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High-risk family colorectal cancer screening service in Ireland: Critical review of clinical outcomes

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ABSTRACT

Background: We present the 15-year experience of a family colorectal cancer screening service in Ireland with emphasis on real life experience and outcomes.
Methods: Questionnaires were used to assess family cancer history and assign patients to risk categories; 'Moderate Risk', HNPCC, (suspected) genetic syndrome (non-HNPCC), 'Low Risk'. Screening was by full colonoscopy. We report neoplastic yield, examining effect of risk category, age, gender, and index colonoscopy findings.
Results: Between 1998 and 2013, 2242 individuals were referred; 57.3% female, 42.7% male, median age 46 years (range9-85yrs). Median follow up time was 7.9yrs (range 0.5-15.3yrs). Follow up data after exclusion (non-compliance, known CRC) was available in 1496 (66.7%): 'Moderate risk' 785 (52.5%), HNPCC 256 (17.1%), (suspected) genetic syndrome (non-HNPCC) 85 (5.7%), 'Low Risk' 370 (24.7%). Screening was performed in 1025(68.5%) patients; colonoscopy data available for 993 (96.9%); total 1914 colonoscopies. At index colonoscopy, 178 (18.0%) patients had adenomas; 56 (5.5%) advanced adenoma. During the entire study period, 240 (24.2%) had an adenoma; 69 (7.0%) advanced adenoma. Cancers were diagnosed on screening in 2 patients. Older age and male gender were associated with higher adenoma detection rate; $p < 0.001$, $p = 0.01$, respectively. Risk category did not affect adenoma yield. Adenoma and advanced adenoma detection at index colonoscopy were associated with detection of same at follow up screening; $p < 0.001$.
Conclusion: Male gender and age (>50) were the core identifiable risk factors for neoplasia at screening colonoscopy in this family screening setting. Our results would support less intensive surveillance in younger patients (<50), particularly where index colonoscopy is normal.

1. Introduction

Colorectal cancer (CRC) is the second most common cause of cancer death in Europe [1]. Similarly, CRC burden in Ireland is significant, with over 2000 cases diagnosed annually [2]. Prospective trials and observational studies have demonstrated mortality reductions associated with early detection of CRC, as well as the removal of adenomatous polyps [3–6]. This has provided rationale for population screening in many European countries [7,8].

Family history (FHx) of CRC is a risk factor for developing CRC [9–15]. Hereditary syndromes, including FAP and Lynch syndrome (LS), account for 2–5% of CRC [16], though heritable factors are implicated in up to 35% of CRC [9]. Optimal screening regimens for those with FHx CRC remain unclear, and data relating to screening outcomes in this cohort vary considerably [17–29].

The High-Risk Family Colorectal Cancer Screening Clinic was established within a dedicated gastrointestinal unit in a large tertiary referral center in 1998. Its purpose was to develop and implement screening strategies for persons with FHx CRC. This included persons with suspected or confirmed genetic syndromes, in addition to persons with a FHx CRC not comprising a genetic syndrome. The service was nurse-led, with clinical supervision from a gastroenterology registrar (fellow) and consultant

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(attending physician), and dedicated administrative support. Allied disciplines included medical genetics, pathology, radiology, and gynecology. The aims of our study were to report real life referral patterns, risk categorization, and clinical outcomes, with emphasis on neoplasia yield at colonoscopy. A grant from the Mater Foundation partially funded this project.

2. Methods

2.1. Assessment of family cancer history

Referrals were accepted from primary care and hospital settings based on perceived increased risk of CRC due to FHx CRC, or a suspected genetic syndrome. Referred patients were asked to complete a standardized family cancer history questionnaire. This enquired about known diagnosis of *any* cancer, the primary site, and age at diagnosis. A family pedigree was constructed using Cyrillic software (Appendix A). We also accepted referrals of patients with a personal history of CRC. The purpose of such referrals was to facilitate screening of family members, and where appropriate, to pursue genetic testing in the proband. (*Screening performed in such patients with a personal history of CRC is not included in our results.)*

Patients were invited to attend our clinic following receipt of their completed questionnaire, where the family cancer history was reviewed. Where possible and deemed appropriate, verification of cancers was sought by means of death certificates, medical reports, or enquiries to the National Cancer Registry. Occasionally, clinic invites were not sent, and screening recommendations were sent to patients directly by post.

2.2. Risk categorization

Criteria based on FHx cancer were developed to enable risk categorization; (Table 1). Individuals were assigned to appropriate risk categories: 'Moderate risk', HNPCC, (suspected) genetic syndromes (non-HNPCC), and 'Low risk'. In addition to assigning referred individuals to appropriate risk categories, family pedigrees were used to identify other family members who warranted screening.

2.3. Genetic syndromes

Referral to medical genetics was offered where genetic syndromes (e.g. Lynch Syndrome, FAP, MYH associated Polyposis, Peutz-Jeghers) were suspected. Our protocols used Amsterdam II criteria to identify HNPCC kindreds. In the absence of genetic testing, patients of such kindreds were termed 'LS unconfirmed'. Relatives of patients with a confirmed diagnosis of LS by genetic testing were also categorized as 'LS unconfirmed' pending gene testing (regardless of whether Amsterdam II criteria were fulfilled). Where LS was suspected (Amsterdam criteria fulfilled, clinical suspicion), microsatellite instability (MSI) testing or immunohistochemical (IHC) testing for expression of mismatch repair (MMR) proteins; MLH1, MSH2, MSH6, PMS2, was requested. Where tumor tests revealed evidence of MSI, referral for genetic testing was offered. Females with suspected LS were referred for gynecological screening.

2.4. Screening recommendations and implementation

A letter providing written details of screening recommendations was sent to patients following the clinic visit. This assisted patients in relaying information to relevant family members (Appendix B). Screening protocols are described in Table 2. These were formulated based on best available international evidence, according to North American and U.K. guidelines [30–34]. Screening was by full colonoscopy, which was offered on site, and at specified intervals depending on risk category. CT colonoscopy (CTC) was offered where conventional colonoscopy was unsuccessful. Ongoing screening was monitored using a prospectively maintained database. Results of screening colonoscopies were reviewed by our nurse. Screening intervals were amended where necessary based on endoscopy findings.

2.5. Data collection and review

Data was retrieved from our dedicated database and by chart review. This included patient gender, age (at referral, and at first colonoscopy), FHx CRC, risk categorization and details of screening tests performed (i.e. colonoscopies and genetic work up). We included patients referred up to October 2013, and all screening tests performed up to April 2014. We excluded patients referred for screening of GI cancers other than CRC, patients with IBD, and patients who on review had no FHx CRC.

Where necessary, risk categorization was amended for the purpose of this review in keeping with criteria detailed in methods above. We examined colonoscopy screening performed and neoplastic yield (premalignant polyps and cancer) in 'Moderate risk', HNPCC, and 'Low risk' categories. Neoplastic yield is reported for both initial surveillance colonoscopy and during the total study period. (Due to the heterogeneous nature of the 'suspected genetic syndrome (non-HNPCC)' group, colonoscopies in this group were excluded from further analysis.) Only screening colonoscopies

Table 1
Risk categories.

Risk Category	Criteria
Moderate Risk	• 2 x FDR with CRC *or* • 1 x FDR with CRC diagnosed at <60yrs *or* • 2 x FDR or SDR with CRC diagnosed at <60yrs
Lynch syndrome unconfirmed	• Amsterdam II criteria fulfilled *or* • Relative with genetically confirmed LS (with patient's own gene test pending)
Lynch syndrome confirmed	• Genetic mutation known to cause LS identified
(Suspected) genetic syndrome	• Patient or relative with phenotype suggestive of genetic syndrome or with genetic syndrome confirmed by gene testing
Low Risk	• Criteria for other risk categories not fulfilled

FDR = first degree relative, SDR = second degree relative, CRC = colorectal cancer, LS = Lynch syndrome.