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Update on the Differential Diagnosis, Surveillance and Management of Hereditary Non-polyposis Colorectal Cancer

H.T. Lynch, T. Smyrk, J. Lynch, R. Fitzgibbons Jr, S. Lanspa and T. McGinn

Hereditary non-polyposis colorectal cancer (HNPCC) is the most common hereditary form of colorectal cancer (CRC), accounting for approximately 10% of the total CRC burden. HNPCC lacks premonitory physical stigmata, thereby making the family history crucial for diagnosis. Advances in molecular genetics during the past 2 years have led to the cloning of four HNPCC genes (*MHS2*, *MLH1*, *PMS1* and *PMS2*). It is now possible to provide presymptomatic DNA testing followed by genetic counselling for gene carriers. Some studies have shown that adenomas in HNPCC are larger, more villous, and have more high grade dysplasia than sporadic cases, suggesting an accelerated adenoma–carcinoma sequence. Given the early age of onset and proximal predominance of CRC, we initiate colonoscopy at age 20–25 years and we recommend that it be performed every 1–2 years. The wealth of clinical and molecular genetic knowledge currently available to physicians about HNPCC can be used effectively for cancer control.

Key words: HNPCC, cancer genes, genetics, colon cancer, genetic counselling, surveillance
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INTRODUCTION

THE INFLUENCE of primary genetic factors on the incidence of colorectal cancer (CRC) is being increasingly appreciated, a change from most of the past century, when familial adenomatous polyposis (FAP) was thought to be the only hereditary predisposition to CRC. The historical focus on FAP is not surprising, given its striking premonitory phenotype (florid colonic polyposis). Although FAP actually accounts for a minority of hereditary CRC, the syndrome has served the clinical and research community well as a paradigm for hereditary cancer, and has taught us much about the diagnosis, surveillance and management of colon cancer.

In the midst of a virtual explosion of knowledge on molecular biology, FAP became, once again, the critical link for advancing knowledge on the molecular genetics in colon carcinogenesis. Indeed, molecular genetic studies of FAP patients have provided the basis for the elucidation of the currently accepted multistep model of carcinogenesis, in which an array of genetic events underlie the morphological progression from normal colonic mucosa to adenomatous (dysplastic) change to invasive carcinoma [1, 2]. This work culminated in the identification and cloning of the responsible germline mutation (*APC* gene) for FAP at chromosome 5q [3, 4].

It is clear that any discussion dealing with hereditary CRC must build on the database concerning FAP, particularly its complex clinical and molecular genetic heterogeneity. This heterogeneity has been exemplified by the identification of the hereditary flat adenoma syndrome (HFAS), an attenuated FAP variant which results from distinctive mutations in the *APC* gene [5, 6].

There are a variety of hereditary CRC syndromes associated with colonic polyps and occasionally with polyps throughout the gastrointestinal tract, including familial polyposis coli and its variants, familial juvenile polyposis [7] and Peutz–Jegher's syndrome [8] (Table 1). More recently, a hereditary colon cancer prone disorder characterised by an absence of multiple colonic polyps has been described, namely hereditary non-polyposis colorectal cancer (HNPCC). HNPCC is now believed to be the most common form of hereditary CRC [9].

Our purpose is to provide a brief review of hereditary CRC syndromes, with emphasis on HNPCC, its natural history, tumour spectrum and its recent molecular genetic advances. The implications of these findings for cancer surveillance, management and control will be discussed.

FAMILY HISTORY AND CRC

A well orchestrated cancer family history is still the most cost-effective approach to the diagnosis of hereditary cancer. Unfortunately, the cancer family history is often a neglected part of the medical evaluation of cancer patients [10, 11].

The significance of the family history in CRC has been prospectively evaluated by Fuchs and associates [12]. These authors found that the age-adjusted risk of CRC for patients who had an affected first-degree relative, when compared to patients lacking a family history of CRC,

Correspondence to H.T. Lynch.
H.T. Lynch and J. Lynch are at the Department of Preventive Medicine; R. Fitzgibbons is at the Department of Surgery; S. Lanspa and T. McGinn are at the Department of Medicine, Creighton University School of Medicine, Department of Preventative Medicine, 2500 California Plaza, Omaha, Nebraska 68178 and T. Smyrk is at the Department of Pathology, Clarkson Hospital, Omaha, Nebraska, U.S.A.

Table 1. Hereditary CRC syndrome

Hereditary form of colorectal cancer (CRC)	Inheritance pattern/germline mutation	Polyps	Cancer	Non-cancer features	Screening	Surgical management and/or prophylaxis	Presymptomatic DNA testing	Genetic counselling
Familial adenomatous polyposis (FAP)	AD; *APC* gene at chromosome 5q, distal to 5[1]	Adenomatous, often start in distal colon/ rectum; usually >100; adenomas may occur in small bowel and stomach	CRC, average age onset 39 years; many cases in teens and twenties; cancer of small bowel, stomach (particularly in Japan), papillary thyroid cancer, periampullary carcinoma, sarcoma, brain tumour	Gardner's variant–epidermoid cysts of skin, osteomas of mandible, congenital hypertrophy retinal pigment epithelium. Desmoid tumours (intra-abdominal) do not metastasise but may kill by direct extension; desmoids may be initiated by surgery (dissected surfaces); fundic gland polyps, adrenal adenomas	Base line flexible sigmoidoscopy age 10–12 years; flexible sigmoidoscopy annually thereafter, for *APC* germline positive. If at risk but not tested for *APC*, same strategy. If eventually found to be *APC* negative, then baseline flexible sigmoidoscopy at age 15–20 years, if negative, no further screening	Prophylactic subtotal colectomy with low ilial-rectal anastomosis when phenotype (florid polyposis) identified; may consider rectal mucosectomy with ileal pouch anal anastomosis if too many rectal polyps to manage or if compliance for rectal segment follow-up is poor. Consider Sulindac chemoprevention (while reducing polyps, cancer may still occur)	Test for *APC* germline mutation as early as age 10–12 years	Initiate pre-teens, include parents
Hereditary flat adenoma syndrome	AD; *APC* gene at chromosome 5q, proximal to 5[1]	Ordinary adenomas but also flat adenomas with proximal colonic predominance; may be few (5–10), rarely >100	CRC with average age onset at 55 years; occasional periamullary carcinoma	Fundic gland polyps	Colonoscopy and upper endoscopy initiate at age 20 years and annually for *APC* germline-positive patients or every 2 years if at genetic risk but not tested for *APC*	Prophylactic subtotal colectomy if too many polyps to manage; consider chemopreventive Sulindac	Test for *APC* germline mutation at age 20 years	Initiate at age 20 years
Turcot's syndrome	Possible AR; may be AD in some families but confusion with FAP and Gardner's syndrome with brain tumour association	Florid colonic adenomas, 50 to >100	CRC and central nervous system, particularly brain tumours	Rare examples of multiple café-au-lait spots and pigmented naevi but not clear if truly integral to the syndrome	Baseline flexible sigmoidoscopy at age 10–12 years and annual flexible sigmoidoscopy thereafter; consider CAT scan or MRI brain	Prophylactic subtotal colectomy if colonic polyps present, as in FAP	None known	Initiate at age 10–12 years, include parents
Juvenile polyposis coli	AD	Diffuse hamartomatous (may have adenomatous component) of colon, but may occur in small bowel and	CRC	Children may manifest diarrhoea (may be severe)	Initiate colonoscopy at age 10–12 years	Prophylactic subtotal colectomy when phenotype present with too many polyps to manage	None known	Initiate pre-teens, include parents

Peutz–Jeghers syndrome	AD	Peutz–Jeghers polyps (may have adenomatous features) in stomach, small bowel and colon	Stomach, small bowel, colon, sex cord tumours, ovary and testes	Mucocutaneous melanin pigmentation	Baseline colonoscopy and upper endoscopy, initiate at age 20 years; flexible sigmoidoscopy annually thereafter	Consider prophylactic subtotal colectomy if too many polyps to manage and if mixed adenomatous features	None known	Initiate teens and include parents
Discrete colonic adenomatous polyps and CRC of Burt	AD	Occasional (never florid) adenomatous colonic polyps	CRC, average age in accord with population expectations	None known	Initiate baseline flexible sigmoidoscopy at age 40 years and thereafter every 3 years	Standard CRC surgical approach	None known	Initiate at age 25–30 years
Hereditary non-polyposis colorectal cancer (HNPCC)	AD, germline mutations are *MSH2* at chromosome 2p; *MLH1* at chromosome 3p; *PMS1* at chromosome 2p; *PMS2* at chromosome 7q	Occasional colonic adenomas in accord with population expectations	CRC most common with proximal predominance, an excess of synchronous and metachronous CRC. Others include cancer of the endometrium, ovary, small bowel, stomach and transitional cell carcinoma of ureter and renal pelvis. Average of cancer onset is 44 years	Muir–Torre syndrome variant shows cancer features of HNPCC but includes sebaceous adenomas; sebaceous carcinomas and multiple keratoacanthomas of skin	Colonoscopy, initiate at age 20–25 years, annually for germline mutation carriers. Every other year when mutation studies are lacking; endometrial aspiration biopsy at the same time as colonoscopy	Subtotal colectomy for initial CRC; consider option of prophylactic subtotal colectomy for germline carriers. Consider prophylactic total abdominal hysterectomy and bilateral salpingo oophorectomy for patients with initial CRC who have completed their families	Test for germline mutations no earlier than age 18–20 years	Initiate at age 18 years, prior to any consideration for gene testing
Familial CRC	Empirical risk 3-fold increase for CRC in patients with one or more first degree relatives with CRC; likely multifactorial	In accord with population expectations	CRC, comparable to age of onset and colonic location for general population	None	Baseline flexible sigmoidoscopy at age 40 years and repeat every 3 years	Standard surgical procedure for CRC	None	Initiate at age 30–35 years
Familial ulcerative colitis and Crohn's disease	Unknown; possible AD in some families, polygenic also likely	Pseudopolyps (non-adenomatous)	CRC, lymphoma of GI tract	Arthritis, pyoderma gangrenosum, annular erythemas and vascular thromboses, sclerosing cholangitis	Colonoscopy, annual in patients with chronic pan colitis of 8 or more years duration; check for high-grade dysplasia colonic mucosa	Subtotal colectomy for CRC; consider prophylactic subtotal colectomy for patients with persistent high-grade dysplasia of colonic mucosa; proctocolectomy if IBD mandates	None	Initiate at age 18–20 years

AD, autosomal dominant; AR, autosomal recessive; IBD, inflammatory bowel disease, CAT, computerised axial tomography; MRI, magnetic resonance imaging; GI, gastrointestinal.

was 1.72 (95% confidence interval 1.34–2.19). In those patients with two or more affected first-degree relatives, the relative CRC risk was 2.75 (95% confidence interval 1.34–5.63). The risk was magnified for younger individuals with an affected parent or sibling. For example, in those individuals under age 45 years who had one or more affected first-degree relatives, the relative risk was 5.37 (95% confidence interval 1.98–14.6), while the risk was found to decrease with increasing age (P for trend, <0.001). The investigators concluded that "a family history of colorectal cancer is associated with an increased risk of the disease, especially among younger people".

CARDINAL CLINICAL AND GENETIC FEATURES OF HNPCC

In the study of more than 150 HNPCC families, we have identified certain medical genetic findings which appear to best characterise the syndrome, and which are aptly termed "cardinal features of HNPCC" [9]. When assessing these features in any given family, the diagnostician must be cognisant of the variable expressivity and gene penetrance that characterise all hereditary disorders. In some HNPCC families, the clinical variation may be so rampant that the only measure for a secure diagnosis is molecular genetic confirmation (see subsequent discussion). The cardinal features of HNPCC are as follows.

(a) Early age of onset of colorectal cancer (approximately 44 years); (b) proximal predilection of CRC (approximately 70% proximal to splenic flexure); (c) marked excess of synchronous and metachronous CRC (45% second and third primary CRCs when less than subtotal colectomy was performed for initial CRC); (d) a tendency for special histological features of CRC, including poor histological differentiation, abundant extracellular mucin, signet cell histology, and peritumoral host lymphoid reaction.

Before reviewing the clinicopathological features in more detail, we must first summarise the genetics of HNPCC: the syndrome results from a germline mutation involving one of the genes responsible for repairing mismatches that occur during DNA replication. To date, four separate genes concerned with human DNA mismatch repair have been identified, occupying loci on three chromosomes [2, 3, 7]. Affected individuals are heterozygous, i.e. they carry one normal gene and one defective one. For at least one of the genes, the heterozygous state appears to result in normal DNA mismatch repair activity. Only when a second (somatic) mutation occurs, inactivating the wild-type allele, do the affected cells acquire the mutator phenotype. Such cells accumulate mutations at a high rate, presumably acquiring, at some point, the mutation or mutations that result in immortalised cells with the capacity to metastasise.

Tumours homozygous for a defective DNA mismatch repair gene manifest the phenomenon of microsatellite instability: numerous replication errors in bi- and trinucleotide repeat sequences alter the electrophoretic mobility of these so-called microsatellites. The phenotype is referred to as replication error positive (RER+). As might be expected, most colon cancers in HNPCC are RER+, as are many of the associated extracolonic cancers such as endometrial and ovarian carcinoma.

RER+ tumours occur in the sporadic setting, accounting for 12–15% of colorectal cancer in the U.S.A. Here, two somatic mutations must occur before affected cells acquire the mutator phenotype. Interestingly, RER+ colon cancers in the sporadic setting form a more homogeneous group than those seen in HNPCC. Sporadic RER+ colon cancers, for example, arise almost exclusively in the right colon, while only 70% of HNPCC cancers do so.

Previous clinical and epidemiological investigations have noted differences in the frequency of proximal versus distal colon cancer. Distal colonic cancers occur more frequently in western industrialised areas of the world. Proximal colonic tumours are discovered later than their left-sided counterpart [13], and are frequently larger (possibly due to delay in diagnosis). In less industrialised areas, such as South America and India, the ratios of proximal to distal tumours range as high as 5:1. In the U.S.A., the ratio is 1:1.5 [14].

These right-to-left differences in colon cancer rates suggest underlying genetic, as well as dietary interactions [15]. Migrant studies also support these observations in that immigrants coming from Japan, a country with a low CRC incidence, and a proximal colonic cancer excess, have a marked increase in the number of distal colon cancers when they migrate to the U.S.A., where they express findings similar to the host country [16]. It may well be that the majority of proximal colon cancers arise as a result of defective DNA mismatch repair, while the more distal cancers have a different pathogenesis.

The problem of multiple synchronous and metachronous colon cancers in HNPCC is understandable in the light of genetic findings. Affected individuals carry a germline mutation in a mismatch repair allele, and the potential to acquire a second somatic mutation and develop a malignancy persists no matter how many previous malignancies have occurred, so long as there is tissue at risk. (Why the proximal colon is the tissue principally at risk as opposed to another organ, such as lung, remains an unanswered question.)

The genetic basis of HNPCC may also underlie the apparent rapidity with which malignancies may arise in HNPCC. The problem of interval CRC in HNPCC has major implications for the frequency of colonoscopic screening. Lanspa and associates [17] studied the problem of interval CRCs occurring after colonoscopic screening of patients at risk for the Lynch syndromes. There were 225 patients with 313 colon cancers. Six patients from different HNPCC families manifested colon cancers arising within 4.5 years of colonoscopic surveillance. An additional 17 patients had metachronous cancers within 5 years of resection of their first colon cancer. Thus, of the 225 CRC patients from these Lynch syndrome kindreds, 10.2% had CRC within 5 years of colonoscopy or colon resection, suggesting that the potential for interval neoplasms and the malignant potential of missed diminutive adenomas may differ from the general population.

One explanation for these short interval cancer occurrences is that small, early cancers were missed during the first colonoscopic procedure. Another possibility is that the adenoma–carcinoma sequence progresses more rapidly in HNPCC. HNPCC patients develop adenomas about as often as the general population, but Jass and associates [18] reported that adenomas in HNPCC are larger, more villous and show more evidence of severe dysplasia than seen in autopsy controls. They hypothesised that carcinogenesis may occur at a more accelerated rate in HNPCC than in sporadic cases. The same authors have further speculated that the somatic mutation in the wild-type DNA repair gene does not occur until after an adenoma has been produced.

DIFFERENTIAL DIAGNOSIS OF THE LYNCH SYNDROMES

When considering a diagnosis of HNPCC, it is important to exclude FAP, hereditary flat adenoma syndrome (HFAS), the

hamartomatous polyposis syndromes (Peutz–Jeghers syndrome, familial juvenile polyposis syndrome), familial aggregations of CRC without criteria sufficient for hereditary CRC, the hereditary discrete colonic polyp CRC phenomenon, and familial chronic ulcerative colitis [9, 19].

The distinction between FAP and HNPCC is usually easy, given the abundance of adenomas in the former and their paucity in the latter. However, the attenuated variant of FAP may have very few adenomas and it may be confused with HNPCC, as we did in our original description of the disorder [19]. The diagnosis of attenuated FAP (which we originally termed hereditary flat adenoma syndrome) is suggested by the findings of multiple, proximally situated colonic adenomas, often with flat rather than polypoid growth, fundic gland polyps, gastric and duodenal adenomas, and a later age of onset of colonic cancer (approximately 55 years). If molecular genetic testing is available, HFAS patients show a germline mutation in the *APC* locus [5].

The hamartomatous polyposes have distinct pathological features that should allow differentiation from HNPCC. Peutz–Jeghers polyps are made up of thick, branching bundles of smooth muscle that form a scaffold for normal mucosa. Juvenile polyps have an expanded lamina propria with dilated crypts. Both types of hamartomatous polyps can have dysplastic (adenomatous) areas; such areas may give rise to the malignancies that occasionally complicate these syndromes. The perennial problem of familial versus hereditary CRC will no doubt become less difficult when pedigrees are extended and when DNA testing is employed. Even so, the role of environmental influences on the development of CRC cannot be discounted, even when there is a hereditary predisposition.

PATIENT EDUCATION ABOUT HNPCC

Prior to any consideration for DNA predictive testing in HNPCC, candidates must be provided with a full understanding of the disorder's natural history, the purpose of the DNA testing and its limitations, including the possibility of human and technical laboratory errors. The potential for personal and societal consequences of such testing, such as psychological stress as well as insurance, employer or even intrafamily discrimination, must be fully recognised by the counselee.

Patients who are gene positive, in addition to intensive education and genetic counselling, must be advised of all available surveillance options, including prophylactic surgical intervention, which are responsive to HNPCC's natural history. Thus, the patients must be told of the need to initiate full colonoscopy by age 20–25 years, with this procedure repeated every other year until age 30 years, and then annually thereafter. Women who are gene carriers should undergo endometrial aspiration curettage beginning at age 30 years and have this performed annually. They need to be advised that surveillance for ovarian cancer has many limitations with respect to diagnosis of early (Stages I and II) ovarian cancer. They should be advised of the option of ovarian cancer screening with transvaginal ovarian ultrasound, Doppler colour blood flow imagery, and CA-125. However, they must appreciate the limitations of this ovarian cancer screening. It, therefore, follows that they should be encouraged to have their children early so that they can consider the option of prophylactic total abdominal hysterectomy and bilateral salpingo-oophorectomy between ages 35 and 40 years. They must also be informed of the possibility of developing peritoneal cystadenocarcinoma consistent with ovarian origin, even though their ovaries were histologically normal at the time of prophylactic oophorectomy [20].

Figure 1 is a pedigree which depicts a branch from an extended HNPCC family with *MSH2* germline mutation results. Our strategy for the surveillance and prophylactic surgical management of patients in this and other HNPCC families, who are harbingers of the deleterious gene, is depicted in this pedigree.

WHICH PATIENTS SHOULD UNDERGO DNA TESTING?

Progress in molecular biology and genetics has been so rapid during the past decade that we are still learning how to implement this scientific knowledge into clinical practice. For example, the cloning of genes responsible for FAP (*APC*) [3, 4] and HNPCC (*MSH2*, *MLH1*, *PMS1* and *PMS2*) [21–26], will enable physicians to identify who is and who is not a gene carrier in these disorders. When gene carrier status is confirmed in a patient, that individual's cancer destiny will approach 100% (depending on the genes' penetrance). This unprecedented ability to identify presymptomatic gene carriers, even in the first trimester of fetal development, has raised a plethora of ethical, legal and medical management issues for which there are no definitive guidelines.

Any patient who is a member of an HNPCC family and who is of majority age (ideally age 18 years or older), who has been thoroughly educated about his or her genetic risk, the natural history of HNPCC, and who, on his or her own volition, has expressed a desire to be tested, and who has provided in writing signed permission authorising such DNA testing, should be a candidate for DNA predictive testing. In turn, the physician must be certain that the patient requesting this DNA predictive testing has not been pressured to undergo this testing by spouse, family members, employer or any other interested party. Clearly, DNA testing must be the sole choice of the patient.

PSYCHOLOGICAL ISSUES IN GENETIC TESTING

Surveys show that many (but not all) at-risk persons want to learn more about their genetic susceptibility to cancer. For example, in a sample of the public, 83% of respondents expressed interest in a genetic test for colon cancer susceptibility [27]. In a study of first-degree relatives of breast and ovarian cancer patients [28], 75% said they would definitely want to obtain a genetic test for breast and ovarian cancer risk. Comparable estimates of interest have been reported for members of hereditary breast and ovarian cancer families. These figures approximate levels of actual uptake of testing in hereditary breast cancer families [29].

Among individuals who participate in genetic testing, there is likely to be a heavy emotional burden associated with the knowledge that one is a carrier of a cancer-prone gene [30]. Psychological distress may even be observed among persons who are told that they are not carriers of a deleterious gene [29, 31, 32], and those who withdraw from testing or receive equivocal results [33]. In an extensive review of the genetic counselling literature, Sharpe [34] reaffirmed that providing genetic information may provoke strong psychological responses, particularly denial, anxiety, depression and even shame or guilt. If the patient's emotional needs and concerns are not addressed adequately, comprehension of genetic information may be reduced.

The potential for adverse emotional effects of genetic testing for HNPCC raises concerns about the impact of distress on adherence to recommended surveillance. Previous studies have linked psychological distress to non-adherence to breast cancer

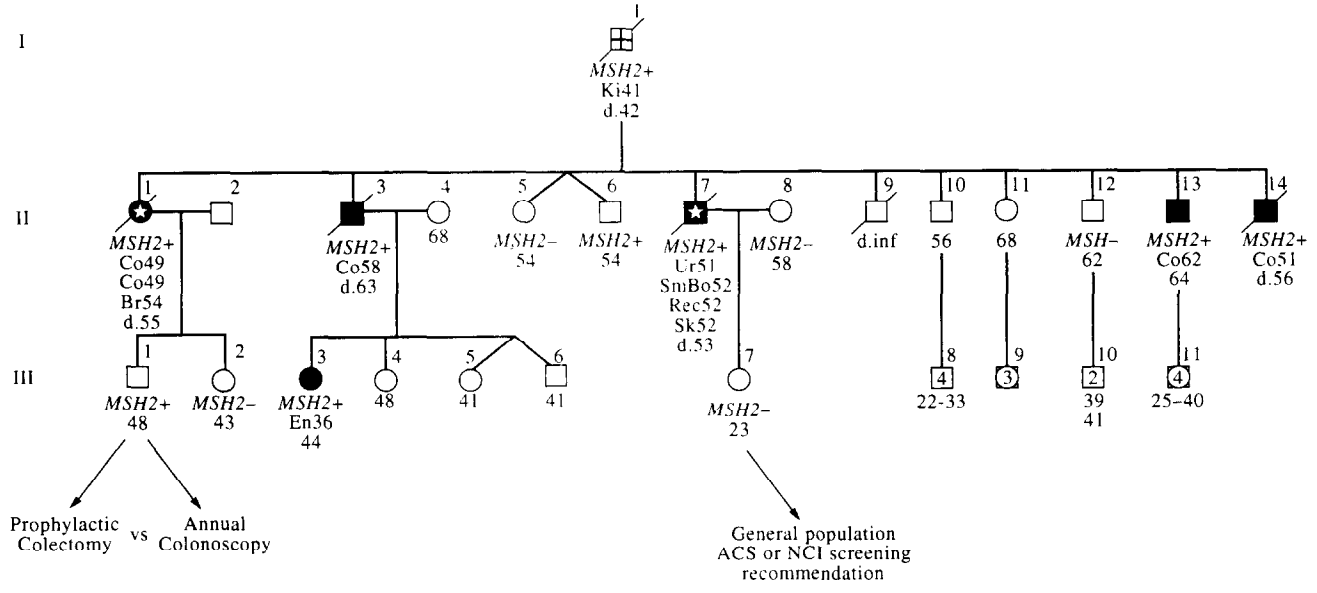

Figure 1. An abbreviated Lynch II pedigree showing an *MSH2* gene carrier (III–1) versus a non-carrier (III–7) where management implications are profound. Cancer site: Co, colon; Br, breast; En, endometrium; Sm, small bowel; Rec, rectum; Sk, skin; Ur, ureter.

screening in women who have familial risk [35, 36]. As yet, there are no comparable studies that examine the impact of distress on adherence to surveillance for colon cancer. However, studies of stool blood testing and sigmoidoscopy indicate that adherence to guidelines is suboptimal, ranging from a low of 8% to a high of 80% [37–41]. Moreover, concern about cancer has been shown to be a barrier to colorectal cancer screening [37].

GENETIC COUNSELLING AND HNPCC

Experience in the clinical utility of DNA predictive testing, in concert with genetic counselling for non-cancer disorders, such as cystic fibrosis and Huntington's chorea, and cancer prone diseases, such as the multiple endocrine neoplasia syndromes and FAP, may also be used advantageously in genetic counselling of HNPCC. This is now possible because of the mentioned newly discovered mutator genes (*MSH2* at chromosome 2p, *MLH1* at chromosome 3p, *PMS1* at chromosome 2p, and *PMS2* at chromosome 7q) in HNPCC. However, there are certain unique problems in hereditary oncological disorders when compared to hereditary diseases which are not associated with cancer. Most important is the urgent need for early cancer surveillance, and in special circumstances, surgical intervention on those organs which are most susceptible to cancer. For example, prophylactic colectomy as a preventive measure for colorectal cancer has become the time-honoured orthodoxy for those FAP patients exhibiting this disorder's phenotype, namely florid colonic polyposis and/or the presence of the *APC* mutation. In sharp contrast to FAP, HNPCC lacks premonitory phenotypic stigmata of cancer risk (Muir–Torre syndrome excepted). In this hereditary setting, prophylactic subtotal colectomy in gene carriers must now be considered as a preventive option versus lifetime colonoscopy. Central to preventive measures in HNPCC is the need for the at risk patient to be cognisant of HNPCC's natural history so that an informed decision about these management options might be prudently exercised. The art of delivering this knowledge to the patient is inherent in the discipline of genetic counselling.

Disclosure of test results, in the ideal situation, must be done in the context of a physician–supervised genetic counselling setting. Results of the DNA testing must never be given in a casual manner. The DNA findings must be held in the strictest possible medical and legal confidence. They must *never* be released to anyone without signed permission from the patient.

Family members at genetic risk for HNPCC, but who decline DNA testing, must be protected against disclosure of their personal genetic risk status whenever such risk information can be gleaned from the DNA findings from one or more at-risk relatives. Unfortunately, this privacy protection might not always be possible since disclosure of genetic risk may be determined by the DNA findings in the patient's respective key relatives.

Patients who are psychologically unprepared to receive DNA test results should not be tested until their physician deems them sufficiently well-adjusted to receive this potentially emotionally laden information. A decision to withhold DNA testing because of psychosocial reasons may be exceedingly difficult. However, every effort must be made to protect a depressed or otherwise unstable patient from harming himself or herself should disclosure of DNA findings indicate that the patient harbours the deleterious gene.

Disclosure of DNA findings in a group of two or more relatives is a difficult and perplexing logistical issue which will require more research. We have provided results to patients on an individual basis, as well as in settings of two or three family members. However, we have only engaged in this "group" counselling when counselees expressed the desire to have one or more loved ones in attendance due to feelings of insecurity and the need for emotional support. The main threat in this approach is the potential for confidentiality violation by one of the parties.

The DNA laboratory should never disclose results in the absence of sound genetic counselling and in concert with the patient's and physician's involvement. Laboratory results, as in any medical situation, should ideally be initially made available to the physician, and only then disclosed to the patient, preferably by the physician with expertise in genetic counselling. In certain circumstances, the patient may not want these DNA

findings disclosed in writing on his/her medical records for fear of insurance discrimination. These wishes of the patient must be honoured. Finally, in the absence of a physician's expertise in genetic counselling, the results should be provided to the patient by a certified genetic counsellor under the physician's supervision.

DISCUSSION

When should DNA knowledge be employed in the management of patients at increased cancer risk? Sidransky [42], in discussing the ability to detect *KRAS* gene mutations prior to the development of colorectal cancer in high risk patients, suggests that we cannot afford to wait to employ such molecular genetic knowledge inherent in this and other molecular genetic predictive tests. Once highly sensitive and specific molecular genetic screening tests become clinically available, patients whose cancer risk may be inordinately high can be readily identified. They can then be offered a better prospect for cure through timely surgical intervention. Physicians can immediately employ this knowledge to save lives. Indeed, the number of lives that might be saved through the implementation of this molecular genetic knowledge could surpass that for all available therapeutic approaches which now exist for HNPCC. Thus, Kinzler asks the logical question, "How long can we afford to wait before initiation of molecular screening trials?"

How should molecular genetic knowledge be given to patients and utilised for clinical management? Much of this is addressed under our comments on genetic counselling. However, we must nevertheless emphasise the tentative nature of genetic counselling with its absence of well established guidelines, as well as the tentative nature of the cancer control guidelines we have addressed, relevant to the option of prophylactic colectomy in HNPCC germline mutation carriers. We believe that experience over time will undoubtedly lead to important insights with respect to our genetic counselling and our suggested cancer control practices.

HNPCC clearly poses an extremely difficult management problem given the absence of premonitory physical stigmata of genotypic risk status. Yet it is this very concern that makes DNA predictive testing extremely important for those individuals from HNPCC families who are at inordinately high cancer risk. Thus, disclosure of their gene carrier status may prove to be the most important event in their life since this knowledge has the potential for highly targeted surveillance and/or the mentioned prophylactic surgical interventions that could prove to be life-saving.

Studies by Lanspa and colleagues [43] have shown that colonic adenomas in HNPCC do not exceed estimates of the general population. However, they may occur earlier in HNPCC than expected in the general population.

Jass and associates [18] have focused particular attention upon the importance of benign neoplastic polyps in HNPCC as the source of CRC. These adenomas are believed to be clonal and each are considered to serve as a marker of a single initiating mutation which may then progress as evidenced by increasing size, dysplasia and villosity, pathology features which these investigators reason are ". . .the morphological counterparts of the step-wise accumulation of mutations implicating oncogenes and tumour suppressor genes. . . .and which link the morphogenesis of hereditary colorectal cancer with recent insights into the role of DNA mismatch repair genes."

If the theory of these investigators is proven, namely that the evolution of CRC in HNPCC harbours a markedly accelerated course, then this will impact heavily upon the frequency for recommendations for colonoscopy. It is important to note that there is not a consensus for the frequency of colonoscopy screening in HNPCC in that some physicians recommend that colonoscopy be repeated every 3–5 years for at-risk patients, while others, including ourselves, recommend that this screening procedure be performed every year and that it be initiated between the ages of 20 and 25 years.

It is clear that the rapid pace of developments in DNA testing for all varieties of genetic disorders mandates that physicians embrace this knowledge and learn to work effectively with their medical genetic colleagues. However, given the public health magnitude of hereditary diseases, coupled with the severe limitation of qualified medical geneticists, it is also clear that much of the responsibility for dissemination of DNA predictive genetic test results will necessarily become the responsibility of the practising physician. Thus, it will be incumbent upon medical educators to incorporate more information about hereditary diseases and their appropriate molecular genetic implications into the already crowded medical school and postgraduate medical educational curricula.

When clinical testing becomes perfected and universally available for the several HNPCC germline mutations, it could then be immediately employed for genetic counselling and cancer control among those countless well-defined HNPCC families known to exist throughout the world. In conclusion, there is a wealth of clinical and molecular genetic knowledge currently available to physicians which can be used effectively as part of their CRC control armamentarium. Our task is to devise ways in which this informational explosion about CRC aetiology, pathogenesis and control can immediately impact upon patient care.

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