



## Confirming a diagnosis of hereditary colorectal cancer: the impact of a Familial Bowel Cancer Registry in New Zealand

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### Abstract

**Aims** The optimal management of familial bowel cancer is thought to involve specialised familial cancer units and registries that facilitate a multidisciplinary approach. We studied the impact this approach had on the investigation and management of affected families in our register.

**Method** A review of the outcomes of assessment for 25 families was undertaken. These families have completed assessment by the Northern Regional Genetic Service Familial Bowel Cancer Registry because of the possibility of a hereditary bowel cancer syndrome. Details of the cancer history and screening advice known at the time of initial referral to the genetic service, and at the end of assessment, were compared.

**Results** Detailed family history revealed 130 cancers, 90 of which were known at referral. Eighty-four cancers were confirmed, of which 73 belonged to the spectrum of cancers associated with hereditary nonpolyposis colorectal cancer (HNPCC). The mean age of diagnosis was 56.3 years. Eight families met the modified Amsterdam Criteria for the diagnosis of HNPCC, compared to four families at the time of referral. Familial hyperplastic polyposis was diagnosed in one family. 164 asymptomatic at-risk first-degree relatives were identified, 48 from families who met the Amsterdam criteria and were thereby recommended to have intensive colonoscopic screening.

**Conclusion** Assessment by the Familial Bowel Cancer Registry increased the number of cancers identified in families, thus facilitating a diagnosis of HNPCC in a third of the referred families and a diagnosis of hyperplastic polyposis in one other. Consequently specialised genetic testing and intensive colonoscopic surveillance could be targeted to the asymptomatic first-degree relatives most at risk. Ongoing coordination of colonoscopic surveillance by the registry for those individuals identified to have disease causing mutations or to be at-risk, is anticipated to reduce the number of deaths from colorectal cancer in these families.

Familial forms of colorectal cancer account for 5–10% of bowel cancers in countries of high incidence of sporadic colorectal cancer. Although only a minority of the total cases, this represents around 200 cancers per year in New Zealand which through timely investigation and intervention could potentially be prevented.<sup>1</sup>

Consequently, specialised services have been developed to investigate and manage affected families. Familial Bowel Cancer Registries facilitate the collection of accurate family data, identify at-risk individuals, and coordinate the provision of evidence-based colonoscopic surveillance for this cohort.

Registry-based programmes have been effective in achieving gratifying improvements in both the incidence of colorectal cancer and the overall survival in families affected

by either of the two most common genetic conditions causing bowel cancer—namely, hereditary nonpolyposis colorectal cancer (HNPCC) and familial adenomatous polyposis (FAP).<sup>2-5</sup>

A Familial Bowel Cancer Registry was established as a clinical service in Auckland in 1996. To evaluate the impact of registry assessment on the management of families with an inherited predisposition to bowel cancer, we used the registry records to compare the available information, and resulting management advice, at completion of assessment with that available at the time of initial referral.

## Methods

The study was performed through an audit of the records of the Familial Bowel Cancer Registry of patients referred for evaluation, by the Registry team.

The multidisciplinary Registry team is comprised of a clinical geneticist, gastroenterologist, registry coordinator, and a researcher, as well as associated members from the colorectal and oncology teams.

Following referral to the service, a family pedigree involving at least three generations was constructed initially using information provided by the proband and augmented by other available family members who consent to be involved. Details of all cancers in the pedigree were confirmed where possible through medical records, death certificates, or the National Health Index database—all of which were accessed with written consent.

In each instance where a cancer was confirmed, histology was sought for review. The Registry team then reviewed all information and an assessment of the families' colorectal cancer (CRC) risk status made. Specific recommendations regarding colonoscopic and appropriate extracolonic surveillance procedures were then advised.

Twenty-five consecutive families who completed their assessment from November 2000 until June 2002 were included in the review. Information compiled during the assessment was compared to the family history as known at the time of referral and to any information present in the medical records of the proband.

## Results

In the 25 families reviewed there were 90 cancers known to the referring doctor at the time of referral. Following assessment by the Registry, a history of 130 cancers was established in these families—an average of just over 5 cancers per family (Table 1). In a further 9 cases there was a history of colonic polypectomy for adenomas associated with at least moderate dysplasia. In two-thirds (85/130) of the cases of malignancy it was possible to obtain direct confirmation of the diagnosis. In 56 of the 66 confirmed cases of colorectal cancer histology was obtained for review.

**Table 1. Number of cancers per family and median age at diagnosis**

Cancer	Number of cancers			Median age ( years)	
	At referral	On assessment		All families	Amst. +ve families
		All	Confirmed		
Total cancers	90	130	85	57	54
HNPCC spectrum	87	97	74	58	56
Colorectal cancer	77	82	66	60	61

Amst.=Amsterdam criteria; +ve=positive; HNPCC=hereditary nonpolyposis colorectal cancer.

The large majority of the confirmed cancers (87%) belonged to the spectrum of malignancy that makes up the diagnostic criteria for HNPCC.<sup>6</sup> Ten of the 25 families had histories of extracolonic tumours from this spectrum. Furthermore, 3 cases of endometrial adenocarcinoma, 2 small bowel tumours, and 1 case each of gastric cancer and transitional cell carcinoma were confirmed (Table 2).

**Table 2. HNPCC-associated extracolonic tumours per family**

Cancer	Extracolonic tumours	
	Confirmed	Unconfirmed
Endometrial	3	6
Small intestine	2	
Gastric cancer	1	1
Transitional cell cancer	1	
Ovarian cancer	3	1
Renal cell cancer	2	
Other	4	19

The age and site distribution of the observed colorectal cancers differed from that described in the general population (Table 3).<sup>7</sup> The median age at diagnosis tended to be lower (median 60 years). In addition, an increase in right-sided colorectal cancers was found when compared to available data on the site distribution of colorectal cancers in the New Zealand population (Table 3).<sup>7</sup>

**Table 3. Site of colorectal cancer (CRC) in families compared with site distribution CRC in general population**

Variable	RC	LC	Rectum	Unknown
All cases	25 (47%)	10 (19%)	18 (34%)	14
Amsterdam +ve	9 (70%)	1 (8%)	3 (22%)	8
Jass 1991	2908 (37%)	2124 (27%)	2850 (36%)	415

RC=right colon (caecum and transverse colon to the splenic flexure); LC=left colon.

Eight of the 25 families at completion of assessment met the modified Amsterdam Criteria for the diagnosis of HNPCC compared to four families at the time of referral. These 8 families were referred directly for genetic testing to detect mutations in the mismatch repair genes identified to cause HNPCC.

In 6 of the 25 families, the Amsterdam criteria for a diagnosis of HNPCC were not met—but in line with the Bethesda Criteria, tumour immunohistochemistry (or microsatellite status), to support the involvement of the mismatch repair genes in these families, was requested.<sup>8</sup> In one other family, review of the histology led to a diagnosis of FAP.

164 asymptomatic individuals were identified on the basis of their family history or the age (<55 years) at which a first-degree relative developed CRC to have a least a moderate increase in their lifetime risk for developing CRC. Of these, 48 individuals were from families meeting the Amsterdam criteria.

Individuals were referred to the Registry mostly by their oncologist or surgeon, and accounted for two-thirds of referrals. Other individuals were referred severally by gastroenterologists, general practitioners, or self-referral.

## Discussion

Causative factors for familial bowel cancer include several inherited disorders that are distinct at both the clinical and molecular level from the common forms of sporadic bowel cancer.

Overall, 3–5% of bowel cancers are due to HNPCC and a further 0.5–1% to FAP.<sup>5</sup> The remaining familial cases are due to either rare genetic conditions such as Peutz-Jeghers syndrome or familial hyperplastic polyposis (HP), or represent familial clustering for which the underlying inherited basis is unknown.

HNPCC and FAP are autosomal dominant single gene disorders where first-degree relatives of an affected individual have a 50% risk of inheriting the predisposing mutation. Research and confirmation of the family cancer history is an essential component of the investigation of affected families. Histological review of the location and nature of colonic tumours and confirmation of the profile of extracolonic tumours allows a more accurate assessment of the true likelihood of an autosomal dominant cancer syndrome in a family and facilitates the diagnosis of the more unusual polyp syndromes—e.g. attenuated FAP or HP.

Verification of both the tumour site and age at diagnosis is a requirement for a diagnosis of HNPCC according to the modified Amsterdam criteria.<sup>6</sup>

This study has shown that referral to the Familial Bowel Cancer Registry has a large impact on the amount of information available for the assessment and management of individuals belonging to families with a history of CRC. In the 25 families studied, the Registry assessment process identified 40 (44% of total) additional cancers, to the 90 reported at the time of referral. This is consistent with other studies which have shown that as many as 25% of individuals are unaware of a diagnosis of colorectal cancer in a first-degree relative.<sup>9</sup>

At the completion of assessment, one-third of our referred families met the modified Amsterdam criteria for a diagnosis of HNPCC. This is a high proportion in comparison with data from other familial cancer registries, thus suggesting that (in our local setting) referrals to the Registry are only made when there is a high index of suspicion for the existence of a familial syndrome.

We also found that the Registry has an important public health function in that a large number of relatives were identified on the basis of their family history or the age (<55 years) at which a first-degree relative developed CRC to have a least a moderate increase in their lifetime risk for developing CRC.

Of the 164 at-risk first-degree relatives identified from the 25 families and offered colonoscopic surveillance, less than a third (48 of 164 individuals) were from families meeting the modified Amsterdam criteria for HNPCC. Registry assessment restricted the recommendation for intensive colonoscopic surveillance to this smaller group in line with the evidence that in HNPCC families such surveillance results in a significant reduction in both the incidence of colorectal cancer and overall mortality.<sup>3</sup>

For the majority of at-risk first-degree relatives identified at assessment (116 of 164), 5-yearly colonoscopic surveillance beginning at the age of 50 years (or at an age 10 years before the earliest age at which CRC was diagnosed in the family) was advised. In some cases this represented a reduction in their current surveillance recommendations. The Registry also provided education and reassurance to many individuals in the wider families of people affected by bowel cancer, although this benefit is difficult to quantify.

HNPCC has been documented to be caused by mutations in one of four mismatch repair genes, with the majority of mutations being identified in two of the four genes (hMLH1 and hMSH2).<sup>10</sup> These genes normally repair errors that occur in DNA as a result of cell replication.

In New Zealand, the limited resources for predisposition genetic testing need to be targeted to those most likely to benefit. Registry assessment facilitated this with the eight families (meeting the modified Amsterdam criteria for HNPCC) being referred directly for genetic testing to detect germline mismatch repair gene mutations.

Molecular techniques that detect microsatellite instability or immunohistochemical tests revealing loss of expression for hMLH1, hMSH2 or hMSH6 proteins can aid in the detection of tumours resulting from defective mismatch repair. This is particularly helpful in families where the Amsterdam criteria for HNPCC are not met, but clinical features (as outlined in the Bethesda Criteria)<sup>8</sup> suggest this diagnosis.

Of the 25 families assessed, 6 are in this category but genetic testing will only be requested if tumour immunohistochemistry or microsatellite status supports the involvement of the mismatch repair genes.

Referral to the Familial Bowel Cancer Registry facilitated the diagnosis of a dominantly inherited bowel cancer syndrome with appropriate targeting of specialised genetic testing and intensive colonoscopic surveillance.

Ongoing coordination of colonoscopic surveillance by the Registry, for those individuals identified to have disease-causing mutations or to be at-risk, is anticipated to reduce the number of deaths from CRC in these families.

The New Zealand Guidelines on the surveillance and management of groups at increased risk of CRC advise offering individuals or families with hereditary CRC syndromes referral to a Familial Bowel Cancer Registry.<sup>11</sup> To facilitate these referrals, a National Registry based in both Auckland and Christchurch is now being established.

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