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Review

Familial colorectal cancer: Patient assessment, surveillance and surgical management

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Abstract

Germline mutations account for 5–10% of colorectal cancer. Most mutations are autosomal dominant with high penetrance and affected patients benefit greatly from appropriate treatment. This review presents the current knowledge regarding familial colorectal cancer and provides practical information based on international guidelines and the best available evidence regarding patient assessment, surveillance and surgical management.

Surgeons are often the first point of contact and frequently, the main provider of care for families with cancer syndromes or patients with familial cancer. Patients with a polyposis phenotype should undergo appropriate genetic testing. In non-polyposis patients with a cancer diagnosis, tumor testing for Lynch syndrome can guide the use of genetic testing. In patients without a personal history of cancer or polyposis, a carefully obtained family history with testing of available tumor tissue or of a living relative affected by colorectal cancer informs the need for genetic testing. Surveillance and surgical management should be planned following thorough assessment of familial cancer risk.

Evidence exists to provide guidance as to the surveillance strategies required, the specific indications of genetic testing and the appropriate timing of operative intervention. A carefully obtained family history with selective genetic testing should inform surveillance and surgical management in patients who have a genetic predisposition for the development of colorectal cancer.
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Introduction

Colorectal cancer is caused by genetic mutation. Genetic changes can be due to environmental factors, inherited factors or a combination of both. Current knowledge estimates that 5–10% of colorectal cancer is due to inherited genetic susceptibility[1] however as our understanding evolves this number is sure to increase. Appropriate management of patients and families with known syndromes through the use of registries and dedicated clinics has a profound positive effect on both cancer incidence and overall survival.[2]

Until recently, genetic testing could only be performed in laboratories associated with medical genetics departments however advances in technology have resulted in widely available, affordable genetic screening panels.[3] While at first glance this may seem attractive, such broad panels can show combinations of genetic anomalies not associated with any known condition. These findings, known as variations of unknown significance (VUS) leave the physician in both a clinical and (potentially) medico-legal quandary.[4,5] While large scale germline testing will ultimately expand our understanding of the heritable component of colorectal cancer, its current role in patient management is unclear.

In this new paradigm where access to genetic testing is no longer the limiting factor, it behooves the surgeon,

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who is often the first point of contact for the patient, to inform him or herself as to the identification of syndromes associated with colorectal cancer, the specific surveillance patterns required and the complexities regarding surgical management. This review will provide information for the practicing physician to aid in the management of patients who present with a possible genetic predisposition for colorectal cancer.

Patients present in two separate ways. One group has a diagnosis of colorectal cancer and certain features, both patient related and tumoral, raise a suspicion of an inherited component. The second group does not have a diagnosis of cancer however due to their family history either the patient or the family physician feel assessment of risk of familial cancer syndromes is warranted. These groups are distinctly different and will be discussed separately.

The patient with a diagnosis of cancer or polyposis

Assessment/consideration for genetic testing

Patients with colorectal cancer often present due to symptoms attributable to the disease: Anemia, bleeding per rectum or altered bowel habit prompts the treating physician to order a colonoscopy or sigmoidoscopy. Initial features at diagnosis may give rise to a suspicion of familial cancer. Young age at presentation and a personal or family history of cancer indicate a predisposition and form the basis for diagnostic criteria such as Amsterdam or Bethesda. Similarly colonoscopic findings can indicate inherited disease.[6]

The presence of multiple polyps indicates a polyposis syndrome that may be due to germline mutation (Table 1).

Table 1
Syndrome, gene, location and colorectal cancer risk.[63]

Syndrome	Associated gene	Position	Lifetime colorectal cancer risk
Familial adenomatous polyposis (FAP) attenuated FAP (aFAP)	APC	Chr 5p22.2	>60%
Lynch syndrome	MLH 1 MSH 2 MSH 6 PMS 2 EPCAM	Chr 3p21.3 Chr 2p22 Chr 2p16 Chr 7p22 Chr 2p21	>60%
MYH associated polyposis (MAP)	MUTYH	Chr 1p34.1	21–40%
Peutz–Jeghers syndrome (PJS)	STK 11	Chr 19p13.3	21–40%
Juvenile polyposis syndrome (JPS)	BMPR1A SMAD4	Chr 10q23.2 Chr 18q21.2	21–40%
Cowden syndrome	PTEN	Chr 10q23.31	5–20%
Serrated polyposis syndrome (SPS)	No causative gene identified		>50%

Polyps can be adenomatous, hamartomatous or have morphology consistent with serrated or hyperplastic polyps. Three adenomatous polyposis syndromes are described: familial adenomatous polyposis (FAP), attenuated FAP (aFAP) and MYH associated polyposis (MAP). Peutz–Jeghers Syndrome, juvenile polyposis syndrome and Cowden's disease are associated with hamartomatous polyps. Serrated or hyperplastic polyp syndrome shall also be discussed.

Syndromes associated with multiple adenomas

Familial adenomatous polyposis

FAP is an autosomal dominant condition arising from mutations in the "adenomatous polyposis coli" (APC) gene (Chromosome 5p 22.2).[7] Patients, without a known mutation most commonly present in the third decade.[8] An adenomatous polyp burden greater than 100 is characteristic with an increased distribution in the distal colon.

Attenuated familial adenomatous polyposis

aFAP is also associated with APC mutation and is inherited in an autosomal dominant fashion. The phenotype is different however with patients presenting slightly later with typically less polyps than classical FAP. There is some debate as to the number of polyps required to describe a phenotype of aFAP but typically, patients have less than 100 polyps and there is preponderance for the proximal colon.[9]

MYH associated polyposis (MAP)

MAP is an autosomal recessive disorder associated with biallelic "mut Y homolog (*E. coli*)" (MUTYH) mutations.[10] It is most commonly characterized by 20–99 adenomatous polyps but can be found in patients with greater than 100 adenomas.[11]

Patients who are found to have an adenomatous polyposis syndrome should be counseled as to the implications of germline testing. Testing should include both APC and MUTYH.[12] If a mutation is found, it should provide the basis for testing of first degree relatives. If no mutation is found but there remains a strong clinical suspicion, surveillance should be performed as per families with a known adenomatous syndrome.

Syndromes associated with multiple hamartomas

Peutz–Jegher's syndrome is associated with multiple gastrointestinal hamartomas and muco-cutaneous hyperpigmentation (classically circum-oral freckling). Patients are at risk of developing multiple GI cancers over their lifetime.[13] Germline mutations in "serine/threonine protein kinase 11" (STK11) are found in 50–70% of patients.[14]

Juvenile polyposis syndrome is associated with germline mutations in "mothers against decapentaplegic, drosophila, homolog of", 4 (SMAD4) and "bone morphogenetic protein receptor-1A" (BMPR1A) in approximately 50% of

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