMLH1</td>
<td>ins T exon 19</td>
<td>Protein elongation</td>
<td>No MLH1 protein expression</td>
</tr>
<tr>
<td>20</td>
<td>hMLH1</td>
<td>ins T exon 19</td>
<td>Protein elongation</td>
<td>No MLH1 protein expression</td>
</tr>
</tbody>
</table>

HNPCC, hereditary non-polyposis colorectal cancer.
Total families observed 34; tested 24; positive 6 (25%).
respect, our subgrouping of patients and families with clinical characteristics of HNPCC (group A Mut+ MS1+; group B Mut− MS1−; and group C Mut− MS1−; table 3) is of practical relevance. Groups A and B showed a similar tumour spectrum, an earlier age of cancer onset, a higher risk of cancer during follow up, and an overall better prognosis; this close similarity suggests the involvement of DNA mismatch repair genes, even when mutations are not detectable. In contrast, it is possible that group C families have mutations in other genes not yet identified and not linked to DNA repair mechanisms.22

Thus in our investigation the frequency of HNPCC was closely dependent on the definition adopted. “Clinical” HNPCC (Amsterdam criteria) was diagnosed in 2.4% (58 of 2462) of registered patients while “molecular” HNPCC (constitutional mutations) was detected in 0.5% (12 of 2462). These figures are within the range of values reported in other population based investigations.54–56 Moreover, as indicated by Terdiman in a recent editorial,57 molecular testing in HNPCC families is undoubtedly useful but not essential. In order to save lives, the key issue is to identify individuals at risk on clinical grounds, and to ensure that they receive appropriate surveillance, regardless of the results of molecular analysis.58 Indeed, failure to detect an index mutation or even failure to detect a tumour with high frequency MSI in a given person does not exclude the diagnosis of Lynch syndrome or obviate the need for close surveillance in high risk individuals. These concepts are further illustrated by the close similarities of the two HNPCC families shown in fig 2; although constitutional mutations were found in only one (fig 2A), clinical follow up and the main recommendations for family members at risk are identical.

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