COLORECTAL CANCER SCREENING

Guidance on large bowel surveillance for people with two first degree relatives with colorectal cancer or one first degree relative diagnosed with colorectal cancer under 45 years

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These guidelines are intended to consider the place of large bowel screening for relatives of people who have developed colorectal cancer, as there is evidence for an increased risk of colorectal cancer in such people.

Colorectal cancer is common and many people have an affected relative. Some 4% to 7% of control cohorts report at least one affected relative, while the greater the number of affected relatives (particularly at younger ages) is paralleled by a proportionately greater personal risk of the disease.[1–4] However, apart from tumour microsatellite instability, which indicates a significant chance of germline mutation in a DNA mismatch repair gene[5 6] and hereditary non-polyposis colorectal cancer (HNPCC),[5] there are no pathognomonic features of familial colorectal cancer that indicate an increased familial risk. Hence, at risk groups outwith HNPCC and FAP have to be defined by empiric risk data from their family history. People with a first degree relative affected by colorectal cancer when aged <45 years or those with two affected first degree relatives have sufficiently high risk to merit consideration for invasive surveillance.

This document aims to provide guidance by defining the level of empiric risk at which it is appropriate to consider clinical surveillance. This guidance specifically excludes people whose family history fulfils criteria for HNPCC or other autosomal dominant genetic syndrome associated with colorectal cancer susceptibility. It also excludes people who carry mutations in colorectal cancer susceptibility genes (for example, APC or DNA mismatch repair genes), irrespective of the family history. These scenarios are considered in separate guidance.

Although the aggregate risk of colorectal cancer for a group of people can be defined by family history parameters, it is important to consider the heterogeneity of risk for *individuals* within any risk category group thus defined. Some people who are not offered screening because their family history does not indicate sufficient risk may be destined to develop colorectal cancer. It is essential that this residual risk is made explicit so that it can be appreciated by the person referred as well as by the respective GP.

EXECUTIVE SUMMARY

(1) Personal risk of colorectal neoplasia can be estimated from family histories using empiric risk data. Indirect evidence suggests a marginal benefit for large bowel surveillance for people with *one first degree relative affected by colorectal cancer aged <45 years* or with *two affected first degree relatives*. People fulfilling these criteria should be considered at significantly increased risk and surveillance discussed. People fulfilling these criteria and who have other distant affected relatives should be assessed by Clinical Genetics Services as they might represent HNPCC kindreds. Those with a lesser degree of family history should be considered at insufficient risk to justify screening and reassured. **Recommendation Grade: B**

(2) Total colonic assessment is recommended at consultation about family history or between the ages of 35–40 years, whichever is the later and repeat total colonic assessment at the age of 55 years. If the colon is clear of neoplasia, then recommend measures relevant to population risk. Polyps must be snared and histologically characterised. If adenomatous polyp confirmed at either of these screening episodes, then adenoma surveillance guidance applies. **Recommendation Grade: B**

(3) The method of large bowel surveillance for people at increased risk because of their family history must afford assessment of the whole colon, in view of the presence of lesions restricted to the proximal colon in a substantial proportion of cases. Colonoscopy is also indicated in view of the option for simultaneous therapeutic intervention or biopsy but barium enema with targeted follow up endoscopy is an acceptable alternative. **Recommendation Grade:B**

(4) People with less family history do not merit surveillance over and above that recommended for the general population. It should be emphasised that there remains a residual risk equivalent to population risk and such persons should avail themselves of population based screening measures where relevant. **Recommendation Grade: B**

(5) Referrals from the community solely on the basis of family history should be centralised and audited. This has resource implications, and might be done through the Regional Genetics Service. Audit of referrals should comprise documentation of degree of risk and correlation with outcome measures including; proportion of consultands offered screening, screening related complication rate, long term cancer incidence/mortality in screened *and* unscreened groups through central NHS flagging. **Recommendation Grade: C**

DEFINITION OF EMPIRIC RISK BY FAMILY HISTORY PARAMETERS

Empiric risk of colorectal cancer can be estimated from family history parameters. These parameters consist of the *current age* of the patient whose risk is being considered, *the age at onset of each affected relative* as well as *the number and relationship of those affected relatives*. The risk categories referred to here specifically exclude criteria for HNPCC. It is apparent from table 1 that only people with a first degree relative who was affected by colorectal cancer when aged <45 years and those with two affected first degree relatives have sufficiently high relative risk to merit consideration for invasive surveillance. However, it is important to consider that young people with even quite a high relative risk (about RR5) have a low absolute risk because the population incidence is markedly skewed towards elderly people. Calculation of the absolute risk of colorectal cancer in the next 10 years[7] shows that the most important

Table 1

Risk group	Office of National Statistics* and Scottish ISD†	Houlston (lifetime risk of dying from CRC)‡	St John (odds ratio)	Fuchs (relative risk)	Slattery (odds ratio)	
					(m: male)	(f: female)
General population	~5%	1:50	N/A	N/A	N/A	N/A
Any family history	N/A	1:17	1.8	1.72	2.15 (m)	2.43 (f)
One affected relative <45 years	N/A	1:10	3.7	N/A	3.61 (m)§	7.18 (f)
Two affected relatives	N/A	1:6	5.7	2.75	9.24 (m)	5.00 (f)

*Office of National Statistics. Series MB1 no 23 table 3. †http://www.show.scot.nhs.uk/publications/isd/cancer_registration/ . ‡Derived from data collected in 1970. §Affected relative aged <50 years.

determinant of risk is current age, as population risk at the age of 60 years *exceeds* the absolute risk for people aged age 40 and 50 who have a significantly increased risk because of their family history. Furthermore, using systematic population data (http://www.show.scot.nhs.uk/publications/isd/cancer_registration/) it can be calculated that people aged 70 years have a 4% chance of developing colorectal cancer in the next 10 years. This is substantially greater than the 1.1% 10 year risk for people aged 40–60 years carrying a RR of 5.

There is a spectrum of risk in the general population, which is heavily predicated on current age. Hence, it is clear that there must be a balanced approach for people with this family history when recommending surveillance over and above that for the general population. It is not logical to offer intensive screening to people with an absolute risk fourfold less than those aged 70 years when 10 year life expectancy in the absence of cancer is only marginally different.

FREQUENCY—PREVALENCE AND INCIDENCE

As colorectal cancer is common in the general population, the prevalence of a family history of the disease is particularly pertinent to determining the potential demand for surveillance. This is highly dependent on the criteria laid down. The prevalence in control populations of reporting one or more affected first degree relative is 4% to 7%.[1 2 8–10] It is possible that these data are not representative of population prevalence, because cohorts of controls will be elderly people when matched by age with colorectal cancer patients in case-control studies. Accordingly, controls have elderly first degree relatives who are at high risk of cancer by nature of their age. However, this potential bias is minimised by considering data from a large US cohort study of 119 116 participants with a mean age of about 50 years in which 9.8% of participants reported at least one affected first degree relatives.[4] Thus, the general population prevalence is substantial when *any* family history is taken as an inclusion criterion.

The prevalence of a family history associated with greater empiric risk is lower but still appreciable. In the two largest case-control studies 0.4% of controls[1] had two affected first degree relatives,[1 2] although in the US cohort study,[4] only 0.006% had two relatives with colorectal cancer. Data from an Australian study suggest that prevalence of a family history of an affected relative aged <45 years in control populations is about 0.2%.[1] Thus, based on limited published data, population prevalence of a family history for which screening is recommended in this guideline is around 0.5% of people in the age group 40–75 years, comprising 0.4% with two affected first degree relatives and 0.2% with one under 45 years. This allows for some people who have a family history encompassing both these risk parameters.

INTERVENTION

The method and frequency of surveillance interventions has been the focus of much controversy. However, there are no primary data to inform practice and so much of this recommendation is based on suboptimal observational data and on projecting from other study cohorts with use of relative risks to assume parameters such as adenoma and cancer rates.

Many studies have shown a substantial proportion of proximal neoplasms in people with a family history of colorectal cancer (reviewed in Dunlop[14])[2 15–17] and around 30% of these would not have been identified by flexible sigmoidoscopy to target colonoscopic assessment of those people most likely to have proximal neoplasms. There seems to be a particular excess risk of proximal lesions for women who have a family history. Thus, a full colonic assessment is recommended for people in the risk category of this guideline. Colonoscopy is indicated in view of the option for simultaneous therapeutic intervention or biopsy but barium enema with targeted follow up endoscopy is an acceptable alternative.[16] However, it is important to note that even colonoscopy will miss 6% of adenomas 1 cm or greater.[18]

COLONIC EVALUATION IN THIS RISK GROUP SHOULD BE LIMITED TO A MAXIMUM OF TWO SURVEILLANCE EPISODES:

(1) Full colonic evaluation at consultation about family history or between the ages of 35–40 years, whichever is the later. This is a relative recommendation, as discussion with the consultant about potential risks and benefits may result in a decision to defer colonic assessment. **Recommendation Grade: B**

Surveillance at the age of 35–40 years aims to identify those (very few) people who have a considerable predilection to develop adenoma/cancer. However, it will also alleviate concerns in many patients about waiting until age 55 years. The likelihood of identifying a polyp in the age group 30–39 years is only 2%.[19] The chance of detecting an established large bowel malignancy in this group can be estimated by applying a relative risk of RR=5 to systematic population data (http://www.show.scot.nhs.uk/publications/isd/cancer_registration/) and by assuming that the asymptomatic dwell time of a cancer is a maximum of three years. Using these parameters in the estimation, there is only a **1:1660** chance of detecting cancer by colonoscopy in this risk cohort aged when 30–39 years. Furthermore, as current population five year survival after a diagnosis of colorectal cancer when aged 45–54 years is 46% (http://www.show.scot.nhs.uk/publications/isd/, ONS Statistics) and colonoscopy is estimated to reduce mortality by 85%,[21] then there is only **1:3618** chance that a colonoscopy will prevent death from large bowel cancer. Thus, the benefit of advising *any* screening intervention at this age in this risk group is debatable. None the less, a single colonoscopy seems reasonable to meet patient concerns and the small number of instances where there is a strong risk because of a gene of major effect. As, surveillance at the age of 35–40 is only relatively indicated, it can be guided by the patient's wishes and degree of psychological morbidity associated with the perceived risk after explanation of the risk/benefit ratio.

(2) Full colonic evaluation at the age of 55 years. If the colon is clear of neoplasia, then recommend measures relevant to

population risk. Polyps must be snared and histologically characterised. If an adenomatous polyp is confirmed at either of these screening episodes, then adenoma surveillance guidance applies (see separate guidance). **Recommendation Grade: B**

The projected benefit of surveillance at the age 55 years in this risk group is somewhat more tangible than at younger age groups. The proportion of people in this age group with a polyp is 17%–21%,[15 19] making the potential of cancer prevention by polypectomy feasible.[20] Furthermore, assuming a relative risk of RR about 3[4] at this age for a person fulfilling this risk criteria, and an asymptomatic cancer natural history of three years, then **1:181** people will harbour a cancer in the large bowel when screened (http://www.show.scot.nhs.uk/publications/isd/cancer_registration/, ONS Statistics). Thus there is a projected chance of **1:213** that a single colonoscopy at the age of 55 years in this risk group will prevent a death from colorectal cancer. However, in addition to identifying prevalent cancers, the identification and removal of polyps, and the enrolment on adenoma surveillance programme will result in an expected reduction of 66% in colorectal cancer incidence.[20] Thus there is considerable rationale in single colonoscopy at the age of 55 years for people fulfilling this risk from family history criteria because an appreciable reduction in cancer related mortality could be reasonably expected.

COSTS AND BENEFITS

It is calculated that colonoscopy at two to three yearly intervals in a high risk group will reduce mortality by 85%[21] but there has been no formal assessment of cost effectiveness of a single screening colonoscopy at age 55 years recommended in this guidance. One analysis indicates that regular colonoscopy is only cost effective in people with two affected first degree relatives,[22] while another[23] indicates that three yearly colonoscopy would cost £18 750/cancer detected, £26 250/life saved, and £3000/life year saved. Hence, screening does seem, in principle, to be cost effective in comparison with (say) population breast cancer screening. However, the intensity of screening merits careful consideration because the risk of surveillance related morbidity is cumulative with each screening episode.

There is a small but appreciable risk of adverse outcomes associated with colonoscopy. However, there are no studies in which large numbers of people have had colonoscopy solely because of a family history of the disease. Hence, available data largely relate to symptomatic people undergoing diagnostic procedures. Although these data may be biased, they do at least give a guide to the order of magnitude of potential complications. Using aggregate data from a large colonoscopy case series (mixed diagnostic and therapeutic), the overall risk of perforation is 9.34 (Poisson 95% confidence intervals 7.39 to 11.6) per 10 000 procedures,[24 25] whereas perforation rate after polypectomy is 22 (95% CI 13.8 to 33.3) per 10 000.[25 26 29 30] Post-polypectomy bleeding occurs in a further 89 (95% CI 71.5 to 109.5) per 10 000.[25 26 30] Fortunately, colonoscopy related mortality is rare, but none the less appreciable. Mortality reported in large colonoscopy series was 0.83 (95% CI 0.025 to 3.69) per 10 000 procedures.[24 25] Whereas mortality after polypectomy is 3.9 (95% CI 1.1 to 8.8) per 10 000.[25 26 29 30] Most fatalities arise in older patients but the cohorts reported in these series are reasonably representative of those who have a family history of the disease. The perforation and mortality rate is substantially higher after polypectomy and it is essential to consider that the "raison d'être" for colonoscopy in the risk groups relevant to this guideline is to identify people with polyps—the polyp prevalence in these groups is 14% to 20%.[15 19] Hence, overall morbidity and mortality in this screened risk group is probably between the figures for colonoscopy alone and that for polypectomy. Thus, aggregate perforation, bleeding, and mortality rate should be taken as 0.3%, 0.3%, and 0.014% respectively.

Financial costs associated with implementing the guidance outlined here comprise: definition of risk by appropriately trained staff; endoscopy costs; treatment of the complications of surveillance, indirect social costs related to time away from work and travel for those screened.

Based on current demographic data, there are 150 000 people within the screening age group (35–70 years) in a population of 300 000 served by a district general hospital. Within this group, there are a projected 750 people with a family history fulfilling low to moderate risk criteria (250 with one affected relative aged <45 years, and 500 with two affected first degree relatives). Assuming 80% compliance, these criteria would generate a projected **35** *additional* colonoscopies annually (assuming a maximum of two colonoscopies per at risk person), at a total cost of £5250 per annum (at £150/colonoscopy). There would also be addditional costs associated with treatment of complications, but this would be negligible for such a small target screening population and could be disregarded. It is important to note that there is likely to be an initial surge of referrals and so the projected annual caseload may appear to be an underestimate when such guidelines are brought into clinical use. However, as referral rates stabilise with time, the number will eventually settle to the projected 35 extra colonoscopies per year, unless there is a change in the proportion of people fulfilling the criteria. It should be noted that the estimated workload is very sensitive to the family history criteria and, because there are many people with a lesser degree of family history, any relaxation of family history criteria will result in a disproportionate increase in colonoscopy workload.

RECOMMENDATIONS FOR AUDIT

In the absence of compelling data from available observational comparative studies and the fact that a randomised controlled trial is highly unlikely, it is recommended that there should be a rolling audit of outcomes for people attending because of concern about a family history of colorectal cancer. Such audit represents an achievable mechanism for accruing data on the effectiveness and acceptability of the strategy laid out in this guidance. Outcomes to be audited should include: total number of referrals (including those dealt with using postal advice to GPs/patients); extent of family history and risk category assigned; proportion recommended surveillance; compliance with recommended surveillance; surveillance related morbidity/mortality; adenoma and cancer prevalence in those recommended surveillance; cancer incidence in those not fulfilling criteria for this guideline; overall survival in all referrals by risk category assigned.

As many people referred with a family history will not merit surveillance and also in view of the protracted nature of the process, several of the outcome measures listed above are best collected through central NHS flagging systems. Furthermore, a common clinical and administrative structure that processes all family history referrals within a hospital or even a whole region is advisable to ensure coherent unitary protocols and advice. Audited data must include all referrals to regional clinical genetics services as well as to medical and surgical gastroenterology. The nature of the operational system is likely to vary between regions, with some centres processing all referrals through clinical genetics services while others primarily being through committed specialists in gastroenterology. However, comprehensive coverage of the population of referrals on the basis of family history is essential to avoid the considerable potential for biased auditing of outcomes. Hence, a mechanism should be in place to assimilate referral data from both gastroenterological and clinical genetic specialties.

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