

Cancer Genetics for Primary Care Assessment of the Family History

Abstract: Assessment of the cancer family history by the primary care provider can potentially save lives. In this article, the authors review the principles of cancer genetics and their application to the interpretation of family histories. Specific genetic syndromes are extensively discussed, including hereditary breast and ovarian cancer, hereditary nonpolyposis colorectal cancer, and familial adenomatous polyposis, as well as other less common familial cancer syndromes. Psychological, legal, and insurability issues in cancer genetics are also reviewed. The importance of the genetic counselor in the evaluation and counseling of patients is emphasized.

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It is now well understood that cancer is a genetic disease, occurring as a result of mutations that provide a selective survival advantage to cancer cells. Predisposition to the development of cancer is a result of a complex interaction of factors, including environment, lifestyle, and heredity. In this article, we explore the rapidly expanding knowledge concerning hereditary predisposition to cancer. In doing so, we will focus on the central importance of the cancer family history, a simple yet powerful tool to identify individuals and families at greatest risk.

Basic cancer genetics

Genes, segments of DNA, encode hereditary information that is passed from one generation of a cell to the next. Genes consist of an ordered sequence of chemicals called nucleotides, designated by the symbols A (adenine), G (guanine), C (cytosine), and T (thymine). Each gene is situated on 1 of the 23 pairs of human chromosomes; almost all of the approximately 100,000 genes in the human genome carry the instructions for the production of a protein.

Each of us is born with 2 sets of genes—1 set from our mother, the other from our father—with each cell having 2 copies of each gene. In some

cases, mutation of just 1 of the 2 genes can bring about abnormal cellular function. When this type of mutation occurs, the abnormality is said to display “autosomal dominant” inheritance. Cancers displaying autosomal dominant inheritance are usually caused by “oncogenes.” Oncogenes are mutated forms of normal genes called proto-oncogenes, which function to encourage and promote the normal growth and division of cells. When proto-oncogenes mutate to become carcinogenic oncogenes, the result is excessive cell multiplication. The term oncogene itself is derived from the Greek word “oncos,” meaning tumor. There are approximately 100 known oncogenes.

In some cases, a cell can function well with only 1 healthy version of a given gene, with no medical consequences. However, if both copies of the gene are altered—that is, mutated—or if a cell needs both copies to function, then an alteration in a critical portion of a gene may compromise the functioning of a cell. Traits that require abnormalities in both genes to be expressed are called “autosomal recessive.” Tumor suppressor genes normally function to inhibit or “put the brakes on” the cell growth and division cycle; they

function to prevent the development of tumors. Mutations in tumor suppressor genes cause the cell to ignore one or more of the components of the network of inhibitory signals; as a result, the brakes from the cell cycle are removed and a higher rate of uncontrolled growth—cancer—occurs. Tumor suppressor genes are defined by the impact of their absence and thus tend to be recessive; both normal alleles must mutate before cancerous growth begins.

One important point to remember about tumor suppressor genes is that although their mechanism is recessive, they are, for practical purposes, inherited through a dominant mechanism because development of tumors requires 2 separate mutational events. One of these events may occur in the germline and be inherited; the other occurs somatically or after birth. This “2-hit hypothesis” has helped to explain the natural history of retinoblastoma and the development of other tumors as well.

In addition to proto-oncogenes and tumor suppressor genes, a third group of cancer-causing genes are emerging as sources of cancer: DNA repair genes. These genes ensure that each strand of genetic information is accurately copied during cell division in the cell cycle. More than 130 different DNA repair genes have been identified, although only a small number have been linked to hereditary predisposition to cancer. Like tumor suppressor genes, DNA repair genes generally function through a recessive mechanism but exhibit dominant inheritance.

Recognizing familial cancer syndromes

Although most cancer is not inherited, individuals with an inherited cancer syndrome have a risk of developing cancer that is significantly greater than the general population. Recognizing families who may be at an increased risk of having a cancer syndrome is essential to provide appropriate surveillance and management for those individuals at risk. The family history is the most basic but also one of the most important tools in identifying families at risk. Genes for hereditary cancer syndromes are inherited in equal frequency from men and women, meaning that both sides of the family tree are equally important, even in families where the major concern is a history of breast, ovarian, or prostate cancer.

Before beginning with the family history, health care providers should ask individuals about their own medical history, including any history of benign or malignant tumors, major illnesses and hospitalizations, biopsy history, reproductive history, environmental exposures, and current cancer surveillance. The family history should include brothers, sisters, children, and both parents’ history of cancer or benign tumors. Second- and third-degree relatives’ histories may also be important, including those of grandparents, aunts, uncles, nieces, nephews, and cousins. Important questions to ask and document include age of onset, the type of cancer or benign tumor (if any) that occurred, and the type of

treatment they received for it. The importance of obtaining information about treatment is primarily to help verify the history provided. For example, a patient’s description of a treatment that a family member received for liver or bone cancer may indicate that the primary tumor may likely have been located in the colon or breast. Where possible, documentation with pathology and surgical reports of these cancers should be obtained.

Once the family history has been obtained, there are several features that can raise concern for the presence of an inherited cancer syndrome.

These features include the following:

- Cancer in 2 or more close relatives (not necessarily the same type of cancer)
- Multiple primary tumors in the same individual
- Earlier-than-usual onset of cancer
- Bilateral cancer in paired organs
- Specific array of cancer or tumors in a family associated with a known cancer syndrome

- Rare or unusual cancers (including men with breast cancer or early lung cancer in nonsmokers)

If the family history collection raises any suspicions, it is appropriate to refer the individual on for a genetic risk assessment.

Familial cancer syndromes

In this section, we explore some of the familial cancer syndromes that health care providers may encounter in their own practices and for which genetic testing is available. Recognition of

these syndromes can be lifesaving for patients and families.

Hereditary breast and ovarian cancer

It is estimated that 5% to 10% of all breast cancers are hereditary. This means that in the state of Minnesota, up to 360 new cases of breast cancer per year are directly attributable to the presence of a breast cancer predisposition gene.

There are many well-known risk factors for breast cancer, including late age of menarche,

later age at birth of first child, alcohol use, benign breast disease, use of hormone replacement therapy, and family history of breast cancer. Breast cancer risk-assessment models use combinations of these factors to give women a patient-specific

risk estimate for development of breast cancer. However, the presence of an hereditary breast cancer predisposition far outweighs other breast cancer risk factors. If an individual carries a familial breast cancer gene change, these risk-assessment models will dramatically underestimate his or her true risk to develop cancer.

The most common cause of familial breast cancer risk is an inherited mutation in either the BRCA1 or the BRCA2 gene. Mutations in BRCA1 and BRCA2 are found in individuals of every ethnic background. In the general population, between 1 in 300 to 1 in 800 people carries a mutation in one of these genes. The incidence can vary by ethnic group; approximately 2.5% of individuals of Ashkenazi Jewish heritage have a mutation in one of these genes, while about 0.6% of Icelanders have an

inherited mutation. Because the majority of women who develop breast cancer do not have an inherited mutation in BRCA1 or BRCA2, genetic testing is not a useful screening test for individuals in the general population. When genetic testing is performed on individuals with an increased chance of having a mutation

(either because of a personal or family history of cancer), it can be a powerful tool for risk assessment and medical management.

The exact risk of developing cancer in an individual varies depending on the gene change, the sex of the individual, and other environmental and genetic factors. Research continues to accurately delineate

cancer risks and genotype/phenotype interactions. A recent study¹ found that women with a mutation in BRCA1 have a 39% risk of developing breast cancer by age 50 and an 81% risk by age 80. Women with a BRCA1 mutation also had a 54% risk of developing ovarian cancer by age 80. Women with mutations in the BRCA2 gene had a 34% chance of developing breast cancer by age 50, and an 85% chance of breast cancer by age 80. These gene changes were also associated with a 23% chance of developing ovarian cancer by age 80. Interestingly, half of the patients with inherited mutations were from low-incidence families, with no breast cancers in mothers, sisters, grandmothers, or aunts. In nearly all of these patients, the mutation was inherited from their father.

In addition to high risks of developing a primary breast or ovarian cancer, women with a BRCA1 or BRCA2 mutation who have been diagnosed with a previous breast cancer have a 48% to 64% risk of developing a second breast cancer (as compared with the general population risk of 2% to 11%) and a 16% risk of developing ovarian cancer following their breast cancer.² Other cancer risks reported to be increased for women with mutations in BRCA1 or BRCA2 include cancers of the uterus and cervix.³

Men with a mutation in BRCA2 have a 6% risk of developing breast cancer by age 70. The risk for men with a BRCA1 mutation to develop breast cancer is less well defined but is

Genes for hereditary cancer syndromes are inherited in equal frequency from men and women, meaning that both sides of the family tree are equally important.

likely less than 1%. In addition, men with one of these mutations have an increased risk of developing prostate cancer; lifetime risk is 8% to 20%.^{2,4}

Sequencing of the BRCA1 and BRCA2 genes is available to identify high-risk families. The testing laboratory estimates that it is able to identify mutations in about 85% of individuals who have familial breast or ovarian cancer related to the BRCA1 and BRCA2 genes.⁵ Because this testing is not able to identify all causes of familial breast and ovarian cancer, individuals who have a negative genetic test may still be at increased risk to develop these cancers. Other limitations of the testing include the possibility of receiving inconclusive results (ie, a change in a gene may be identified, but it may not be clear if that change is detrimental or not). After a gene change is identified in a family, testing can be done to evaluate only for the cancer-predisposing mutation present in their family.

Individuals with a BRCA1 or BRCA2 mutation have many options for cancer surveillance or risk reduction. The National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology (v.1.2004)⁶ suggests the following management for gene carriers:

(1) *Female breast cancer surveillance.* Monthly breast self-exams starting at age 18, semiannual clinical breast exams starting at age 25, and yearly mammograms starting at 25 years or individualized based on

age of onset in family.

(2) *Ovarian cancer surveillance.* Pelvic exam and transvaginal ultrasound (to evaluate the ovaries), done concurrently with measurements of CA 125 levels in the blood every 6 months starting between the ages of 30 and 35 years.

(3) *Investigational imaging and screening studies.* May be considered when available.

(4) *Use of chemopreventive medications* (eg, tamoxifen). May be considered to reduce the risk of cancer.

(5) *Use of risk-reducing surgeries* (mastectomy or salpingo-oophorectomy). May be considered.

(6) *Male breast cancer surveillance.* Monthly breast self-exams, yearly clinical breast exams; baseline mammogram may be considered, and annual mammogram should be done if gynecomastia or parenchymal/glandular breast density is detected at baseline screening.

(7) *Colon cancer surveillance and prostate cancer surveillance.* Population screening guidelines should be followed.

Several recent studies have demonstrated the benefits of cancer risk-reducing strategies. Women who had prophylactic salpingo-oophorectomy reduced their risk of developing ovarian cancer by 90% and reduced their risk of developing breast cancer by 50%.^{7,8} Women who chose to have risk-reducing mastectomies reduced their risk of developing breast cancer by approximately 90% (those who had

both mastectomies and oophorectomy had approximately a 95% reduction in breast cancer risk).⁹⁻¹¹ Use of tamoxifen appears to decrease the risk of developing breast cancer by about 50%,¹² although the protection provided to carriers of a BRCA1 mutation (which is more frequently associated with an estrogen-receptor/progesterone-receptor-negative tumor remains controversial.¹³ Oral contraceptives have been shown to decrease the risk of ovarian cancer in the general population; however, studies on women with BRCA1 or BRCA2 mutations have shown conflicting results.¹⁴⁻¹⁶ Because each of these options carries possible risks (including increased anxiety, side effects of medications, and complications of surgeries), the plan for medical management must be individualized to meet the needs of each at-risk patient.

Hereditary colorectal cancer syndromes

The 2 most common forms of hereditary colorectal cancer are hereditary nonpolyposis colorectal cancer (HNPCC) and familial adenomatous polyposis (FAP). Together, these conditions account for less than 5% of all cases of colorectal cancer.¹⁷ When present, however, they are very powerful risk factors.

(a) Hereditary non-polyposis colorectal cancer (Lynch syndrome)

HNPCC is responsible for 3% to 5% of all colorectal cancer and is due to a germline defect in DNA repair.

Mutations in MLH1 (chromosome 3p) and MSH2 (chromosome 2p) account for more than 90% of all germline mutations in HNPCC families.¹⁷ Other identified genes are PMS1, PMS2 and MSH6. The products of these genes all participate in a multimeric DNA mismatch repair complex.

The cumulative incidence of HNPCC-related cancers was determined in HNPCC gene carriers up to age 70 years in the Finnish Cancer Registry.¹⁸ By age 70 years, the percent of individuals with HNPCC developing these cancers were as follows: colon/rectum, 82%; endometrium, 60%; stomach, 13%; ovary, 12%; bladder, urethra, and ureter, 4.0%; brain, 3.7%; kidney, 3.3%; and biliary tract and gallbladder, 2.0%.

Suspicion of HNPCC relies on an accurate assessment of family history. The Amsterdam criteria were developed to assist in the definition of HNPCC and are still widely used. The most recent Amsterdam criteria (Amsterdam II)¹⁹ are as follows:

- (1) There should be at least 3 relatives with an HNPCC-associated cancer (colorectal cancer; cancer of the endometrium, small bowel, ureter, or renal pelvis).
- (2) One should be a first-degree relative of the other 2.
- (3) At least 2 successive generations should be affected.
- (4) At least 1 should be diagnosed before age 50.
- (5) Familial adenomatous polyposis should be excluded in the colorectal cancer cases.

(6) Tumors should be verified by pathological examination.

Because many families who have proven mutations do not meet the Amsterdam criteria, new guidelines were developed. According to these guidelines (known as the Bethesda criteria²⁰), a patient qualifies for genetic testing if he or she

- (1) meets the Amsterdam criteria;
 - (2) has 2 or more HNPCC-related tumors;
 - (3) has colorectal cancer and a first-degree relative with HNPCC-related cancer, with 1 of the cancers diagnosed before age 45;
 - (4) has colorectal cancer or endometrial cancer diagnosed before the age of 45;
 - (5) has a colorectal adenoma diagnosed before age 40;
 - (6) has a right-sided colorectal cancer with an undifferentiated pattern (solid, cribriform) on histopathology diagnosed at or before age 45, defined as poorly differentiated or undifferentiated carcinoma composed of irregular, solid sheets of large eosinophilic cells and containing small gland-like spaces;
 - (7) has a signet-ring-cell type colorectal cancer diagnosed at or before age 45 (ie, cancer is composed of 50% or more of signet-ring cells).
- One of the strategies commonly used for identification of potential HNPCC cases is testing of tumors for “microsatellite instability” (MSI). Microsatellites are repeated sequences of DNA. Although the length of these microsatellites is highly variable from person to person, each individual has

microsatellites of a set length. In cells with mutations in DNA repair genes, however, some of these sequences accumulate errors and become longer or shorter. The appearance of abnormally long or short microsatellites in an individual’s DNA is referred to as microsatellite instability. MSI is found in 95% of HNPCC-associated tumors and only 15% of sporadic tumors. Using this strategy, patients whose tumors demonstrate microsatellite instability are then referred for genetic testing.

Regular colonoscopy with removal of precancerous polyps reduces the incidence of colon cancer in individuals with HNPCC. Colonoscopy is recommended rather than flexible sigmoidoscopy because of the predominance of proximal colon cancers in HNPCC. Experts recommend that individuals at risk for HNPCC-related colon cancer undergo colonoscopy every 1 or 2 years beginning between age 20 to 25 years or 10 years before the earliest age of diagnosis in the family, whichever is earlier.

Endometrial cancer and ovarian cancer surveillance is less well established than that for colon cancer. In addition to an annual Pap smear and pelvic examination, providers may also consider annual transvaginal ultrasound examination, endometrial biopsy, and CA 125 blood test beginning between 25 and 30 years of age. However, the efficacy of these screenings is unclear. In a study of the use of transvaginal ultrasound examination to screen for endometrial

cancer, no cancers were detected; however, 2 cancers were detected on the basis of symptoms manifested during the course of the study. Further studies are needed to determine if the combination of transvaginal ultrasound examination and endometrial biopsy detect endometrial cancers at an early age. No specific ovarian cancer screening trials have been conducted in women with HNPCC.

Prophylactic colectomy is generally not recommended for individuals with HNPCC who are at risk for colon cancer because routine colonoscopy is an effective preventive measure. Prophylactic removal of the uterus and ovaries can be considered after childbearing is completed.

(b) Familial adenomatous polyposis

The adenomatous polyposis coli (APC) gene, located on chromosome 5q, is mutated in patients with FAP. APC functions as a tumor suppressor gene. Both copies of APC gene must be lost to demonstrate the malignant phenotype. The protein product of the gene serves as a binding site for beta-catenin. Beta-catenin is involved in organizational tissue architecture and polarity. It is important for activation of E-cadherin, an adhesion molecule that controls the formation and maintenance of adherent junctions between epithelial cells.

Familial adenomatous polyposis (FAP) is an autosomal dominant disorder which typically presents with colorectal cancer in early adult life

secondary to extensive adenomatous polyposis of the colon. In the past, patients with extracolonic features were treated as a distinct phenotype labeled Gardner's syndrome. Detailed evaluation, however, has shown that a majority of FAP patients have one or more extracolonic features. Gardner's syndrome and FAP may occur in sibships, map to the same chromosomal location and may be associated with identical pathological mutations in the APC gene, so the terms are regarded as synonymous.

Clinical diagnosis of FAP is based on characteristic polyposis (usually more than 100 polyps) or characteristic extracolonic features. Extracolonic features may be examined in 3 groups: adenomatous polyps and cancers of the upper gastrointestinal tract, which have become a major determinant of long-term morbidity; ocular, cutaneous, and skeletal features, which are important diagnostic features but are usually benign; and malignancy in organs outside the gastrointestinal tract.

The most common sites of polyps and cancers in the upper gastrointestinal tract of FAP patients are the duodenum and periampullary region (including the duodenal papilla and ampulla of Vater). Adenomas of the jejunum and ileum also occur but are rare. Gastric adenomas occur with some frequency in FAP patients, but gastric carcinomas are rare. The exception is with FAP patients of Japanese and Korean descent, whose risk for stomach polyps becoming

cancerous has been reported to be 3 to 4 times greater than that of other FAP patients.

Congenital hypertrophy of the retinal pigment epithelium, known by the acronym CHRPE, is common in FAP, especially in patients who have other extracolonic abnormalities. Additional features often found in FAP patients include desmoid tumors (areas of fibrous growth, usually found in the abdominal area, which can achieve enormous proportions), osteomas of the skull and mandible, and dental abnormalities.

Additional malignancies known to be associated with FAP include childhood hepatoblastoma, thyroid cancer, adrenal adenomas and carcinomas, and brain tumors. It turns out that brain tumors can be associated with hereditary colorectal cancer syndromes and can occur in both FAP and HNPCC. In FAP patients, the brain tumor is usually medulloblastoma. In HNPCC, patients tend to develop glioblastoma multiforme. These conditions are known by the acronym Turcot's syndrome.

Attenuated FAP is a syndrome in which the clinical features of FAP are present but are less severe than classic cases. In these cases, mutations tend to be in the 5-prime region of the FAP gene.

For individuals with classic FAP, colectomy is recommended after adenomas emerge; colectomy may be delayed depending on the size and number of adenomatous polyps. For

individuals with attenuated FAP, colectomy may be necessary, but it may be deferred until polyps become difficult to control. The types of colectomy include (1) total colectomy with mucosal proctectomy with ileoanal pouch and (2) subtotal colectomy with ileorectal anastomosis. Colectomy with permanent ileostomy is rarely needed. Colectomy with ileorectal anastomosis is often used for individuals with attenuated FAP or in instances in which the rectum is spared of polyps. If total colectomy with ileo-anal pouch is performed, routine endoscopic surveillance of the pouch is recommended every 2 years. If subtotal colectomy is performed, surveillance of the remaining rectum is recommended every 6 to 12 months, depending on the number of polyps that develop. Cancer may still occur in the remaining rectum, but the risk is small with the current management. Additionally, the risk of cancer in the surgical transition zone, although very low, has been reported.

Surveillance is recommended for (1) individuals who are known to have FAP or an APC disease-causing mutation and (2) individuals who are at risk for FAP who have not undergone molecular genetic testing or who are members of families in which molecular genetic testing did not identify a disease-causing mutation. This surveillance should include the following:

- Annual screening for hepatoblastoma from birth to 5 years of age, by physical examination and/or

abdominal ultrasound examination and measurement of serum concentration of alpha fetoprotein

- Sigmoidoscopy every 1 to 2 years beginning at age 10 to 12 years

- Colonoscopy if polyps are detected

- Annual colonoscopy if colectomy is delayed more than a year after polyps emerge. If individuals are 10 to 20 years old and adenomas are less than 6 mm without villose component, delay in colectomy may be considered.

- Esophagogastroduodenoscopy (EGD) beginning when colonic polyposis is detected or by age 25 years and repeated every 1 to 3 years. The frequency of EGD is dependent on the severity of duodenal adenomas. A side-viewing instrument should be used to visualize the duodenal papilla. As adenomatous tissue is commonly found at the papilla, biopsy may be justified if no polyps are visualized but the papilla seems enlarged. In some cases, endoscopic retrograde cholangiopancreatography (ERCP) may be necessary to evaluate for adenomas of the common bile duct.

- Small bowel x-ray (small bowel enteroclysis or abdominal and pelvic computed tomography (CT) scan with orally administered contrast) before colectomy or when duodenal adenomas are detected, repeated every 1 to 3 years depending on findings and presence of symptoms

Early recognition of FAP and attenuated FAP may allow for timely intervention and improved final

outcome; thus, surveillance of asymptomatic at-risk children for early manifestations of FAP is appropriate. The use of molecular genetic testing for determining the genetic status of at-risk relatives when a clinically diagnosed relative is not available for testing is problematic, and test results need to be interpreted with caution. A positive test result in the at-risk family member indicates the presence of an APC disease-causing mutation in the at-risk family member and indicates that the same molecular genetic testing method can be used to assess the genetic status of other at-risk family members. In contrast, when genetic testing is offered to an at-risk family member before testing a family member known to be affected, the failure to identify a disease-causing mutation in the at-risk family member does not eliminate the possibility that an APC disease-causing mutation is present. The genetic status of such individuals cannot be determined through molecular genetic testing and those individuals need to follow the recommendations for clinical surveillance of at-risk family members.

Familial malignant melanoma

Approximately 5% to 7% of all melanoma patients are from high-risk families.²¹ Approximately 25% of these melanoma-prone kindreds have been found to have a germline mutation in CDKN2A, a tumor suppressor gene located on

chromosome 9p. CDKN2A codes for p16, an inhibitor of the cyclin D1-dependent kinase 4 complex. Germline mutations of CDK4 on chromosome 12q have also been described in 3 families. This gene acts as a dominant oncogene.

Patients with familial malignant melanoma (FMM) have increased numbers of moles with variability of mole size and 2 or more first-degree relatives with a history of melanoma. The tendency to develop multiple primary melanomas and early age at diagnosis are characteristic of these families. Genetic testing is available, but the clinical utility of genetic testing is not proven.

Families with mutations in CDKN2A have a relative risk of developing melanoma of 75:1 compared to the population at large, and a relative risk of pancreatic cancer of 13:1. Families with mutations in CDKN2A and astrocytomas have also been described.

Von Hippel-Lindau syndrome

Von Hippel-Lindau (VHL) syndrome is a rare disorder characterized by tumors in the retina and central nervous system. Other tumors (both benign and malignant) occur in the adrenal glands, kidneys, and pancreas. VHL syndrome is caused by a germline mutation in the VHL gene located on chromosome 3p. This protein appears to play a role in the transduction of growth signals generated by changes in oxygen tension. The syndrome displays autosomal dominant inheritance. The

frequency is one in 36,000, with nearly complete penetrance by 65 years and an average life expectancy of 49 years.

Diagnosis is based on clinical criteria as follows:

- 1) CNS plus retinal hemangioblastoma
- or**
- 2) CNS or retinal hemangioblastoma plus 1 of the following:
 - a) multiple renal, pancreatic, or hepatic cysts
 - b) pheochromocytoma
 - c) renal cell carcinoma
- or**
- 3) Definite family history plus 1 of the following:
 - a) CNS or retinal hemangioblastoma
 - b) multiple renal, pancreatic, or hepatic cysts
 - c) pheochromocytoma
 - d) renal cell carcinoma

Germline VHL mutations have been identified that produce 3 distinct cancer phenotypes: (1) renal carcinoma without pheochromocytoma, (2) renal carcinoma with pheochromocytoma, and (3) pheochromocytoma alone. Genetic testing is available. The utility is not proven, but is likely as VHL patients may benefit from careful screening for renal cell carcinoma, pheochromocytomas, and retinal hemangioblastomas.

Multiple endocrine neoplasia type 2

Multiple endocrine neoplasia type 2 (MEN 2) is classified into three subtypes: MEN 2A, familial

medullary thyroid carcinoma (FMTC), and MEN 2B. In MEN 2, mutations are found in a proto-oncogene called RET, located on chromosome 10q. MEN2B is characterized by a single mutation in codon 918 in all cases studied so far.

All three subtypes of MEN have a high risk for development of medullary carcinoma of the thyroid (MTC). MEN 2A and MEN 2B have an increased risk for pheochromocytoma, and MEN 2A has an increased risk for parathyroid adenoma or hyperplasia. Additional features in MEN2B include mucosal neuromas of the lips and tongue, distinctive facies with enlarged lips, ganglioneuromas of the gastrointestinal tract, and an asthenic marfanoid body habitus. The onset of MTC is in early childhood in MEN 2B, early adulthood in MEN 2A, and middle age in FMTC. The condition is diagnosed on the basis of an RET mutation presence and endocrinologic tests (ie, elevated calcitonin after pentagastrin stimulation and/or elevated metanephrines, parathyroid hormone, and calcium). Disease associated with MEN 2B can occur at younger ages and be more aggressive. MTC is usually always diagnosed before age 40 in MEN 2A and MEN 2B. Pheochromocytomas are found in 10% to 50% of individuals with MEN2A and MEN 2B.

Prophylactic thyroidectomy with autotransplantation of the parathyroids is the primary preventive measure for all subtypes of MEN 2. It is safe for all age groups; however, the timing of the

surgery is controversial. According to the consensus statement from the international MEN97 Workshop,²² the age at which prophylactic thyroidectomy is performed can be guided by the codon position of the RET mutation.

Screening for pheochromocytoma is recommended in affected individuals.

Genetic testing for mutations of the RET proto-oncogene is available. Testing should be offered to at-risk children by age 5, since medullary carcinoma of the thyroid has been reported to occur in children.

Hereditary diffuse gastric cancer

Diagnostic criteria for hereditary diffuse gastric cancer

(HDGC) are (1) the presence of 2 or more documented cases of diffuse gastric cancer in first- or second-degree relatives, with at least 1 case diagnosed before age 50 years or (2) 3 or more documented cases of diffuse gastric cancer in first- or second-degree relatives, regardless of age of onset. CDH1 is the only gene known to be associated with hereditary diffuse gastric cancer. Sequence analysis of the CDH1 gene is available on a research basis.

Clinical confirmation of CDH1 mutations identified in patients through research testing is available. Testing is performed only for the specific mutation identified in the research study.

For an individual, the psychological benefits of testing can include an improved ability to cope with cancer risk and reduced uncertainty. But finding a genetic mutation may cause increased feelings of anxiety.

Li-Fraumeni syndrome

The classical definition of Li-Fraumeni syndrome requires 1 patient with a sarcoma under the age of 45, a first-degree relative with cancer (type not specified) and a third affected family member with either sarcoma or any other cancer under the age of 45. Known associated cancers include sarcomas, breast

cancer, brain tumors, leukemia, adrenal cortical carcinoma, and others. Patients with this syndrome may also have an increased propensity to develop radiation-induced cancers.

Approximately 50% of Li-Fraumeni patients have identifiable mutations in the p53 gene, located on chromosome 17p. The tumor suppressor p53 inhibits cell growth through activation of cell-cycle arrest and apoptosis. Additionally, mutations in the CHK2

gene have been found to cause Li-Fraumeni syndrome. DNA analysis of TP53 is available with proper counseling, although the clinical utility is not proven.

Psychological, legal, and insurability issues

Genetic testing for cancer predisposition has implications not only for that individual's present medical care, but also for his or her future health and for his or her family's health. Because of this, genetic information has many psychosocial implications and, therefore, should be undertaken only after consideration is given to the impact that the results will have for the patient and his or her family.

For an individual, the psychological benefits of testing can include an improved ability to cope with cancer risk and reduced uncertainty. Many individuals feel that they are fulfilling a responsibility by taking actions that may benefit other family members. On the other hand, finding a genetic mutation may cause increased feelings of anxiety, depression, or loss of control over one's own health.

The process of genetic counseling and testing may strain relationships within families. Interpretation of test results is dependent on accurate family history information; patients are often requested to discuss the family history of cancer with their family or to allow others to review their medical records. Family members may be reluctant to discuss their own or a loved one's cancer diagnosis, or they

Additional reading

For further information on genetic testing and genetic counseling, consult the following resources:

- Braithwaite D, Emery J, Walter F, Prevost AT, Sutton S. Psychological impact of genetic counseling for familial cancer: a systematic review and meta-analysis. *J Natl Cancer Inst* 2004;96(2):122-133
- Hampel H, Sweet K, Westman JA, Offit K, Eng C. Referral for cancer genetics consultation: a review and compilation of risk assessment criteria. *J Med Genet* 2004;41(2):81-91
- American Society of Clinical Oncology policy statement update: genetic testing for cancer susceptibility. *J Clin Oncol* 2003;21(12):2397-406
- Pakakasama S, Tomlinson GE. Genetic predisposition and screening in pediatric cancer. *Pediatric Clin North Am* 2002;49(6):1393-1413
- Offit, K. *Clinical Cancer Genetics: Risk Counseling & Management*. New York: Wiley-Liss, 1998

may prefer to keep their medical information private.

Although the results of a genetic test are confidential, the test result may have implications for other family members. Parents are unable to control what genetic information they pass down to their children; nevertheless, they may feel guilt or

fear about potentially passing on the family cancer risk to their children.

Family dynamics may change after further information about cancer risk is obtained. For example, individuals who did not inherit the family cancer risk may experience survivor guilt or may find it difficult to have different experiences from their family. Rarely, unanticipated information is also discovered, such as misattributed paternity.

Many individuals choose to pursue genetic testing to decrease uncertainty; however, regardless of testing results, some degree of uncertainty remains. For an individual who tests positive for an inherited cancer predisposition, it is not possible to predict whether they will ultimately develop cancer, where their cancer will originate, or at what age it will be diagnosed. This lack of certitude makes informed medical decision-making difficult. Individuals who receive a negative test result may have some reassurance that they are at reduced risk of developing cancer. Despite this reassuring test result, the interpretation of this result will vary from one individual to another. For some individuals, a negative test result will indicate that they are at the baseline population risk of developing cancer. For others, a negative test result will have little impact on their cancer risk. Occasionally, an individual will have a gene change identified that is of uncertain clinical significance. Risk assessment in these families would then depend solely on that individual's medical and family history, but

patients may be understandably frustrated and disappointed to have obtained additional information and not know what to do with it.

Many patients are concerned about the impact genetic testing may have on their employment and insurability. Genetic discrimination occurs when an individual who does not have a condition—and may never develop the condition—is treated differently based on their genetic status. In insurance, this difference may constitute being denied coverage or being charged higher premiums. Anecdotal evidence of genetic discrimination, coupled with little documented evidence that genetic discrimination is occurring, makes this a confusing issue for patients. In general, the fear of genetic discrimination appears to outweigh the actual risks. For example, in one study of 184 individuals eligible for BRCA1/BRCA2 testing, 25% of patients declined because of concerns about cost, confidentiality, and discrimination. However, in the 106 patients who had genetic testing, there were no documented instances of test-result-based discrimination.

The majority of Americans with public or private health insurance have some protection from discrimination in health insurance from the Health Insurance Portability and Accountability Act (HIPAA). HIPAA is a federal law that provides individuals with group health insurance from being denied insurance, having their insurance canceled, or having their rates

individually increased because of a preexisting health condition. Individuals who have individual health insurance are not covered under this law. Additional legislation varies by state. The state of Minnesota prohibits health insurers from using information from genetic testing to determine eligibility, establish premiums, limit coverage, or renew coverage in both group and individual health insurance policies. Minnesota allows the use of genetic testing for coverage decisions in life insurance. The state of Minnesota also has legislation prohibiting genetic discrimination in employment.

The role of the genetic counselor

Genetic counselors are medical professionals trained to help families understand genetic disorders and to provide support to those families. In an hereditary cancer clinic, genetic counselors work with physicians and families to obtain and interpret family histories, provide and communicate risk assessment, and discuss genetic testing options. Genetic counselors play an integral role in helping patients understand their individualized risk, consider the pros and cons of genetic testing, and to decide if genetic testing is right for them. After testing, genetic counselors assist patients in

Counseling resource

The Park Nicollet Cancer Center now offers genetic counseling services. Consultation may be arranged by calling 952-993-3248.

understanding the test results and in helping communicate that information to other family members or medical professionals.

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