

Managing hereditary gastrointestinal cancer syndromes: the partnership between genetic counselors and gastroenterologists

Wendy S Rubinstein* and Scott M Weissman

SUMMARY

A standard of care for the recognition and management of patients and families with hereditary gastrointestinal cancer syndromes is emerging, and both gastroenterologists and genetic counselors have an important role. This Review considers these roles and outlines the partnership needed between gastroenterologists and genetic counselors. The role of the gastroenterologist involves careful sampling of polyps and tumors, and requires a basic working knowledge of the features of hereditary gastrointestinal cancer syndromes. The role of the genetic counselor is to gather and synthesize family history and pathology information, formulate a genetic differential diagnosis, determine a genetic testing strategy, guide medical management and help patients communicate information to their relatives. Managing the complex logistics of testing the best candidate in the family, facilitating informed consent, outlining costs to patients and interpreting test results are also responsibilities assumed by genetic counselors. In addition, genetic counselors help physicians meet their ethical and medicolegal obligations with respect to patient management and family communication. Referral schemata for patients with polyposis and nonpolyposis features are presented in this Review, along with comprehensive tables that outline the features of well-known and rare syndromes that heighten the risk of gastrointestinal malignancy.

KEYWORDS gastrointestinal neoplasms, genetic counseling, genetic predisposition, intestinal polyps, practice guidelines

REVIEW CRITERIA

Ovid MEDLINE was searched in April 2008 for full-length English language articles published from 1950 to 2008. The subject headings "colorectal neoplasms", "gastrointestinal neoplasms" and "intestinal polyps" were combined with the following subject headings and keywords for the search: "genetic counseling", "genetic predisposition to disease", "risk assessment", "colorectal neoplasms", "stomach neoplasms", "hereditary nonpolyposis", "adenomatous polyposis coli", "practice guideline", and "position statement". Articles were retrieved and their reference lists reviewed to identify any additional relevant articles, including websites.

CME

WS Rubinstein is Medical Director and SM Weissman is a Licensed and Certified Genetic Counselor at the Evanston Northwestern Healthcare Center for Medical Genetics, Evanston, IL, USA.

Correspondence

*Center for Medical Genetics, 1000 Central Street, Suite 620, Evanston, IL 60201, USA
wrubinstein@enh.org

Received 25 April 2008 Accepted 17 July 2008 Published online 16 September 2008

www.nature.com/clinicalpractice
doi:10.1038/ncpgasthep1235

Medscape Continuing Medical Education online

Medscape, LLC is pleased to provide online continuing medical education (CME) for this journal article, allowing clinicians the opportunity to earn CME credit. Medscape, LLC is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide CME for physicians. Medscape, LLC designates this educational activity for a maximum of 1.25 **AMA PRA Category 1 Credits**TM. Physicians should only claim credit commensurate with the extent of their participation in the activity. All other clinicians completing this activity will be issued a certificate of participation. To receive credit, please go to <http://www.medscape.com/cme/ncp> and complete the post-test.

Learning objectives

Upon completion of this activity, participants should be able to:

- 1 Describe the gastroenterologist's role in caring for patients and families at risk for hereditary gastrointestinal cancer.
- 2 Describe surveillance and treatment for patients with Lynch syndrome.
- 3 Identify the best candidates for genetic testing for hereditary gastrointestinal cancer.
- 4 Describe the process of genetic counseling and testing for gastrointestinal cancer.

Competing interests

The authors and the Journal Editor N Wood declared no competing interests. The CME questions author CP Vega declared that he has served as an advisor or consultant to Novartis, Inc.

INTRODUCTION

Numerous hereditary cancer syndromes involve the gastrointestinal tract, and virtually all of the gastrointestinal tract can be affected (Tables 1 and 2). Most of these syndromes also pose an increased risk of extraintestinal cancers. The recognition of familial cancer syndromes provides an opportunity to predict and manage medical risks effectively through early detection and through prevention strategies. Colorectal cancer (CRC) mortality can be reduced by surveillance and polypectomy, and individuals at highest risk of CRC according to genetic predisposition could gain decades of life through careful medical management and/or prophylactic surgery. Accomplishing the goal of improved recognition and management of familial cancer risk requires a close partnership

Table 1 Hereditary gastrointestinal cancer syndromes without polyposis.^{57–60}

Syndrome	Gene(s) (chromosomal locus)	Inheritance pattern	Component gastrointestinal neoplasms	Features other than component gastrointestinal neoplasms	
				Malignant neoplasms	Benign neoplasms and other features
CoLoN syndrome ^a	<i>MLH1</i> (3p21) ^b <i>MSH2</i> (2p21) ^b <i>MSH6</i> (2p15) ^b <i>PMS2</i> (7p22) ^b	AR	Childhood onset colon cancer; duodenal cancer; colon adenomas	Childhood onset brain tumors; leukemia; lymphoma; endometrial and ovarian cancers ³⁷	Features of neurofibromatosis (café-au-lait spots; neurofibromas)
FAMMM	<i>CDKN2A/p16</i> (9p21) ^b Others	AD	Pancreatic cancer	Melanoma	Dysplastic nevi
Familial Colorectal Cancer Type X	Unknown	Presumed AD	Colon cancer	Families meet Amsterdam I criteria but MSI stable ⁶¹	None
Familial GIST	<i>KIT</i> ^b and <i>PDGFRA</i> (4q12)	AD	GIST	None	<i>KIT</i> : hyperpigmentation; mast cell tumors; dysphagia <i>PDGFRA</i> : large hands
Familial intestinal gastric cancer	Unknown	AD	Intestinal gastric cancer	None ^{62,63}	None
Hereditary diffuse gastric cancer	<i>CDH1</i> (16q22.1) ^b Others?	AD	Diffuse gastric cancer; possible association with signet-ring colon cancer ^{62–64}	Lobular breast cancer	None
Hereditary pancreatitis	<i>CFTR</i> (7q31) ^b <i>PRSS1</i> (7q35) ^b <i>SPINK1</i> (5q32) ^b	<i>CFTR</i> : AR <i>PRSS1</i> and <i>SPINK1</i> : AD	Pancreatic cancer	None	Pancreatitis
Lynch syndrome (HNPCC)	<i>MLH1</i> (3p21) ^b <i>MSH2</i> (2p21) ^b <i>MSH6</i> (2p15) ^b <i>PMS2</i> (7p22) ^b	AD	Colon, gastric, duodenal and/or small bowel, hepatobiliary and pancreatic cancers	Endometrial and ovarian cancers; ureteral and/or renal pelvis cancers; glioblastoma	None
Muir-Torre syndrome ^a	<i>MLH1</i> (3p21) ^b <i>MSH2</i> (2p21) ^b <i>MSH6</i> (2p15) ^b	AD	Same as Lynch syndrome	Sebaceous gland carcinomas; extracolonic Lynch syndrome cancers ⁶⁵	Sebaceous gland epitheliomas and adenomas; keratoacanthomas
MEN1	<i>MEN1</i> (11q13) ^b	AD	Gastroenteropancreatic endocrine tumors such as gastrinoma with Zollinger–Ellison syndrome, VIPoma, insulinoma and glucagonoma	Foregut carcinoids, anterior pituitary tumors	Parathyroid adenomas; facial angiofibromas, collagenomas, lipomas, meningiomas and ependymomas
Turcot syndrome ^a	<i>MLH1</i> (3p21) ^b <i>MSH2</i> (2p21) ^b <i>MSH6</i> (2p15) ^b <i>PMS2</i> (7p22) ^b	AD	Same as Lynch syndrome	Typically glioblastoma multiforme (other brain tumors reported), extracolonic Lynch syndrome cancers	None

^aLynch syndrome variant. ^bGenes for which there is a commercially available genetic test.⁶⁶ Abbreviations: AD, autosomal dominant; AR, autosomal recessive; CoLoN, colon tumors and/or leukemia or lymphoma and/or neurofibromatosis features; FAMMM, familial atypical mole-malignant melanoma syndrome; GIST, gastrointestinal stromal tumor; HNPCC, hereditary nonpolyposis cancer syndrome; MEN1, multiple endocrine neoplasia type 1; MSI, microsatellite instability; VIPoma, vasoactive intestinal peptide tumor.

between gastroenterology specialists and genetics professionals, primarily genetic counselors.

In this article, we review the respective roles of gastroenterologists and genetic counselors in the identification and management of patients and families with gastrointestinal cancer syndromes. As gastroenterologists are at the ‘front line’ of patient care, they must be able to recognize key features of hereditary cancer syndromes to know

when to refer patients for genetic consultation. Although information abounds regarding the identification and management of hereditary cancer syndromes,¹ the process of recognition and referral remains suboptimal.² Before referring a patient for genetic counseling, there are several things that the gastroenterologist can do to maximize the efficiency of the subsequent genetic evaluation. Once a patient has been referred, genetic

Table 2 Hereditary gastrointestinal cancer syndromes with polyposis.^{57–60}

Syndrome	Gene(s) (chromosomal locus)	Inheritance pattern	Component gastrointestinal neoplasms	Features other than component gastrointestinal neoplasms	
				Malignant neoplasms	Benign neoplasms and other features
AFAP ^{11,15}	<i>APC</i> (5q21) ^b	AD	0–100 colon adenomas; duodenal and other small bowel adenomas; colon cancer possible upper gastrointestinal cancer risk	Questionable whether FAP extraintestinal features seen (see FAP list)	Questionable whether FAP extraintestinal features seen (see FAP list)
FAP	<i>APC</i> (5q21) ^b	AD	100–1,000 colon adenomas; duodenal and other small bowel adenomas; fundic gland polyps; colon, duodenal, gastric, ampullary and pancreatic cancer, hepatoblastoma	Thyroid (typically papillary) and CNS cancers	Desmoid tumors; osteomas; odontomas; CHRPE; supernumerary teeth; epidermoid cysts
Familial gastric polyposis ^{67,68}	Unknown	AD	Hyperplastic polyps; gastric cancer	None	Cutaneous psoriasis
Gardner syndrome ^a	<i>APC</i> (5q21) ^b	AD	Same as FAP	Same as FAP	Same as FAP
HMPS	<i>BMPR1A</i> (10q23) ^b <i>CRAC1</i> (15q13) Others?	AD	Hyperplastic, adenomatous and juvenile and/or atypical colonic polyps; colon cancer	None ^{69–71}	None ^{69–71}
Hyperplastic polyposis syndrome	Unknown	Unknown	Hyperplastic colon polyps; colon cancer	None ^{72,73}	None ^{72,73}
JPS	<i>BMPR1A</i> (10q23) ^b <i>SMAD4</i> (18q21) ^b Others?	AD	Juvenile polyps (stomach, duodenum, small bowel, colon); colon, gastric, duodenum, small bowel, pancreatic and biliary tree cancers	None	Congenital heart defects with <i>BMPR1A</i> mutations?
JPS/hereditary hemorrhagic telangiectasia	<i>SMAD4</i> (18q21) ^b	AD	Same as juvenile polyposis syndrome plus gastrointestinal tract and hepatic AVMs; more pronounced gastric polyposis	None	Epistaxis; mucocutaneous telangiectasias; pulmonary, spinal and cerebral AVMs; digital clubbing; migraine headaches; cerebral abscess ⁷⁴
MAP	<i>MYH</i> (1p34.3) ^b	AR	0–<1,000 colonic adenomas; duodenal polyposis (rare); colon cancer; gastric cancer (rare)	None	Some reports of CHRPE; osteomas; dental abnormalities; dermal cysts ^{75,76}
Peutz–Jeghers syndrome	<i>STK11/LKB1</i> (19p13.3) ^b Others?	AD	Peutz–Jeghers polyps in small intestine, colon and stomach; esophageal, stomach, small intestine, colon and pancreatic cancer	Lung, breast, testes and gynecological adenocarcinomas; sex cord tumor with annular tubules of the ovary; adenoma malignum of the cervix	Mucocutaneous pigmentation of lips, buccal mucosa, hands, feet, periorbital, perianal and genitalia; hamartomas of the urinary bladder, lungs, renal pelvis and nares
Turcot syndrome ^a	<i>APC</i> (5q21) ^b	AD	Same as FAP	Typically medulloblastoma (but other type of brain tumors reported)	Extracolonic FAP features

^aFAP variant. ^bGenes for which there is a commercially available genetic test.⁶⁶ Abbreviations: AD, autosomal dominant; AFAP, attenuated familial adenomatous polyposis; AR, autosomal recessive; AVM, arteriovenous malformation; CHRPE, congenital hypertrophy of the retinal pigment epithelium; CNS, central nervous system; FAP, familial adenomatous polyposis; HMPS, hereditary mixed polyposis syndrome; JPS, juvenile polyposis syndrome; MAP, MYH-associated polyposis.

counselors gather and synthesize information to formulate a genetic differential diagnosis, guide the strategy for genetic testing (see Box 1 for a glossary of specialist terms used in this article) by using

patients' and families' germline DNA and tumor specimens, outline a management strategy, guide families through multifaceted psychosocial issues and help disseminate information to relatives.

Box 1 Glossary of specialist terms.**Autosomal dominant**

A pattern of inheritance in which an affected individual has one copy of a mutant gene and one copy of a normal gene on a pair of autosomal chromosomes (i.e. non-sex chromosomes). Individuals who have autosomal dominant diseases have a 50% chance of transmitting the mutant gene and, therefore, the disorder (or predisposition to the disorder) to any one child.

Autosomal recessive

A pattern of inheritance in which an affected individual has two copies of a mutant gene on a pair of autosomal chromosomes (i.e. non-sex chromosomes). Individuals with an autosomal recessive condition receive a copy of the mutant allele from each parent. As the parents have only one copy of the mutant allele they do not exhibit the trait because the gene is recessive to its counterpart normal (wild-type) allele—the parents are, therefore, said to be carriers. If both parents are carriers, there is a 25% chance of a child inheriting both abnormal genes and, consequently, developing the disease.

Consanguinity

A relationship between two people who share a common ancestor.

De novo

A gene mutation that occurs spontaneously.

Dysmorphology

A general term that is used to describe the study of, or the subject of, abnormal development of tissue form.

First-degree relative

A parent, sibling or child.

Genetic testing

Analysis, usually of DNA, to look for a genetic alteration that might indicate an increased risk for developing a specific disease or disorder.

Germline

The cell line from which gametes are derived.

Immunohistochemistry

A technique for recognizing proteins according to the binding of specific antibodies to antigens in biological tissue.

Microsatellite instability

A change to a polymorphic locus consisting of an increase or decrease of the number of variable tandem repeat mononucleotide, dinucleotide, trinucleotide or tetranucleotide units.

Mutation (germline)

Any permanent heritable change in the sequence of genomic DNA.

Obligate carrier

An individual who might be clinically unaffected by a disorder but who, on the basis of their family tree, must carry a specific mutated gene.

Pedigree

A family history diagram indicating the family members, their relationship to the proband, and their health status with respect to a particular hereditary condition.

Proband

The family member through whom an affected family is identified.

Second-degree relative

A grandparent, aunt, uncle, niece, nephew, grandchild or half-sibling.

Somatic cell

Any cell except a reproductive cell.

True negative

An individual who is found not to have a known familial gene mutation.

Variant of uncertain significance

A gene mutation for which the implications of the mutation are unknown, or a gene change that is not known to be pathogenic or benign.

THE ROLE OF THE GASTROENTEROLOGY SPECIALIST**Recognition and referral**

Numerous publications and position statements address genetic testing for hereditary gastrointestinal cancer syndromes.^{3–8} The National Comprehensive Cancer Network's Clinical Practice Guidelines in Oncology for colorectal cancer screening provide one of the more complete schemata when considering referral for genetic counseling referral and detail several management pathways for high-risk patients.⁹ These guidelines do not, however, address the hamartomatous polyp syndromes. Moreover, very few guidelines specify when a referral should be made for patients who do not meet established criteria. It is, therefore, important to understand the features of hereditary cancer syndromes and where to set the threshold for referral.

Typical features of hereditary cancer syndromes include cancer in two or more first-degree relatives and/or second-degree relatives within the same lineage, early age of onset (≤ 50 years), multiple or bilateral tumors, rare neoplasms, constellations of specific malignancies traveling in the same family (e.g. colon and endometrial cancer) and evidence of autosomal dominant or autosomal recessive inheritance. The same features apply to hereditary gastrointestinal cancer syndromes with the additional need to take into account the presence (or absence), number, and histologic subtypes of colonic and extracolonic polyps. It is important to note that while current American Gastroenterological Association guidelines recommend genetic testing for attenuated familial adenomatous polyposis (AFAP) for individuals with 20 or more adenomas, there is a growing movement to lower this threshold to 10 or more adenomas.^{2,10,11}

With the exception of Lynch syndrome, most hereditary gastrointestinal cancer syndromes are associated with benign neoplasms and other features that serve as clues as to the existence of a syndrome and the identity of the specific syndrome(s) in the differential diagnosis (Tables 1, 2 and 3 [a full-length version of Table 3 is available as Supplementary Table 1 online]). The genetic workup of Lynch syndrome is unique in its incorporation of tumor studies. Schemata outlining points for consideration before referring a patient to a genetic counselor are provided in Figures 1 and 2.

Table 3 Other hereditary cancer syndromes with some gastrointestinal involvement.⁶⁰

Syndrome	Gene(s) (chromosomal locus)	Inheritance pattern	Component gastrointestinal neoplasms
Ataxia telangiectasia	<i>ATM</i> (11q22.3) ^b	AR	Pancreas and stomach cancers
Bannayan–Riley– Ruvalcaba syndrome	<i>PTEN</i> (10q23) ^b	AD	Hamartomas (juvenile, ganglioneuromas, lipomas, inflammatory) throughout gastrointestinal tract
Beckwith–Wiedemann syndrome	<i>BWS</i> (11p15) ^b	Sporadic with occasional AD	Gastric teratoma; hepatoblastoma; hepatocellular carcinoma
Bloom syndrome	<i>BLM/RECQL3</i> (15q26.1) ^b	AR	Esophageal, gastric and colon cancers
Blue rubber bleb nevus syndrome	<i>TIE2</i> (9p21)?	AD	Gastrointestinal tract hemangiomas
Cowden syndrome	<i>PTEN</i> (10q23) ^b	AD	Hamartomas (juvenile, ganglioneuromas, lipomas, inflammatory) throughout gastrointestinal tract
Familial carcinoid syndrome	<i>SDHD</i> (11q23) ^b Others?	AD	Intestinal and appendiceal carcinoid tumors; malignant carcinoid tumor of the ileum
Fanconi anemia	At least 13 genes; of note: <i>FANCD1</i> (<i>BRCA2</i> ^b) and <i>FANCN</i> (<i>PALB2</i>)	AR	Esophageal, anal and hepatocellular carcinomas
Gorlin syndrome ^a	<i>PTCH1</i> (9q22.3) ^b	AD	Lymphomesenteric cysts (often calcified); stomach hamartomas
Hereditary breast and ovarian cancer syndrome	<i>BRCA1</i> (17q21) ^b <i>BRCA2</i> (13q12) ^b	AD	Pancreas, bile duct, and gallbladder cancers; possible colon and/or gastric cancers
Hyperparathyroidism–jaw tumor syndrome	<i>HRPT2</i> (1q25) ^b	AD	Pancreatic cancer
Li–Fraumeni syndrome	<i>TP53</i> (17p13.1) ^b	AD	Colorectal, stomach and pancreatic cancers
Multiple endocrine neoplasia type 2b	<i>RET</i> (10q11.2) ^b	AD	Ganglioneuromatosis of the intestine
NAME syndrome	<i>CNC2</i> (2p16) <i>PRKAR1A</i> (17q23) ^b Others?	AD	Colorectal and pancreatic cancers
Tuberous sclerosis	<i>TSC1</i> (9q34) ^b <i>TSC2</i> (16p13.3) ^b	AD	Hamartomatous rectal polyps
von Hippel–Lindau syndrome	<i>VHL</i> (3p25) ^b	AD	Pancreatic cysts and cystadenomas; islet cell tumors; PNETs
Xeroderma pigmentosum	7 genes	AR	Stomach cancer

^aAlso known as nevoid basal cell carcinoma syndrome. ^bGenes for which there is a commercially available genetic test.⁶⁶ Abbreviations: AD, autosomal dominant; AR, autosomal recessive; NAME, nevi, atrial myxoma, myxoid neurofibromas, and ephelides; PNET, primitive neuroectodermal tumour. A full-length version of this table including non-gastrointestinal features is available as Supplementary Table 1 online.

Assisting the genetic workup

Before endoscopy

Before a patient undergoes endoscopy, questions should be posed regarding whether there is a history of cancer, gastrointestinal polyps or other benign neoplasms in the patient and their first-degree and second-degree relatives. The answers to these questions should alert the gastroenterologist

to the likelihood of identifying benign or malignant neoplasms during the procedure.¹²

During endoscopy: counting multiple polyps

If multiple polyps are identified during endoscopy, taking as many biopsy samples as possible and counting (rather than estimating) the polyp number will greatly help to narrow the differential

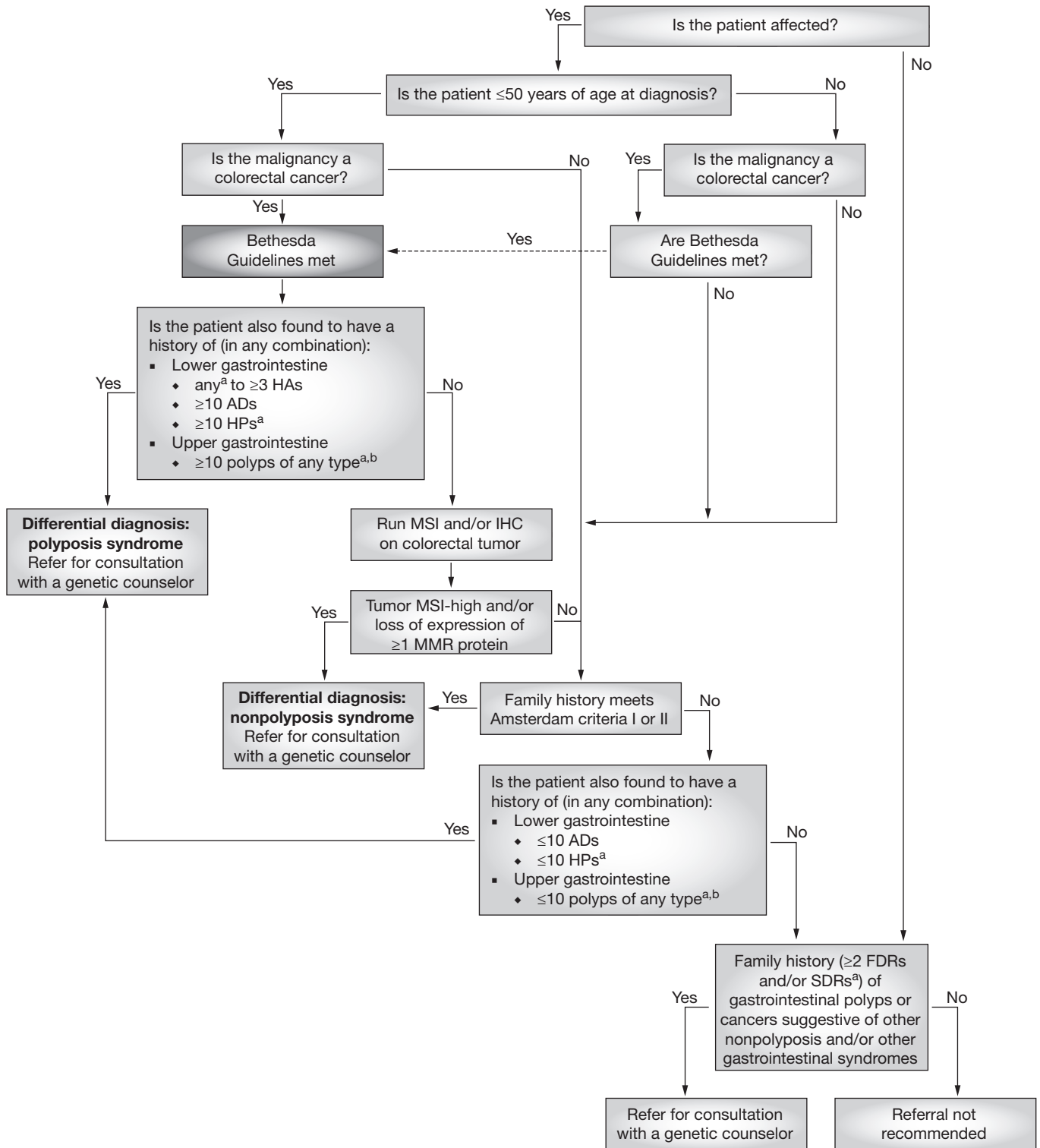


Figure 1 Referral schema used for patients with gastrointestinal cancers at the Evanston Northwestern Healthcare Center for Medical Genetics, Evanston, IL. Figure created using information from multiple references.^{4,6,8,11,13,14} ^aRecommendation based on clinical judgment; consider reviewing the case with a genetic counselor. ^bIf fundic gland polyps are identified, consider whether the lesions are secondary to proton pump inhibitor use and review the case with a genetic counselor. Abbreviations: AD, adenoma; FDR, first-degree relative; HA, hamartoma; HP, hyperplastic polyp; IHC, immunohistochemistry; MMR, mismatch repair; MSI, microsatellite instability; SDR, second-degree relative.

diagnosis, which relies heavily on the total polyp count (over the course of time), and pathological polyp subtypes. Of course, if profuse polyposis is identified, counting the number of polyps is not feasible and estimation is acceptable, but taking a large number of biopsies is still desirable. If the polyps are all of one pathological type, the differential diagnosis is limited and genetic testing should generally be straightforward. However, if a mix of polyps is identified—for example hyperplastic polyps and hamartomas—the differential diagnosis will be quite large (Tables 2 and 3 [a full-length version of Table 3 is available as Supplementary Table 1 online]). In this situation, a genetics professional might be required to perform a dysmorphology exam and prompt additional imaging tests and/or laboratory tests to narrow the differential diagnosis for genetic testing.

If genetic testing is inconclusive or not pursued, the counting of polyps is particularly important for making appropriate surveillance recommendations.^{9,13} For example, to make a clinical diagnosis of juvenile polyposis syndrome (JPS), AFAP, familial adenomatous polyposis (FAP) or hyperplastic polyposis syndrome, documentation of the presence of more than 5, 20, 100 or 30 polyps, respectively, can be required.^{14–16} For practical purposes, insurance companies in the US require documentation of polyp burden before genetic testing is deemed medically necessary, although the approximate polyp number can be provided as a notation in the endoscopy report, even if not all polyps were biopsied. For example, most US insurers require that a patient has at least 20 adenomas for them to be covered for *APC* gene testing if they do not have a first-degree relative with FAP or AFAP.

During endoscopy: malignancy

If a CRC is identified during endoscopy, and the patient meets the revised Bethesda Guidelines¹⁷ or has a family history that meets or approaches the Amsterdam Criteria (Box 2),^{18,19} the presence of Lynch syndrome should be considered. In this situation, the gastroenterologist should take additional biopsies of the CRC for tumor studies, such as microsatellite instability (MSI) testing or immunohistochemical (IHC) staining of the protein products of the mismatch repair genes.^{17,20}

A section of normal mucosa (or a blood sample) is needed as a control sample for MSI. Taking multiple biopsies is critical for MSI and IHC studies of rectal cancers as MSI testing and IHC staining are unreliable after chemoradiation,

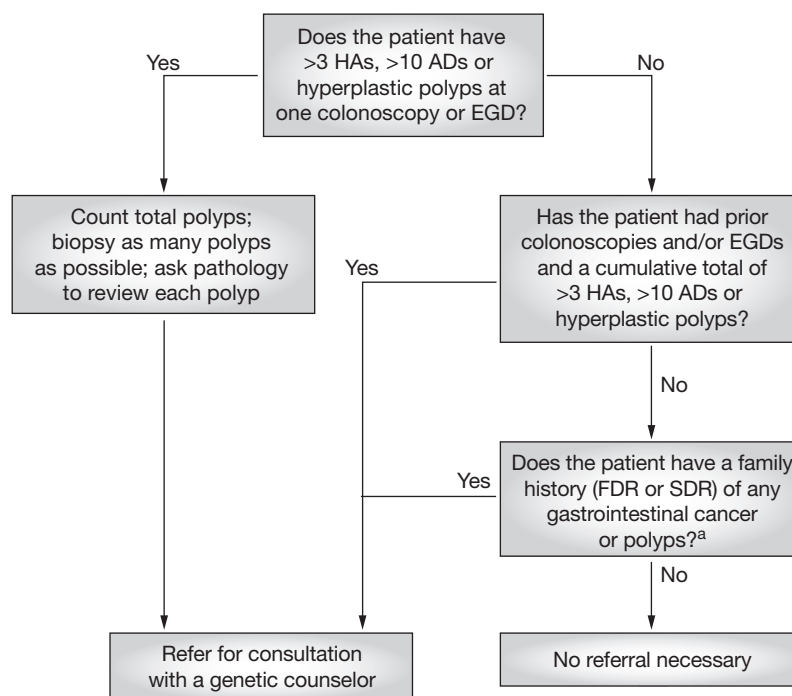


Figure 2 Referral schema used for patients with gastrointestinal polyps found on endoscopy at the Evanston Northwestern Healthcare Center for Medical Genetics, Evanston, IL. Figure created using information from multiple references.^{4,6,8,11,13,14} ^aRecommendation based on clinical judgment; consider reviewing the case with a genetic counselor. Abbreviations: AD, adenoma; EGD, esophagogastroduodenoscopy; FDR, first-degree relative; HA, hamartoma; SDR, second-degree relative.

and rectal cancer treatment schemata often involve neoadjuvant therapy.²¹ If MSI and IHC studies are performed in-house, the gastroenterologist requesting the MSI and/or IHC test on the CRC should alert the pathologist to the personal and family history of the patient, so the pathologist can decide whether the patient meets the Bethesda Guidelines. This information is of importance as the personal and family history of the patient make up three of the five criteria in the Bethesda Guidelines. Another option would be to refer the patient to a genetic counselor who can coordinate MSI and IHC testing. Referral to a genetic counselor is the recommended option if MSI and/or IHC studies are not performed in-house.

If the MSI and/or IHC results are suggestive of Lynch syndrome, referral for genetic counseling before genetic testing is mandatory.^{5–9} If MSI and/or IHC results are inconclusive or not suggestive of Lynch syndrome, referral might still be warranted depending on the family history or if the patient was found to have multiple polyps in addition to cancer. For Lynch syndrome, various computer software programs have been developed to predict

Box 2 Definitions and criteria for Lynch (HNPCC) syndrome.^{17–19}**Amsterdam Criteria I for HNPCC¹⁸**

All the following criteria must be met to make a clinical diagnosis of HNPCC:

- At least three affected relatives with histologically verified colorectal cancer
- At least one is a first-degree relative of the other two
- At least two successive generations affected
- At least one of the relatives with colorectal cancer diagnosed at age <50 years
- FAP has been excluded

Amsterdam Criteria II for HNPCC¹⁹

All the following criteria must be met to make a clinical diagnosis of HNPCC:

- At least three affected relatives with an HNPCC-associated cancer (colorectal, endometrial, small bowel, ureter or renal pelvis)
- At least one is a first-degree relative of the other two
- At least two successive generations affected
- At least one of the relatives with HNPCC-associated cancer diagnosed at age <50 years
- FAP has been excluded

Revised Bethesda Guidelines for testing colorectal tumors for microsatellite instability (MSI)¹⁷

Tumors from individuals should be tested for MSI in the following situations:

- Colorectal cancer diagnosed in a patient who is less than 50 years of age
- Presence of synchronous, metachronous colorectal, or other HNPCC-associated tumors,^a regardless of age
- Colorectal cancer with the MSI-H histology^b diagnosed in a patient who is less than 60 years of age
- Colorectal cancer diagnosed in a patient with one or more first-degree relatives with an HNPCC-related tumor, with one of the cancers being diagnosed under age 50 years
- Colorectal cancer diagnosed in two or more first-degree or second-degree relatives with HNPCC-related tumors, regardless of age

^aColorectal cancer; endometrial, stomach, ovarian, pancreas, ureter and renal pelvis, biliary tract, and brain (usually glioblastoma as seen in Turcot syndrome) tumors; sebaceous gland adenomas and keratoacanthomas in Muir–Torre syndrome; and carcinoma of the small bowel.

^bPresence of tumor-infiltrating lymphocytes, Crohn's-like lymphocytic reaction, mucinous/signet-ring differentiation, or medullary growth pattern. Abbreviations: CRC, colorectal cancer; FAP, familial adenomatous polyposis; HNPCC, hereditary nonpolyposis cancer syndrome; MSI, microsatellite instability; MSI-H, microsatellite instability-high.

the probability of detecting a germline mutation in a mismatch repair gene, including the PREMM1,2 model, which has now been validated.²²

The NIH consensus MSI marker panel has been optimized for CRCs,²³ but tumor studies can also be performed on endometrial cancers^{24–26} and skin tumors from patients with Muir–Torre syndrome.²⁷ Although detection of high MSI in an adenoma has utility, MSI analysis demonstrates lower sensitivity for adenomas than for CRC and negative results must be interpreted with caution.

Although the initial Bethesda Guidelines recommended performing MSI testing on adenomas found in individuals younger than 40 years of age, this recommendation was removed from the revised guidelines because “the value of MSI and IHC assays in identifying MSI in early adenomatous lesions is not firmly established”.¹⁷

Post-endoscopy

Gastroenterologists should strongly consider scoping other parts of the gastrointestinal tract in patients deemed to be candidates for referral for genetic counseling, as most hereditary gastrointestinal cancer syndromes can involve the entire gastrointestinal tract (i.e. if a colonoscopy was done, an esophagogastroduodenoscopy should be performed and vice versa). The genetic counselor can then take into account the results of both the upper and the lower endoscopies when they perform their consultation. The use of more-sensitive imaging techniques such as chromoendoscopy or narrow band imaging can also be considered; however, data regarding the clinical utility of these techniques in the diagnosis of hereditary CRC syndromes are sparse and use of these techniques should ideally be within the context of a research study.

Confirming the diagnosis of a hereditary gastrointestinal cancer syndrome before a definitive surgical procedure is performed can alter the recommended surgical procedure (e.g. a subtotal colectomy might be performed instead of a hemi-colectomy), thus preventing secondary cancers and lessening the challenges of future surveillance.²⁸ The gastroenterologist should be cognizant that they can request an urgent genetic consultation in some situations, for example when surgical management might be altered by genetic information and/or genetic counseling could assist in the patient's decision making.

Informing surgical treatment decisions for patients with Lynch syndrome who have newly diagnosed CRC

Elucidation of genetic status before surgery is critical for patients with CRC or advanced adenomas given that CRC is often associated with Lynch syndrome; in fact, the rate of metachronous CRC in patients with Lynch syndrome is estimated at 45%.²⁸ One surgical approach for patients with Lynch syndrome is subtotal colectomy with ileorectal anastomosis, following which annual rectal surveillance is mandatory. Another surgical approach is total proctocolectomy, which

has higher long-term morbidity than subtotal colectomy and might leave patients affected by frequent daily bowel movements. For young patients and those with early-stage incident CRC, gains in life expectancy after subtotal colectomy as compared with hemicolectomy or segmental resection are in the order of 2–3 years.²⁹

Pathologic staging before definitive resection can be imprecise, which means that patients who have more-advanced disease will benefit less from surgery than will those with early-stage disease. A crucial part of the decision-making process comprises considering quality of life after prophylactic extended resection and this factor can mitigate against an overall benefit for particular patients.³⁰ On the other hand, fear of cancer can be lessened after subtotal colectomy, and surveillance is far easier, with rectoscopy replacing frequent colonoscopy. For young noncompliant patients, the gain in life expectancy after prophylactic colectomy is projected to be in the order of 15 years.³⁰ The possibility of large gains in life expectancy after resection is an important reason to confirm the genetic diagnosis before embarking on a definitive surgical procedure for CRC.

Women with Lynch syndrome have a 40–60% lifetime risk of endometrial cancer and a 10–12% lifetime risk of ovarian cancer.³¹ Prophylactic hysterectomy with bilateral salpingo-oophorectomy is effective in women with Lynch syndrome³¹ and a survival advantage is predicted in such patients.³² The current consensus is that this procedure should be offered at the time of colon surgery if the patient is postmenopausal, if she does not want to have any further children, or if she is undergoing surgery for another indication.^{9,28}

It is clear that male and female patients coping with a new diagnosis of CRC face additional challenges when they are confronted with information about the possibility of developing other cancers in the future. Genetic counseling during this uniquely stressful period can clarify the risks and help the patient navigate complex decisions regarding treatments and outcomes.

THE ROLE OF THE GENETIC COUNSELOR

Genetic counseling deals with the human problems associated with the occurrence, or risk of occurrence, of a genetic disorder in a family.³³ Genetic counseling differs from the traditional medical approach in that it focuses on family health, as opposed to primarily (or solely) on

individual health. Although the term ‘genetic counseling’ is often used to loosely describe professional activities related to familial conditions, genetic counseling is a distinct profession that has its own code of ethics, nationally accredited master’s degree level training programs, clinical internships, and certification.³⁴

Genetic counselors are specifically trained and experienced in discussing risks and benefits pertaining to hereditary factors and medical interventions. Counseling on familial cancer risk has emerged concurrently with advances in the field of hereditary cancer.¹² Familial cancer risk counseling is a communication process between a health care professional and an individual concerning the occurrence, or risk of occurrence, of cancer in the individual’s family. A directory of cancer genetics service providers is available on the website of the National Cancer Institute.^{1,35} To the extent that other professionals have also gained the appropriate training and experience needed to perform cancer genetic counseling (e.g. the International Society of Nurses in Genetics), we invite the use of these resources as well.

Assisting the gastroenterologist in making a genetic diagnosis

Taking family history

The genetic counselor begins the counseling process by taking a patient’s medical history and reviewing the data provided by the gastroenterologist and pathologist. Next, a three to four generation pedigree is constructed, mapping out the details of living and deceased relatives including ages, affected and unaffected status with regard to cancer, polyps, and other syndromic features, age at diagnosis of cancer and/or polyps, and any results of genetic testing and/or tumor studies.³⁶ The family history is a vital tool for delineating constellations of cancer that are suggestive of particular syndromes, indicating a mode of inheritance, guiding the genetic workup strategy, and exploring social relationships and family communication.

A psychosocial assessment is also performed by the genetic counselor, including an evaluation of the patient’s risk perception. The patient is educated in the basic principles of inheritance and cancer etiology, as well as management issues once these are determined. A thorough assessment of possible extracolonic features is also conducted in the patient and their family (e.g. sebaceous gland carcinomas in the Muir–Torre variant of Lynch syndrome; lobular breast cancer

in hereditary diffuse gastric cancer; arteriovenous malformations, epistaxis, and mucocutaneous telangiectasias in the hereditary hemorrhagic variant of JPS; non-Hodgkin's lymphoma, acute leukemia, severe growth deficiency and butterfly rash in Bloom syndrome, etc.), as nongastrointestinal features can provide important clues about the individual's syndrome (Tables 1, 2 and 3 [a full-length version of Table 3 is available as Supplementary Table 1 online]).

Certain aspects of a family history are worth noting. Several syndromes can occur *de novo* (e.g. FAP and JPS), and, therefore, a negative family history for such a disorder does not rule out a heritable syndrome that can be transmitted to the patient's children. Consanguinity can indicate the presence of autosomal recessive conditions (e.g. MAP and CoLoN;³⁷ Tables 1 and 2). In addition, a small family size (or the presence of early noncancer deaths) can mask a heritable syndrome such that the family history does not meet diagnostic criteria.

Elucidation of a family history involves very detailed questioning, and some patients are unable to report accurately information beyond that regarding their first-degree relatives.³⁸ Clinical overlap between syndromes (e.g. Lynch syndrome and AFAP), and borderline family histories (especially with respect to age of cancer onset and degree of relationship), can make it difficult to know how stringent to be when considering making a genetics referral. One advantage of developing a professional partnership between the gastroenterologist and the genetic counselor is the ability to discuss such nuances before referral.⁸

Given all these considerations, a case can be made for using clinical judgment to modify the threshold for genetic testing³⁹ and for a population-based approach to MSI and IHC tumor studies.^{40,41} However, the limitations of a population-based screening approach for CRC patients include a low yield in patients over the age of 55 years, a high rate of *MLH1* silencing in older patients through somatic (noninherited) modification of the gene, and overall cost.⁴² An additional problem is that IHC loss of *MSH2* is so closely tied with germline mutation of *MSH2* that some consider this to be a genetic test meriting pre-test counseling. We concur with Lynch *et al.*⁴² that these issues would need to be addressed before population-based screening is implemented. Hospitals that perform MSI and IHC studies have the ability to develop regional

approaches and ideally should contribute their experiences to the literature.

Reviewing the medical records of a patient and their relatives

Given the specific polyps or cancers associated with different syndromes, extensive data gathering is typically needed to confirm the pathological variant. This data gathering includes obtaining affected family members' colonoscopy reports to count polyps, pathology reports to confirm polyp or cancer type and location (e.g. ascending versus descending colon), death certificates or, if available, genetic test results.^{38,43} On occasion it might be necessary to collect slides for review by a pathologist who has expertise in identifying and differentiating gastrointestinal neoplasms, particularly polyp types.¹² Ultimately, the differential diagnosis can generally be narrowed to one or two syndromes.

Choosing the proband wisely

The proper selection of an initial individual (proband), for genetic counseling and testing has far-reaching implications within families.⁴⁴ A prevalent assumption among patients and physicians is that a negative genetic test result for an individual who has not had cancer is sufficiently informative. This is not the case. The fact that alterations in risk status cannot be made without first identifying a mutation in the family cannot be overemphasized. Even in ideal circumstances, such as when families meet diagnostic criteria, the sensitivity of genetic testing is only ~60–80%.^{10,45–47} Some families will, therefore, have mutations that are not detectable with currently available technology. Until a relative with an identifiable mutation is found, it is not possible to distinguish families for whom informative genetic testing is possible from families for whom genetic testing cannot currently be effectively used. Once a mutation is detected in a particular family, testing is fully informative in subsequent relatives, with sensitivity and specificity approaching 100%. Relatives with a 'true negative' status can follow routine surveillance guidelines (bar those with additional familial or hereditary risks).

Genetic counselors strive, therefore, to outline a testing strategy that can efficiently identify the familial mutation. They achieve this by first testing affected family members or obligate carriers, if possible, based on their position in the family. Genetic testing is avoided in those who are

unaffected or who might have sporadic cancers (phenocopies).

Variants of uncertain significance, typically missense sequence variants, are particularly vexing.⁸ During pre-test counseling, patients should be informed about this category of results.^{8,39} In addition, management should be tailored to address the family history and not the variant,³⁹ and further evaluation of the variant through family studies should be pursued on a research basis.⁴⁸

Performing an efficient, cost-effective genetic workup

Genetic counselors work closely with patients to gather information on their relatives necessary to make a genetic diagnosis. Genetic counselors also outline the costs associated with genetic testing and tumor studies and assist with obtaining insurance preauthorization. Until the familial mutation is identified, testing is expensive (for every relative), because one or more genes must be tested in their entirety owing to the hundreds of possible mutations that are present in most cancer predisposing genes. Not infrequently, the best strategy involves testing an individual who might have little to gain themselves from the information generated, or who is not interested in the information. Once the mutation in a particular family is identified, testing can be accomplished at ~20% of the initial cost by focusing on the familial mutation, with highly informative results.

Procuring informed consent for genetic testing

Genetic testing for hereditary cancer syndromes mandates full pre-test and post-test informed patient consent,⁷ which includes several basic elements that must be reviewed.⁴⁹ In addition to having features suggestive of a heritable condition and having interpretable tests available, the indications for genetic testing emphasize that testing should be used when the results will aid in diagnosis or influence the medical or surgical management of the patient or at-risk family members. A family-centered approach is important not only on ethical grounds, but also for accurate risk assessment and for many logistical reasons such as obtaining informative genetic test results.

Mediating family communication

Another vital service performed by genetic counselors is the facilitation of risk communication within families so that genetic testing and heightened cancer surveillance can be accomplished. It

has been shown for Lynch syndrome that genetic screening and lifelong cancer screening are very cost-effective, particularly when patients with cancer are considered along with their children and siblings.⁵⁰

Physicians have a medicolegal responsibility to their patients' relatives known as the 'duty to warn', which entails alerting a relative about a genetically inherited disease even if the clinician has no patient-physician relationship with this individual.⁵¹ For example, in the case of *Safer v Estate of Pack*, the plaintiff developed FAP and CRC at 36 years of age and won a unanimous ruling against the estate of the physician who had treated the plaintiff's father for FAP in 1964, when the plaintiff was aged 10 years.⁵¹

Although health professionals cannot directly contact relatives with whom they have no prior relationship, genetic counselors enlist the help of their patients by explaining the health implications associated with a heritable cancer syndrome and devising workable strategies for the patient to disseminate information in the family.⁸ Many centers will provide a patient with a family letter that provides them with information on the genetic syndrome, the mode of inheritance, and broad management implications. The family letter also notes the specific familial mutation that is present and provides information on how to find genetic counselors in the region, but stops short of stating who in the family was tested and what medical problems they have faced. The patient can then send the letter to their relatives, with guidance from the genetic counselor regarding who is at risk.

Genetic discrimination: reality versus myth

In the US, national legislation called the Genetic Information Nondiscrimination Act (GINA) has been signed into law by President George W Bush.^{52,53} GINA, which includes provisions for violation penalties, will take effect 21 May 2009 for health plans and 21 November 2009 for employers. Until this bill was passed, legislation in the US has involved a patchwork of federal and state laws, including the Health Insurance Portability and Accountability Act (HIPAA) of 1996.⁵⁴

GINA requires that genetic information be treated as "protected health information" under HIPAA, bars the use of genetic information for health plan eligibility, premium adjustment or underwriting, prohibits the requirement of genetic testing by group health plans or insurers, and protects workers from the use of genetic information in hiring, termination of employment,

and promotion decisions. Under GINA, there will be no exception for small group health plans, as occurs now under HIPAA. More than 30 states in the US already ban or limit genetic discrimination for employment purposes and all but a few have adopted laws prohibiting genetic discrimination for health insurance purposes. It has been difficult to document actual cases of genetic discrimination, and early reports of alleged discrimination were based on actual disease rather than predisposition.⁵⁴

Despite the safeguards of GINA and other legislation, the fear of genetic discrimination is palpable and could discourage patients from seeking information through genetic counseling and from undergoing genetic testing. Genetic counseling is separate to genetic testing, and the risk of genetic discrimination as a result of a counseling session is slim to none. Physicians should also be aware that according to the experiences of the very large number of people who have undergone genetic testing, the actual risk of discrimination is low. The possible risk of genetic discrimination, which will be lessened under GINA, should be balanced against the documented lifesaving potential of genetic risk management.

Genetic privacy

Genetic information is managed with close attention to privacy, and patients often maintain a high level of control over dissemination of such information. Risks and protection are reviewed by genetic counselors as part of patients' decisions about whether or not to undergo genetic testing. Ultimately, the information is intended to help guide management and thus communication between the genetic counselor and the referring physician is paramount. The provision of insurance coverage for high-risk surveillance or prophylactic surgery can usually be justified on the basis of a patient's medical history (e.g. polyposis) or family history rather than by invoking a genetic test result.

Management issues

Optimization of cancer surveillance is one of the key management issues affecting patients who have a heightened susceptibility to gastrointestinal malignancies. For patients who have a confirmed gene mutation, surveillance follows established guidelines that have been detailed elsewhere.^{9,13,55} Put into context, a decision analysis found that high-risk surveillance of a young patient with Lynch syndrome led to an expected gain in life

expectancy of 13.5 years.³⁰ Tailoring surveillance to the patient's specific situation and counseling the patient on the importance of long-term compliance are critically important.

The role of the genetic counselor is to gauge the level of gastrointestinal cancer risk, consider the full spectrum of malignancies for which the patient faces a heightened risk, and discuss a long-term surveillance strategy. Although genetic counselors typically stop short of making medical recommendations, they generally work under the supervision of a physician. In any event, genetic counselors should be able to cite the most up-to-date surveillance recommendations on the basis of their familiarity with the literature, attendance at cancer genetics meetings, and networking through professional alliances and the internet.³⁴ In our experience, opinions are often elicited from other genetic counselors working directly with expert clinician-researchers.

Cancer genetic counseling arose before genetic testing was available. Accordingly, genetic testing is used to guide management, but risk assessment can be performed in the absence of genetic testing, either when the causative gene is not yet known or when testing is not practicable for a particular family. Banking DNA from an affected family member provides options when the causative gene is discovered at a later date. Families with as yet unidentified syndromes can avail themselves of gene discovery research. In addition, mutation carriers can potentially take part in surveillance studies, if available. Genetic counselors can provide a gateway to participation in these research studies.

CONCLUSIONS

Genetic testing for hereditary gastrointestinal cancer syndromes has been in existence for more than a decade, and the development of guidelines by mainstream medical specialty societies is beginning to codify standards of care.⁵⁶ Genetic counselors assist physicians in complex aspects of genetic risk assessment and help physicians address their ethical and medicolegal obligations with respect to patient management and family communication. The endeavor of cancer risk counseling ultimately translates into a reduction in disease burden for patients and families and a more efficient use of health-care resources.

Supplementary information in the form of a table can be found on the *Nature Clinical Practice Gastroenterology & Hepatology* website.

KEY POINTS

- Gastroenterologists can assist in the genetic workup through careful sampling of polyps and tumors and having a basic working knowledge of hereditary gastrointestinal cancer syndromes
- An urgent genetic consultation can be requested at the time of cancer diagnosis, which can help clarify the need for prophylactic colorectal, endometrial or ovarian surgery and aid in patient decision making
- Genetic counselors gather and synthesize detailed information on polyps, tumors and family history to devise a genetic testing strategy according to established algorithms, which might entail testing of relatives' tumor tissue and blood
- Genetic counselors help physicians meet their ethical and medicolegal obligations with respect to patient management and family communication
- The Genetic Information Nondiscrimination Act passed in May 2008 will bolster existing US federal and state protection against the inappropriate use of genetic information by health insurers and employers

References

- 1 Lynch PM (2007) New issues in genetic counseling of hereditary colon cancer. *Clin Cancer Res* **13**: 6857s–6861s
- 2 Grover S *et al.* (2004) Physician assessment of family cancer history and referral for genetic evaluation in colorectal cancer patients. *Clin Gastroenterol Hepatol* **2**: 813–819
- 3 Petersen GM *et al.* (1999) Genetic testing and counseling for hereditary forms of colorectal cancer. *Cancer* **86**: 2540–2550
- 4 Hampel H *et al.* (2000) Hereditary colorectal cancer: risk assessment and management. *Clin Genet* **58**: 89–97
- 5 American Gastroenterological Association (2001) American Gastroenterological Association medical position statement: hereditary colorectal cancer and genetic testing. *Gastroenterology* **121**: 195–197
- 6 Standard Task Force; American Society of Colon and Rectal Surgeons; Collaborative Group of the Americas on Inherited Colorectal Cancer (2001) Practice parameters for the identification and testing of patients at risk for dominantly inherited colorectal cancer. *Dis Colon Rectum* **44**: 1403
- 7 American Society of Clinical Oncology (2003) American Society of Clinical Oncology policy statement update: genetic testing for cancer susceptibility. *J Clin Oncol* **21**: 2397–2406
- 8 Lynch HT *et al.* (2007) Who should be sent for genetic testing in hereditary colorectal cancer syndromes? *J Clin Oncol* **25**: 3534–3542
- 9 National Comprehensive Cancer Network (v.2 online 17 June 2008) NCCN clinical practice guidelines in oncology: colorectal cancer screening [http://www.nccn.org/professionals/physician_gls/PDF/colorectal_screening.pdf] (v.1 accessed 20 April 2008)
- 10 Giardiello FM *et al.* (2001) AGA technical review on hereditary colorectal cancer and genetic testing. *Gastroenterology* **121**: 198–213
- 11 Neklason DW *et al.* (2008) American founder mutation for attenuated familial adenomatous polyposis. *Clin Gastroenterol Hepatol* **6**: 46–52
- 12 Trepanier A *et al.* (2004) Genetic cancer risk assessment and counseling: recommendations of the national society of genetic counselors. *J Genet Couns* **13**: 83–114
- 13 Schreiber IR *et al.* (2005) The hamartomatous polyposis syndromes: a clinical and molecular review. *Am J Gastroenterol* **100**: 476–490
- 14 Jass JR *et al.* (1988) Juvenile polyposis—a precancerous condition. *Histopathology* **13**: 619–630
- 15 Knudsen AL *et al.* (2003) Attenuated familial adenomatous polyposis (AFAP): a review of the literature. *Fam Cancer* **2**: 43–55
- 16 Burt RW and Jass JR (2000) Hyperplastic Polyposis. In *World Health Organization classification of tumours. Pathology & genetics. Tumours of the digestive system* (Eds Hamilton SR *et al.*) Lyon, France: IARC Press
- 17 Umar A *et al.* (2004) Revised Bethesda guidelines for hereditary nonpolyposis colorectal cancer (Lynch syndrome) and microsatellite instability. *J Natl Cancer Inst* **96**: 261–268
- 18 Vasen HF *et al.* (1991) The International Collaborative Group on Hereditary Non-Polyposis Colorectal Cancer (ICG-HNPCC). *Dis Colon Rectum* **34**: 424–425
- 19 Vasen HF *et al.* (1999) New clinical criteria for hereditary nonpolyposis colorectal cancer (HNPCC, Lynch syndrome) proposed by the International Collaborative group on HNPCC. *Gastroenterology* **116**: 1453–1456
- 20 Vasen HF *et al.* (2005) Progress in genetic testing, classification, and identification of Lynch syndrome. *JAMA* **293**: 2028–2030
- 21 Choi MY *et al.* (2007) Microsatellite instability is frequently observed in rectal cancer and influenced by neoadjuvant chemoradiation. *Int J Radiat Oncol Biol Phys* **68**: 1584
- 22 Balaguer F *et al.* (2008) Validation and extension of the PREMM1,2 model in a population-based cohort of colorectal cancer patients. *Gastroenterology* **134**: 39–46
- 23 Kuismanen SA *et al.* (2002) Endometrial and colorectal tumors from patients with hereditary nonpolyposis colon cancer display different patterns of microsatellite instability. *Am J Pathol* **160**: 1953–1958
- 24 Berends MJ *et al.* (2001) MLH1 and MSH2 protein expression as a pre-screening marker in hereditary and non-hereditary endometrial hyperplasia and cancer. *Int J Cancer* **92**: 398–403
- 25 Whelan AJ *et al.* (2002) MSI in endometrial carcinoma: absence of MLH1 promoter methylation is associated with increased familial risk for cancers. *Int J Cancer* **99**: 697–704
- 26 Goodfellow PJ *et al.* (2003) Prevalence of defective DNA mismatch repair and MSH6 mutation in an unselected series of endometrial cancers. *Proc Natl Acad Sci USA* **100**: 5908–5913
- 27 Ponti G *et al.* (2005) Identification of Muir-Torre syndrome among patients with sebaceous tumors and keratoacanthomas: role of clinical features, microsatellite instability, and immunohistochemistry. *Cancer* **103**: 1018–1025
- 28 Guillem JG *et al.* (2006) ASCO/SSO review of current role of risk-reducing surgery in common hereditary cancer syndromes. *J Clin Oncol* **24**: 4642–4660
- 29 de Vos tot Nederveen Cappel WH *et al.* (2003) Decision analysis in the surgical treatment of colorectal cancer due to a mismatch repair gene defect. *Gut* **52**: 1752–1755
- 30 Syngal S *et al.* (1998) Benefits of colonoscopic surveillance and prophylactic colectomy in patients with hereditary nonpolyposis colorectal cancer mutations. *Ann Intern Med* **129**: 787–796

Acknowledgments

Charles P Vega, University of California, Irvine, CA, USA, is the author of and is solely responsible for the content of the learning objectives, questions and answers of the Medscape-accredited continuing medical education activity associated with this article.

Competing interests

The authors declared no competing interests.

- 31 Schmeler KM *et al.* (2006) Prophylactic surgery to reduce the risk of gynecologic cancers in the Lynch syndrome. *N Engl J Med* **354**: 261–269
- 32 Chen LM *et al.* (2007) Gynecologic cancer prevention in Lynch syndrome/hereditary nonpolyposis colorectal cancer families. *Obstet Gynecol* **110**: 18–25
- 33 American Society of Human Genetics (1975) Genetic counseling. *Am J Hum Genet* **27**: 240–242
- 34 National Society of Genetic Counselors [<http://www.nsgc.org>]
- 35 National Cancer Institute Genetic Services Directory [http://cancer.gov/search/genetics_services]
- 36 Bennett RL (1999) *The Practical Guide to the Genetic Family History*. New York: Wiley-Liss
- 37 Bandipalliam P (2005) Syndrome of early onset colon cancers, hematologic malignancies and features of neurofibromatosis in HNPCC families with homozygous mismatch repair gene mutations. *Fam Cancer* **4**: 323–333
- 38 Murff HJ *et al.* (2004) Does this patient have a family history of cancer? An evidence-based analysis of the accuracy of family cancer history. *JAMA* **292**: 1480–1489
- 39 Lynch HT *et al.* (2004) Hereditary nonpolyposis colorectal carcinoma (HNPCC) and HNPCC-like families: problems in diagnosis, surveillance, and management. *Cancer* **100**: 53–64
- 40 Hampel H *et al.* (2005) Screening for the Lynch syndrome (hereditary nonpolyposis colorectal cancer). *N Engl J Med* **352**: 1851–1860
- 41 Hampel H *et al.* (2006) Screening for Lynch syndrome (hereditary nonpolyposis colorectal cancer) among endometrial cancer patients. *Cancer Res* **66**: 7810–7817
- 42 Lynch HT *et al.* (2005) Molecular screening for the Lynch syndrome—better than family history? *N Engl J Med* **352**: 1920–1922
- 43 Madlensky L *et al.* (2007) Accuracy of colorectal polyp self-reports: findings from the colon cancer family registry. *Cancer Epidemiol Biomarkers Prev* **16**: 1898–1901
- 44 Watson P *et al.* (2003) Carrier risk status changes resulting from mutation testing in hereditary nonpolyposis colorectal cancer and hereditary breast-ovarian cancer. *J Med Genet* **40**: 591–596
- 45 Lynch HT *et al.* (2004) A founder mutation of the MSH2 gene and hereditary nonpolyposis colorectal cancer in the United States. *JAMA* **291**: 718–724
- 46 Wagner A *et al.* (2003) Molecular analysis of hereditary nonpolyposis colorectal cancer in the United States: high mutation detection rate among clinically selected families and characterization of an American founder genomic deletion of the MSH2 gene. *Am J Hum Genet* **72**: 1088–1100
- 47 Peltomaki P (2001) Deficient DNA mismatch repair: a common etiologic factor for colon cancer. *Hum Mol Genet* **10**: 735–740
- 48 Goldgar DE *et al.* (2004) Integrated evaluation of DNA sequence variants of unknown clinical significance: application to BRCA1 and BRCA2. *Am J Hum Genet* **75**: 535–544
- 49 Weber B (1996) Breast cancer susceptibility genes: current challenges and future promises. *Ann Intern Med* **124**: 1088–1090
- 50 Ramsey SD *et al.* (2001) Cost-effectiveness of microsatellite instability screening as a method for detecting hereditary nonpolyposis colorectal cancer. *Ann Intern Med* **135**: 577–588
- 51 Offit K *et al.* (2004) The “duty to warn” a patient’s family members about hereditary disease risks. *JAMA* **292**: 1469–1473
- 52 GovTrack.us (online April 2007) HR 493: Genetic Information Nondiscrimination Act of 2008 [<http://www.govtrack.us/congress/bill.xpd?bill=h110-493>]
- 53 Hudson KL *et al.* (2008) Keeping pace with the times—the Genetic Information Nondiscrimination Act of 2008. *N Engl J Med* **358**: 2661–2663
- 54 Greely HT (2005) Banning genetic discrimination. *N Engl J Med* **353**: 865–867
- 55 Lindor NM *et al.* (2006) Recommendations for the care of individuals with an inherited predisposition to Lynch syndrome: a systematic review. *JAMA* **296**: 1507–1517
- 56 Lynch PM (2008) Standards of care in diagnosis and testing for hereditary colon cancer. *Fam Cancer* **7**: 65–72
- 57 Lindor NM *et al.* (1998) The concise handbook of family cancer syndromes: Mayo Familial Cancer Program. *J Natl Cancer Inst* **90**: 1039–1071
- 58 Garber JE *et al.* (2005) Hereditary cancer predisposition syndromes. *J Clin Oncol* **23**: 276–292
- 59 Schneider K (2002) *Counseling About Cancer: Strategies for Genetic Counseling*, edn 2. New York: Wiley-Liss
- 60 Online Mendelian Inheritance in Man [<http://www.ncbi.nlm.nih.gov/sites/entrez?db=omim>]
- 61 Lindor NM *et al.* (2005) Lower cancer incidence in Amsterdam-I criteria families without mismatch repair deficiency: familial colorectal cancer type X. *JAMA* **293**: 1979–1985
- 62 Caldas C *et al.* (1999) Familial gastric cancer: overview and guidelines for management. *J Med Genet* **36**: 873–880
- 63 Oliveira C *et al.* (2006) Genetics, pathology, and clinics of familial gastric cancer. *Int J Surg Pathol* **14**: 21–33
- 64 Huntsman DG *et al.* (2001) Early gastric cancer in young, asymptomatic carriers of germ-line E-cadherin mutations. *N Engl J Med* **344**: 1904–1909
- 65 South CD *et al.* (2008) The frequency of Muir-Torres syndrome among Lynch syndrome families. *J Natl Cancer Inst* **100**: 277–281
- 66 Gene Tests Website [<http://www.genetests.org/>]
- 67 Seruca R *et al.* (1991) Familial gastric polyposis revisited: autosomal dominant inheritance confirmed. *Cancer Genet Cytogenet* **53**: 97–100
- 68 Carneiro F *et al.* (1993) Hyperplastic polyposis and diffuse carcinoma of the stomach: a study of a family. *Cancer* **72**: 323–329
- 69 Tomlinson I *et al.* (1999) Inherited susceptibility to colorectal adenomas and carcinomas: evidence for a new predisposition gene on 15q14-q22. *Gastroenterology* **116**: 789–795
- 70 Jaeger EE *et al.* (2003) An ancestral Ashkenazi haplotype at the HMPS/CRAC1 locus on 15q13-q14 is associated with hereditary mixed polyposis syndrome. *Am J Hum Genet* **72**: 1261–1267
- 71 Cao X *et al.* (2006) Mapping of hereditary mixed polyposis syndrome (HMPS) to chromosome 10q23 by genomewide high-density single nucleotide polymorphism (SNP) scan and identification of BMPR1A loss of function. *J Med Genet* **43**: e13
- 72 Rashid A *et al.* (2000) Phenotypic and molecular characteristics of hyperplastic polyposis. *Gastroenterology* **119**: 323–332
- 73 Ferrandez A *et al.* (2004) Phenotypic characteristics and risk of cancer development in hyperplastic polyposis: case series and literature review. *Am J Gastroenterol* **99**: 2012–2018
- 74 Gallione CJ *et al.* (2004) A combined syndrome of juvenile polyposis and hereditary haemorrhagic telangiectasia associated with mutations in MADH4 (SMAD4). *Lancet* **363**: 852–859
- 75 Lipton L *et al.* (2004) The multiple colorectal adenoma phenotype and MYH, a base excision repair gene. *Clin Gastroenterol Hepatol* **2**: 633–638
- 76 Lipton L *et al.* (2006) The genetics of FAP and FAP-like syndromes. *Fam Cancer* **5**: 221–226