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GENETIC TESTING FOR CANCER PREDISPOSITION

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■ **Abstract** Clinical cancer genetics is becoming an integral part of the care of cancer patients. This review describes the clinical aspects, genetics, and clinical genetic management of most of the major hereditary cancer susceptibility syndromes. Multiple endocrine neoplasia type 2, von Hippel-Lindau disease, and familial adenomatous polyposis are examples of syndromes for which genetic testing to identify at-risk family members is considered the standard of care. Genetic testing for these syndromes is sensitive and affordable, and it will change medical management. Cancer genetic counseling and testing is probably beneficial in other syndromes, such as the hereditary breast cancer syndromes, hereditary nonpolyposis colorectal cancer syndrome, Peutz-Jeghers syndrome, and juvenile polyposis. There are also hereditary cancer syndromes for which testing is not yet available and/or is unlikely to change medical management, including Li-Fraumeni syndrome and hereditary malignant melanoma. Thorough medical care requires the identification of families likely to have a hereditary cancer susceptibility syndrome for referral to cancer genetics professionals.

INTRODUCTION

> But mousie, thou art no thy 'lane,
> In proving foresight might be 'vain,
> The best laid schemes o' mice and men
> Gang aft agley, and leave us nought but grief and pain
> For promised joy
>
> —Robert Burns

To use a simple blood test to make a diagnosis and to predict who will develop cancer and what type of cancer would be a powerful tool for any physician. The last decade and a half has seen the rapid discovery of genes that, when mutated

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in the germline (every cell of the body), are associated with specific inherited cancer syndromes. Technically, therefore, germline gene mutations can be looked for in blood leukocytes of patients with many inherited cancer syndromes (Table 1). Like any test in medicine, the ideal genetic test for cancer would meet the following criteria: It would test for a disease that is potentially lethal but easily cured when detected at an early stage; it would be both sensitive and specific; and its results would alter medical management. The molecular etiology and relationship of genotype (particular mutation) to phenotype (clinical features) and disease expression, as well as whether medical management is altered by the results of genetic testing, are understood to different degrees among the various inherited cancer syndromes.

In general, genetic testing for inherited cancer syndromes can be divided into three broad categories. The first includes those syndromes whose respective genetic tests have all the characteristics of an ideal test and are acknowledged as routine standard of clinical care as of 2000. These are illustrated in this review by the multiple endocrine neoplasia syndromes (MEN 1 and 2), von Hippel-Lindau disease (VHL) and familial adenomatous polyposis (FAP). The second category is comprised of those syndromes for which genetic testing is available as a clinical test, or is in the pipeline to clinical testing, but a variable proportion of cases are known to have mutations and/or it is not altogether clear that a genetic test result does alter management. This category includes the largest number of inherited syndromes and is illustrated here by the hereditary breast cancer syndromes, the inherited hamartoma-tumor syndromes, and hereditary non-polyposis colon cancer syndrome. Finally, in the third category are those syndromes for which genetic testing is strictly on a research basis and efficacy in the clinical arena is unproven.

MULTIPLE ENDOCRINE NEOPLASIA TYPE 2

MEN 1 (Mendelian Inheritance in Man Catalog Number [MIM] 131100) and MEN 2 (MIM 171400 and 162300) have nothing in common except for their name and the fact that hyperparathyroidism is component to both. MEN 2 is presented before MEN 1 because it is the first inherited cancer syndrome for which effective genetic testing was rapidly brought into the clinical setting shortly after the discovery of its gene, and in which medical management is profoundly affected by test results.

Clinical Aspects

MEN 2 is characterized by medullary thyroid carcinoma (MTC), pheochromocytoma, and hyperparathyroidism (2). Although MTC represents 10%–15% of all thyroid cancers, hereditary MTC, i.e. MEN 2, occurs in 25% of all MTC presentations. MEN 2A is the most common clinical subtype, characterized by MTC in 99% of cases, pheochromocytoma in 50% and hyperparathyroidism in 15%–30%. MEN

TABLE 1 Autosomal dominant inherited cancer syndromes with identified susceptibility genes

Syndrome	Incidence*	Susceptibility gene	Mutation frequency
A. Syndromes for which genetic testing is the standard of clinical care			
MEN 2[a]	1/500, 000	*RET*	>92%
VHL	1/36, 000	*VHL*	>95%
FAP	1/10, 000	*APC*	70–90%
MEN 1[b]	1/100, 000	*MEN1*	70–85%
Retinoblastoma	1/14, 000–34, 000	*RB1*	>95%

B. Syndromes for which clinical genetic testing is available, or is in the pipeline to clinical testing, but a variable proportion of cases with a specific syndrome are known to have mutations and/or it is not altogether clear that a genetic test result does alter management

Syndrome	Incidence*	Susceptibility gene	Mutation frequency
Breast and/or ovarian cancer syndrome	1/500–2000	*BRCA1* *BRCA2*	15%–45% 11%–45%
Cowden syndrome	1/250,000	*PTEN*	80%
Li-Fraumeni syndrome	1/500,000	*TP53* *CHK2*	70%–75%
HNPCC	1/1000	*MSH2* *MLH1* *PMS2* *MSH6*	50%–80% (Amsterdam criteria families)
Juvenile polyposis	1/5000–50,000	*DPC4*	3%–50%
Peutz-Jeghers syndrome	1/200,000	*LKB1*	50%–70%

C. Syndromes for which genetic testing is mostly performed on a research basis and clinical benefits are unclear

Syndrome	Incidence*	Susceptibility gene	Mutation frequency
Melanoma	1/5000	*p16*	60%, linked families
		CDK4	<10%?
Gastric carcinoma	1/20,000	*CDH1*	30%–50%
Nevoid basal cell carcinoma syndrome	1/56,000	*PTC*	50%–60%

TABLE 1 *(Continued)*

Syndrome	Incidence*	Susceptibility gene	Mutation frequency
Neurofibromatosis 1	1/2500–8000	*NF1*	?
Neurofibromatosis 2	1/40,000	*NF2*	65%–70%
Papillary renal cell cancer	?	*MET*	80%?
Familial paraganglioma	?	*SDHD*	?
Tuberous sclerosis	1/10,000	*TSC1*	14%
		TSC2	64%
Wilms tumor	1/20,000–100,000	*WT1*	>70%

*Incidence figures are either derived from epidemiologic studies, calculated as 5%–10% of the incidence of all such tumors in the general population, and/or estimated with the input of exponents of the field.

[a] MEN 2, multiple endocrine neoplasia syndrome 2; VHL, von Hippel-Lindau disease; FAP, familial adenomatous polyposis.

[b] MEN 1, multiple endocrine neoplasia syndrome 1.

2B is the least common and is characterized by MTC and pheochromocytoma and other stigmata such as marfanoid habitus, medullated corneal nerve fibers, mucosal neuromas, and ganglioneuromatosis of the gut. The age of tumor onset in MEN 2B is a mean 10 years younger than in MEN 2A cases. Familial MTC (FMTC) is a diagnosis of exclusion characterized by MTC in two or more blood relatives and objective evidence against pheochromocytoma and hyperparathyroidism.

Like most, if not all, inherited cancer syndromes, the MEN 2 component tumors are multifocal, and if paired organs are involved (e.g. adrenal glands), bilateral involvement is common. Synchronous and metachronous component tumors and multiple primary tumors occur with some frequency. In MEN 2, MTC is almost always the first presenting sign. Pheochromocytoma or hyperparathyroidism as the first and only presenting sign is unusual.

Genetics

MEN 2 is an autosomal dominant trait with age-related penetrance. In MEN 2A, follow-up cohort studies have shown that by age 70, approximately 65%–70% of individuals with MEN 2A have manifested one of its component tumors (3). Germline gain-of-function (activating) mutations of the *RET* proto-oncogene, on 10q11.2, were shown to cause MEN 2 (4–6). The International *RET* Mutation Consortium (C Eng and LM Mulligan, Coordinators and Co-Chairs) demonstrated that >92% of all MEN 2 cases have a germline *RET* mutation (6). Over 98% of MEN 2A patients, ≥97% of MEN 2B patients, and 88% of FMTC patients were found to have germline *RET* mutations. In MEN 2B, >95% of those with a mutation had a single mutation, M918T in exon 16, and another 5% had the A883F (exon 15) mutation (6, 7). MEN 2A–type *RET* mutations are distinct from

MEN 2B–type mutations and affect cysteine residues in the extracellular domain of the RET receptor tyrosine kinase. FMTC-type mutations are similar, though not identical, to those in MEN 2A except for a few unique FMTC mutations such as those at codons 768 and possibly 804 (7).

Clinical Cancer Genetic Management

All first-degree relatives (parents, siblings, children) of affected individuals have a 50% probability of harboring the family-specific mutated *RET* gene. Before DNA-based predictive testing became possible, all such individuals were subjected to prophylactic thyroidectomies and lifelong annual surveillance for pheochromocytoma and hyperparathyroidism. Because *RET* mutations occur in >95% of MEN 2 families (6), DNA-based testing is sensitive, specific, and not age-dependent. In a known MEN 2A or FMTC family, a clinically at-risk individual should undergo DNA testing prior to age six (8), or certainly prior to prophylactic surgery. In a known MEN 2 family with an identified family-specific mutation, therefore, the detection of the same mutation in a clinically at-risk individual indicates that that person has MEN 2. Conversely, if a mutation is not detected, that individual does not have MEN 2.

Individuals found to carry a germline *RET* mutation can be subjected to targeted screening for the presence of pheochromocytoma and hyperparathyroidism annually from age six and offered prophylactic thyroidectomy (reviewed in 9). The only exception is the discovery of the MEN 2B–specific M918T or A883F mutations. Individuals carrying these mutations should be offered prophylactic thyroidectomy at a younger age. Clinically at-risk individuals who test mutation-negative can be reassured; they do not have to undergo annual biochemical screening and can be spared prophylactic thyroidectomy.

Approximately 2%–10% of apparently sporadic MTC presentations have been found to have occult germline *RET* mutations (10, 11). Accordingly, the International Multiple Endocrine Neoplasia Workshop consensus and the International *RET* Mutation Consortium recommend that all apparently isolated MTC presentations, regardless of age at diagnosis, should be subjected to routine *RET* testing so that hereditary cases may be differentiated from truly sporadic MTC (2). Because *RET* testing is highly accurate and the results alter medical management, it is recommended by the American Society of Clinical Oncology (12) and is the clinical standard of care for MEN 2 in the United States and other countries. However, it should be emphasized that no *RET* testing should be performed without clinical cancer genetics consultation, which includes genetic counseling.

MULTIPLE ENDOCRINE NEOPLASIA TYPE 1

Clinical Aspects

MEN 1 is characterized by hyperparathyroidism (>90% of cases), pituitary adenomas (15%–50%), and endocrine pancreatic tumors (50%–80%) (13). Multifocal

disease is the rule, and hyperparathyroidism is usually the first component to manifest. A presentation with a component tumor without the coexistence or prior existence of hyperparathyroidism is rare.

Genetics

MEN 1 is an autosomal dominant disorder. Germline loss-of-function mutations in the *MEN1* tumor suppressor gene on 11q13, encoding MENIN, which acts as a repressor of the JUN-D transcription factor, are associated with 75%–95% of familial and isolated MEN 1 cases (14, 15). To date, >260 distinct mutations have been described that are spread across the 10-exon *MEN1* gene. A subset of families with familial isolated primary hyperparathyroidism have been found to harbor germline *MEN1* mutations, which suggests that these two conditions are allelic (16). Another subset of familial isolated primary hyperparathryoidism is genetically distinct, mapping to the putative locus on 1q25–q32 for hyperparathyroidism jaw tumor syndrome, which also includes jaw tumors, hamartomas, and a range of renal disorders (17).

In MEN 2, genotype-phenotype correlations have been noted and confirmed functionally (6). In contrast, such associations have not been observed in MEN 1, with the possible exception of a predominance of missense mutations in familial isolated hyperparathyroidism.

Clinical Cancer Genetic Management

Like MEN 2 testing, routine clinical MEN 1 testing is used for molecular diagnosis in families and individuals whose clinical findings are reminiscent of MEN 1 but not classic. It is also used for predictive testing of as yet unaffected clinically at-risk members of a known MEN 1 family with an identified family-specific mutation. All such genetic testing must be performed in the setting of clinical cancer genetic consultation. There is some disagreement in the international MEN 1 community regarding the appropriate aggressiveness of surveillance, and there has never been a real consensus in the International Multiple Endocrine Neoplasia Workshops in this regard. However, there is worldwide agreement that individuals who are *MEN1*-mutation–positive should have close clinical follow-up, which might include biochemical and imaging studies. There is also consensus that no surgery should be performed until hyperfunction or neoplasia is demonstrated.

VON HIPPEL-LINDAU DISEASE

Clinical Aspects

VHL (MIM 193300) is characterized by clear-cell renal cell carcinoma (RCC), pheochromocytoma, and hemangioblastomatosis. The clinical diagnostic criteria require the presence of a single retinal or cerebellar hemangioblastoma, RCC,

or pheochromocytoma if there is a family history of retinal or central nervous system (CNS) hemangioblastoma. However, in the absence of a family history, two typical manifestations are required, e.g. two or more hemangioblastomas (retinal or CNS), or a single hemangioblastoma in association with a visceral manifestation.

VHL shows age-dependent and tumor-specific penetrance. Onset is earlier for hemangioblastomas than for RCC but for all manifestations is almost complete by age 60 (18). The lifetime cumulative probability of a VHL patient developing retinal or cerebellar hemangioblastoma or RCC is >70% for each tumor. A retinal hemangioblastoma is often the earliest manifestation of VHL, and most are detected between the ages of 10 and 30.

Genetics

VHL is an autosomal dominant disease caused by germline mutations in the *VHL* tumor suppressor gene, which maps to 3p25 (19). When a comprehensive mutation analysis is performed to look for small intragenic mutations and large alterations, germline *VHL* mutations are detected in virtually 100% of VHL families (20, 21). Thus, the sensitivity and specificity of VHL testing of this type are close to 100%.

Genotype-phenotype analyses have consistently revealed an association between missense mutations and the presence of pheochromocytoma (22). Large deletions and truncating mutations are associated with a lower risk of pheochromocytoma compared to missense mutations (9% versus 59%, respectively) (22, 23). A founder missense mutation originating in the Black Forest region of Germany is associated with a less severe form of VHL, which features pheochromocytoma but lacks RCC. Indeed, there exist families with only pheochromocytoma and no other associated VHL features that segregate *VHL* missense mutations (24).

Paragangliomas share the same origin as pheochromocytoma but typically occur in the carotid bodies. Families may have paragangliomas with or without pheochromocytoma. Initially thought to be allelic to VHL, familial paraganglioma is genetically distinct; germline mutations in *SDHD*, which encode a mitochondrial complex II gene on 11q23, account for a subset of such families (25). There are at least two other minor susceptibility genes for familial paragangliomas, one at 11q11–13 and another at an unidentified locus.

Clinical Cancer Genetic Management

Regular clinical, ophthalmologic, and radiological surveillance are essential for patients and individuals at risk for VHL. Detailed screening protocols have been described (18) [6th and 7th International Multiple Endocrine Neoplasia and von Hippel-Lindau Workshops, Amsterdam 1997 and Gubbio 1999] and the application of these reduces morbidity and mortality. However, such programs are complex and time-consuming and need to occur serially on an annual basis from early childhood until the seventh decade for all at-risk individuals. Presymptomatic

genetic testing facilitates family management by allowing clinically at-risk relatives who are shown not to be gene carriers to be spared VHL surveillance. Further, the type of mutation, truncating or missense, might give some sense of the likelihood for the development of RCC and pheochromocytoma (above).

Cryptic VHL should always be considered in presentations of early-onset hemangioblastomas of the retina or CNS, familial or multiple clear-cell RCC, and familial or bilateral pheochromocytoma. Assessment of such cases requires a detailed family history and a clinical and radiological work-up for subclinical manifestations of VHL disease; often, *VHL* gene mutation analysis is needed as well. Thus, molecular genetic studies have revealed that approximately 50% of patients with apparently isolated familial pheochromocytoma or bilateral pheochromocytoma may have germline *VHL* mutations (26). Although in some cases the *VHL* mutation identified has previously been associated with classical VHL disease, some specific missense mutations (e.g. L188V, V84L, and S80G) may predispose to pheochromocytoma without any of the other manifestations of VHL disease (26, 27). Therefore, in the setting of clinical cancer genetic consultation, *VHL* gene testing is accurate, diagnostic, and predictive, and it should be considered among the routine clinical armamentarium in suspected cryptic VHL as well as in classic VHL.

The familial paraganglioma gene *SDHD* has only recently been identified, and pending further clinical cancer genetic investigation, it is not known if genetic testing will be helpful in clinical management.

HEREDITARY BREAST CANCER SYNDROMES

The hereditary breast cancer syndromes probably account for 5%–10% of all breast cancer presentations. Hereditary breast cancer includes a broad group of hereditary predisposition conditions in which breast cancer is a component tumor. The main group includes hereditary breast-ovarian cancer syndrome (HBOC), Cowden syndrome (CS), and Li-Fraumeni syndrome (LFS). The National Comprehensive Cancer Network (NCCN) Genetics/Familial High Risk Panel (28) has developed criteria that should raise suspicion of a hereditary breast cancer syndrome. These criteria are (*a*) multiple cases of breast and/or ovarian cancer in the same individual or close relatives; (*b*) clustering of breast cancer with male breast cancer, thyroid cancer, sarcoma, adrenocortical carcinoma, brain tumors, and/or leukemia/lymphoma in the same family; and (*c*) a member of a family with a known mutation in a breast cancer susceptibility gene.

Hereditary Breast-Ovarian Cancer Syndrome

Clinical Aspects Hereditary breast-ovarian cancer syndrome (HBOC) has variable expression and encompasses families with breast cancers only, ovarian cancers only, and both breast and ovarian cancers. For purposes of referral to a clinical

cancer genetics consultation clinic, a diagnosis of HBOC should be considered when two or more first-degree relatives have breast and/or ovarian cancer, especially if they are diagnosed at a young age; if there is multifocal or bilateral disease; and/or if breast and ovarian cancer occur in a single individual. These and other features are reflected in detail by the criteria set forth by the NCCN for referral to a cancer genetics professional (Table 2) (28).

Genetics There are two major HBOC susceptibility genes, *BRCA1* on 17q21 and *BRCA2* on 13q12.3, both of which are tumor suppressor genes (29, 30). Over 1600 distinct pathogenic mutations, polymorphisms, and variants of unknown

TABLE 2 National Comprehensive Cancer Network criteria for diagnosis of hereditary breast-ovarian cancer syndrome

Member of known *BRCA1 or BRCA2* kindred.

Personal history of breast cancer:
(*a*) diagnosed at or under the age of 40, with or without a family history;
(*b*) diagnosed at age at or under 50 or bliateral breast cancer, with one or more close relatives with breast cancer or one or more close relatives with ovarian cancer;
(*c*) diagnosed at any age, with two or more close relatives with ovarian cancer at any age, or breast cancer, especially if one or more female relatives is diagnosed before age 50 or has bilateral disease;
(*d*) if of Ashkenazi Jewish descent and diagnosed at or under the age of 50, no additional family history is required or at any age if family history is positive for breast and/or ovarian cancer.

Personal history of ovarian cancer:
(*a*) one or more close relatives with ovarian cancer;
(*b*) one or more close female relatives with breast cancer diagnosed at or under age 50, or with bilateral disease;
(*c*) two ore more close relatives with breast cancer;
(*d*) one or more close male relatives with breast cancer;
(*e*) if of Ashkenazi Jewish descent, no additional family history is required.

Male breast cancer:
(*a*) one or more close male relatives with breast cancer;
(*b*) one or more close female relatives with breast and/or ovarian cancer.

Family history only:
(*a*) one or more close relatives with breast cancer diagnosed at or before age 40 or with bilateral breast cancer;
(*b*) two or more close relatives with ovarian cancer;
(*c*) two or more close relatives with breast cancer, especially if one or more is diagnosed at or under age 50;
(*d*) one or more close relatives with breast cancer and one or more close relatives with ovarian cancer;
(*e*) if of Ashkenazi Jewish descent, one close relative with breast or ovarian cancer.

significance span the lengths of these two genes (http://www.nhgri.nih.gov/Intramural_research/Lab_transfer/Bic/). The "typical" HBOC family seen in cancer genetic clinics (average two first-degree relatives with breast cancer) has a 15% likelihood of having a *BRCA1* mutation (31). Families with multiple (four or more) affected individuals, especially if ovarian cancer is present, have a >80% likelihood of having a *BRCA1/2* mutation (32). Epidemiologic studies have suggested that *BRCA1* and *BRCA2* together account for virtually all hereditary ovarian cancer syndromes with or without breast cancer as a component (33). In contrast, this study also suggests that there are other predisposition genes for non-*BRCA1/2*-associated hereditary site-specific breast cancer.

There exist founder mutations in certain populations, e.g. the Ashkenazim, Icelandics, and French Canadians (reviewed in 1). Among the Ashkenazim, three founder mutations, 185delAG and 5382InsC in *BRCA1* and 6174delT in *BRCA2*, account for >70% of familial HBOC cases. More important, whereas in other populations only 5%–10% of isolated breast or ovarian cancer cases diagnosed under the age of 40 were found to harbor germline *BRCA1/2* mutations, 20%–35% of such cases in the Ashkenazim are associated with one of the three founder mutations (31, 34).

Clinical Cancer Genetic Management Prior to the isolation of *BRCA1* and *BRCA2*, based on linkage studies in extended HBOC pedigrees, the risk of developing breast and/or ovarian cancer was calculated to be 85%–90% in a lifetime or 50% by age 50 (35). This range of risk figures probably holds for certain mutations and especially in families with multiple (>4) affected individuals. However, population-based studies in the Ashkenazim have revealed lifetime risks of developing breast and ovarian cancers of around 60% and 25%, respectively (reviewed in 1). Other component cancers are also associated with harboring germline *BRCA1* and *BRCA2* mutations. *BRCA1* and *BRCA2* mutation carriers have a slightly increased risk for developing prostate cancer, although age at onset may not be younger than that of the population at large. In *BRCA2* mutation carriers, male breast cancers occur with a lifetime risk of 6%; it is believed that cancers of the pancreas, head and neck, and lung might be components as well.

Given the markedly increased risk of breast, ovarian, and other cancers, individuals with HBOC must be seen in clinical cancer genetics consultation and subjected to heightened surveillance and/or prophylactic measures. The NCCN recommends that women should begin breast self-examination at the age of 25, or five years younger than the earliest breast cancer diagnosis in the family; semiannual or annual clinical breast examination and an annual mammogram should begin at the same time, and semiannual or annual transvaginal ultrasound along with CA-125 should begin at age 25–35 (28). Prophylactic mastectomy and oophorectomy-hysterectomy should be discussed as well. Theoretical modeling and epidemiologic studies suggest that prophylactic surgeries do decrease the risk of developing these cancers but do not abolish it. For male carriers of *BRCA2* mutations, breast self-examination and annual clinical breast examinations should be performed,

and annual mammography considered. The prostate should be screened as well, although it is unclear whether these screenings should commence earlier for carriers than for the general population.

In the era of molecular medicine, it would be ideal to target only those individuals at risk for heightened surveillance or prophylactic measures using the results of genetic testing. Several risk-analysis models have been used (and abused, as well) to calculate probability that a woman will develop breast cancer and the probability that she carries a mutation. These range from models based on clinical epidemiologic studies [e.g. the Gail and Cancer and Steroid Hormone Study (CASH) models] to empiric molecular epidemiologic studies after *BRCA1* and *BRCA2* were identified (e.g. the Couch model). Often, the probability figures vary tremendously even for the same family; this is because each model cannot account for every element that adds to risk, e.g. the Gail model takes only first-degree relatives into account and is not appropriate for high-risk hereditary pattern families. There appears to be some consensus in the clinical cancer genetics community that a 10% prior probability of having *BRCA1/BRCA2* would be the minimum requirement to recommend genetic testing. This is reflected in the clinical inclusion criteria set by the NCCN (Table 2).

Cowden Syndrome

Clinical Aspects CS (MIM 158350) is an under-recognized, under-diagnosed inherited hamartoma syndrome that carries a high risk of breast, thyroid, and endometrial cancers (reviewed in 36). Its prevalence is estimated at 1:250,000, although this is almost certainly an underestimate. The diagnosis of CS is difficult because of its protean manifestations. This difficulty is compounded by the fact that the external signs of this syndrome are often quite subtle. The International Cowden Consortium initially published operational diagnostic criteria to aid its members in assigning affected status for linkage analysis. After the discovery of the gene, these criteria were shown to be robust; they have been revised in light of recent data and will be adopted by the NCCN (Table 3) (28, 37).

CS is characterized by multiple hamartomas that can occur in any organ of the body. The pathognomonic cutaneous feature is the trichilemmoma, which is a hamartoma of the infundibulum of the hair follicle. The major component cancers in CS are adenocarcinoma of the breast (20%–50% lifetime risk in affected females), nonmedullary thyroid cancer (10%), and endometrial carcinoma. Clinicians who specialize in this syndrome suspect that renal-cell carcinoma and perhaps melanoma are minor component cancers of CS as well. Benign pathology is quite common in the breast, thyroid, and uterus as well. For example, hamartomas and fibroadenomas of the breast, follicular adenomas of the thyroid, and uterine fibroids are commonly seen in CS.

Genetics CS is an autosomal dominant disorder caused by germline mutations of *PTEN*, located on 10q23.3 (38, 39). The mutation frequency is 80% if the

TABLE 3 Operational diagnostic criteria of the International Cowden Consortium (Version 2000) (37) to be adopted by the National Comprehensive Cancer Network

Pathognomonic criteria

Mucocutanous lesions:
- Trichilemmomas, facial
- Acral keratoses
- Papillomatous papules
- Mucosal lesions

Major criteria
- Breast carcinoma
- Thyroid carcinoma (nonmedullary), especially follicular thyroid carcinoma
- Macrocephaly (megalencephaly) (~97th percentile or more)
- Lhermitte-Duclos disease
- Endometrial carcinoma

Minor criteria
- Other thyroid lesions (e.g. adenoma or multinodular goiter)
- Mental retardation (IQ ~75 or less)
- Gastrointestinal hamartomas
- Fibrocystic disease of the breast
- Lipomas
- Fibromas
- GU tumors (e.g. renal cell carcinoma, uterine fibroids) or malformation

Operational diagnosis in an individual

1. Mucocutanous lesions alone if there are:
   (*a*) 6 or more facial papules, of which 3 or more are trichilemmoma, or
   (*b*) cutaneous facial papules and oral mucosal papillomatosis, or
   (*c*) oral mucosal papillomatosis and acral keratoses, or
   (*d*) 6 or more palmo plantar keratoses,
2. Two major criteria, one of which is macrocephaly or Lhermitte-Duclos disease
3. One major and three minor criteria
4. Four minor criteria

Operational diagnosis in a family where one individual is diagnosed with Cowden syndrome

1. The pathognomonic criterion or criteria
2. Any one major criterion with or without minor criteria
3. Two minor criteria

*Operational diagnostic criteria are reviewed and revised as new clinical and genetic information becomes available.

families and individuals are ascertained by the International Cowden Consortium operational diagnostic criteria (39). Preliminary data suggest that the *PTEN* genotype is associated with the disease phenotype. The presence of a germline *PTEN* mutation in a clinically diagnosed CS family or case is associated with an increased risk of breast cancer (39). Missense mutations and/or those located in the 5′ end of the gene appear to be associated with multiorgan involvement, a surrogate for disease severity.

Germline *PTEN* mutations have also been found in a subset of the congenital disorder Bannayan-Riley-Ruvalcaba (BRR) syndrome, which is characterized by neonatal onset of macrocephaly, lipomatosis, hemangiomatosis, and speckled penis (40). When BRR families have *PTEN* mutations, they might be at increased risk of neoplasia. This was unknown prior to the discovery that some forms of BRR and CS share a genetic etiology.

Clinical Cancer Genetic Management CS is an extremely difficult diagnosis to make clinically, but the failure to diagnose it has serious consequences for both the patient and his/her family. Genetic differential diagnoses to consider for CS include BRR (although these two entities should now be considered one), Peutz-Jeghers syndrome, and juvenile polyposis (discussed in sections below). Clinical and histologic features differentiate the latter two syndromes from CS. However, should there be any doubt, *PTEN* testing might be considered as a molecular diagnostic tool (41).

Cryptic CS should always be kept in mind in presentations of isolated or combinations of CS component tumor(s). For example, among 62 women under age 40 diagnosed with breast cancer, two were found to have germline *PTEN* mutations (42). In a study that ascertained 64 cases by the presence of breast cancer and thyroid disease (mainly papillary thyroid carcinoma), one was found to harbor an occult germline *PTEN* mutation (43). Recently, a nested cohort of 103 eligible women with multiple primary cancers within the 32,826-member Nurses' Health Study were examined for the occult presence of germline *PTEN* mutations (44). Among 103 cases, 5 (5%) were found to have germline missense mutations, all of which have been shown to cause some loss of function. Of these 5 patients, 2 had endometrial cancer. These studies, therefore, suggest that occult germline mutations of *PTEN*, and by extrapolation, CS, occur with a higher frequency than was previously believed, and the clinician must be vigilant.

The key to proper genetic counseling in CS is recognition of the syndrome. Families with CS should be counseled as for any autosomal dominant trait with high penetrance. What is unclear, however, is the variability of expression between and within families. We suspect that there are CS families who have only trichilemmomas and therefore never come to medical attention. The three most serious, and established, component cancers in CS are those of the breast (in both males and females), thyroid, and endometrium. Patients with CS or those who are at risk for it should undergo surveillance for these three cancers, as outlined by the NCCN (28). Beginning in their teens, these individuals should undergo annual physical

examinations that give particular attention to the thyroid examination. Beginning in their mid-20s, women with CS and those at risk for it should be encouraged to perform monthly breast self-examinations and to have careful breast examinations included in their annual physicals. The value of annual imaging studies is unclear, since there are no objective data. Nonetheless, we usually recommend annual mammography and/or breast ultrasounds, performed by skilled medical professionals, for women at risk beginning at age 30 or five years earlier than the earliest breast cancer diagnosis in the family (whichever is earlier). Some women with CS develop severe, sometimes disfiguring, fibroadenomas of the breasts well before age 30. This situation should be treated individually. For example, if the fibroadenomas cause pain or if they make breast cancer surveillance impossible, then some have advocated prophylactic mastectomies (45). Careful annual physical examination of the thyroid and neck region beginning at age 18, or five years younger than the earliest diagnosis of thyroid cancer in the family (whichever is earlier), should be sufficient, although a single baseline thyroid ultrasound in the early 20s might be considered as well. Surveillance for endometrial carcinoma is recommended perhaps beginning at age 35–40 (no data for age at onset) or five years younger than the earliest-onset case in the family. For premenopausal women, annual blind repel (suction) biopsies of the endometrium should be performed. In the postmenopausal years, uterine ultrasound should suffice. Because there is some indication, albeit anecdotal, that renal-cell carcinoma and melanoma might be minor component tumors of CS, annual urine dipstick testing for blood and/or renal ultrasonography and comprehensive skin examination may be considered.

Li-Fraumeni Syndrome

LFS (MIM 151623) is a rare autosomal dominant cancer syndrome characterized by sarcoma, breast cancer, brain tumor, lymphoma/leukemia, and adrenocortical carcinoma. The major susceptibility gene for LFS accounts for the majority of LFS and its examination does not pose a technical challenge. However, because of the nature and number of organs potentially at risk for neoplasia, knowing the results of the gene test may not necessarily alter medical management.

Clinical Aspects The classic component neoplasias of LFS form the basis for the NCCN inclusion criteria for diagnosis, which in turn are derived from the original operational definition of Li and Fraumeni. Classic LFS is diagnosed when (*a*) a bone or soft tissue sarcoma is diagnosed under the age of 45; (*b*) one first-degree relative of the case with any cancer diagnosed under the age of 45; and (*c*) one first- or second-degree relative of the case in the same lineage with any cancer diagnosed under the age of 45 or sarcoma diagnosed at any age. In LFS overall, >75% of patients who develop cancers do so prior to the age of 45, compared with 10% in the general population. Multiple synchronous and subsequent metachronous cancers occur as well, at a cumulative incidence of 57% at 30 years (reviewed in 46). It is also believed that such common cancers as those of the stomach,

lung, and colon and melanoma might be rare but true component tumors of LFS as well.

Genetics Germline mutations in the *TP53* tumor suppressor gene, on chromosome band 17p13, account for 70%–85% of classic LFS cases (47,48). Mutation frequencies approaching 100% occur in LFS families with at least one case of adrenocortical carcinoma. Genotype-phenotype relationships are complex, and most studies suggest that no such correlations exist. However, some believe that a classic LFS family with a germline *TP53* mutation is at higher risk of developing soft tissue sarcomas and breast cancers at earlier ages, as well as subsequent primary cancers, than a family with *TP53*-mutation-negative LFS (reviewed in 46). Based on small numbers, codon 248 mutations might be associated with higher breast cancer risk and a specific mutation, R175H, with acute leukemia (reviewed in 46).

Clinical Cancer Genetic Management The diagnosis of LFS is made clinically, according to the original operational diagnostic criteria noted by the NCCN guidelines (28). In general, most clinical cancer geneticists and cancer genetic counselors manage LFS based on clinical diagnosis, although *TP53* testing as a Clinical Laboratories Insurance Act (CLIA) laboratory diagnostic test is available and is being utilized. *TP53* testing as a molecular diagnostic aid is helpful. As with all inherited cancer syndromes, gene testing begins with analysis of a known affected member of a given family. Predictive testing for a family-specific mutation has some benefits but also raises other issues. Although both the American Society of Clinical Oncology and the American Society of Human Genetics briefly mention *TP53* testing in their policy statements, the question of who should be tested remains open, probably because the results of such a test might not alter management (12). Instead, the policy statements make such general recommendations as the necessity of having clinical cancer genetic consultation and further research.

Cryptic LFS or LFS-like presentations are important in this syndrome. An LFS-like (LFS-L or LFL) presentation includes some component cancers of classic LFS but does not meet the diagnostic criteria. Depending on the operational diagnostic criteria used to define LFS-L, germline *TP53* mutation frequency varies. For example, the "Manchester criteria" adopted by the NCCN are relatively stringent and call for an index case with any childhood cancer or sarcoma or brain tumor or adrenocortical carcinoma under age 45, plus a first- or second-degree relative with a typical LFS component tumor diagnosed under the age of 60 (28). When the Manchester criteria are used, 25%–30% of LFS-L cases are found to harbor germline *TP53* mutations. If the criteria are relaxed further, e.g. the "Sutton criteria," the mutation frequency falls to ~5%. Apparently sporadic adrenocortical carcinoma cases have an occult germline *TP53* mutation frequency that reaches 70% (40%–70%), so it is particularly important to keep LFS in mind when a child presents with this tumor. In contrast, apparently sporadic rhabdomyosarcoma and

osteosarcoma presentations have mutation frequencies of 5%–15% and 1%–10%, respectively.

If LFS is diagnosed or suspected, the NCCN recommends that women should undergo annual mammography starting at age 20–25, semiannual breast examination beginning at the same age, and training in breast self-examination beginning at age 25 (28). Given the function of the gene, there is some concern that the radiation from mammography might actually be harmful, although there are no conclusive data yet. Some centers advocate using ultrasound or magnetic resonance imaging. In addition, prophylactic mastectomy might be considered on a case-by-case basis, with discussions of the advantages and disadvantages of this irreversible procedure acknowledging the scarcity of direct data for this particular syndrome. Both men and women should receive annual comprehensive clinical examinations beginning at age 20–25, and the clinician should be aware of the high risk of cancers in these patients. Organ-targeted surveillance may be heightened based on family history as well.

HEREDITARY NONPOLYPOSIS COLORECTAL CANCER SYNDROME

Hereditary nonpolyposis colon cancer syndrome [HNPCC (MIM 120436 & 120436)], formerly known as Lynch syndrome types I and II, is the most common form of inherited predisposition to colon cancer.

Clinical Aspects

HNPCC is an inherited condition with an incidence of 1:1000 in the general population and 1–6:100 in individuals with colorectal cancer (1, 49). HNPCC is characterized by an 80% lifetime risk for colorectal cancer and a 60% lifetime risk for endometrial cancer. Indeed, in affected women, the lifetime risk of developing endometrial cancer is higher than their lifetime risk of colorectal cancer. Individuals with HNPCC are also at an increased risk of developing cancers of the stomach (13%) and ovaries (12%). There is also an excess of cancers of the small bowel, biliary tract, uroepithelium, kidney, and CNS (lifetime risk probably 4% at most) in individuals with HNPCC. HNPCC colon cancers differ from sporadic colorectal cancer in several ways: earlier age at diagnosis (mean age, 44), location in the proximal colon (60%–70%), increased risk of synchronous or metachronous colon cancers, and a better prognosis (49–52).

Genetics

HNPCC is an autosomal dominant disorder caused by germline mutations in DNA mismatch repair genes. Germline mutations in *MLH1, MSH2, MSH6,* and *PMS2* have been identified in multiple families with HNPCC. The majority (90%)

of mutation-positive HNPCC cases are caused by mutations in two of these genes, *MLH1* and *MSH2*. No strong genotype-phenotype correlations have been observed to date, but mutations in the *MSH2* gene do appear to be associated with more extracolonic manifestations than are mutations in the *MLH1* gene. When mismatch repair is compromised, changes in small areas of repetitive sequence genetic material, known as microsatellites, are seen in tumors from patients with HNPCC. This characteristic is known as microsatellite instability (MSI) and allows for a preliminary screening test to determine whether a family is more or less likely to have HNPCC.

There are several sets of criteria for the clinical diagnosis of HNPCC. The original diagnostic criteria were established by the International Collaborative Group on Hereditary Nonpolyposis Colorectal Cancer (ICG-HNPCC) and are known as the Amsterdam criteria (Table 4*A*) (50). Approximately 50%–70% of HNPCC families meeting these criteria have been found to have germline *MSH2* or *MLH1* mutations (53; reviewed in 1). The Amsterdam criteria were revised by the ICG-HNPCC in 1999 to include extracolonic cancers (Table 4*B*). The least stringent criteria are the Bethesda guidelines, which aim to determine which patients should have MSI testing (Table 5). There is evidence that the Bethesda criteria are more sensitive (but less specific) than either the Amsterdam I or Amsterdam II criteria in identifying HNPCC families with pathogenic mutations (53). MSI testing should be performed on tumors from all colorectal cancer patients (54, 55), particularly those who were diagnosed under age 50, have at least one first-degree relative with colorectal or endometrial cancer, or have had a previous colorectal or endometrial cancer.

TABLE 4 Operational criteria for the clinical diagnosis of hereditary nonpolyposis colon cancer syndrome (HNPCC)

A. Original Amsterdam criteria (Amsterdam I criteria)
Three relatives with colon cancer: one should be a first-degree relative of the other two; at least two successive generations should be affected; at least one should be diagnosed before age 50.
Familial adenomatous polyposis should be excluded.
B. Revised Amsterdam criteria (Amsterdam II criteria)
Three relatives with an HNPCC-associated cancer (cancer of the colorectum, endometrium, small bowel, ureter, or renal pelvis): one should be a first-degree relative of the other two; at least two successive generations should be affected; at least one should be diagnosed before age 50.
Familial adenomatous polyposis should be excluded.

TABLE 5 Bethesda criteria: Which patients should be screened for microsatellite instability?

Individuals with cancer in families that meet the Amsterdam criteria.
Individuals with two hereditary nonpolyposis colon cancer syndrome (HNPCC)-related cancers, including synchronous and metachronous colorectal cancers or associated extracolonic cancers.*
Individuals with colorectal cancer and a first-degree relative with colorectal cancer and/or HNPCC-related extracolonic cancer and/or a colorectal adenoma: one of the cancers diagnosed by age 45, and the adenoma diagnosed by age 40.
Individuals with colorectal cancer or endometrial cancer diagnosed by age 45.
Individuals with right-sided colorectal cancer with an undifferentiated pattern (solid/cribriform) on histopathology diagnosed by age 45.
Individuals with signet-ring-cell-type colorectal cancer diagnosed by age 45.
Individuals with adenomas diagnosed by age 40.

*Endometrial, ovarian, gastric, hepatobiliary, or small bowel cancer or transitional cell carcinoma of the renal pelvis or ureter.

Clinical Cancer Genetic Management

It is recommended that a colon tumor should be tested for MSI prior to gene testing, since this test is inexpensive and will help predict whether or not an individual has a germline mutation in a DNA repair gene (54, 55). Since up to 5% of HNPCC tumors do not have MSI, negative MSI tests cannot completely rule out HNPCC. Conversely, a positive MSI test is not diagnostic of HNPCC because 10%–15% of all (unselected) colon tumors have MSI whereas only 1%–6% of all colon tumors are associated with detectable HNPCC mutations. If the tumor is MSI-positive, then mutation analysis of the DNA mismatch repair genes is recommended.

Although the ages at which the various cancer screenings should begin and the frequency with which they should be performed are still debated, it is generally recommended that individuals with HNPCC receive at least colorectal and endometrial cancer screening (56). Colonoscopy should begin around age 20–25 and continue every 1–3 years. A controlled 15-year trial on colorectal cancer screening in families with known HNPCC mutations showed that colonoscopic screening at 3-year intervals more than halved colorectal cancer risk, prevented colorectal cancer deaths, and decreased overall mortality by about 65% (52). Endometrial cancer screening including either endometrial aspirates or transvaginal sonography should begin around age 25–35 with follow-up every 1–2 years. Screening for gastric cancers or urinary-tract cancers should only be recommended if those cancers have previously occurred in the family. In such cases, gastroscopy, sonography, and urinalysis should be performed every 1–2 years beginning at age 30–35 (57).

The option of prophylactic subtotal colectomy (or proctocolectomy) with ileorectal anastomosis should be considered at the time of the first colon cancer diagnosis, when adenomas are identified, or for HNPCC patients not willing or able to undergo serial endoscopies. In addition, some patients with HNPCC would consider the option of total abdominal hysterectomy and bilateral salphingo-oophorectomy. Because the risk of endometrial cancer is greater than the risk of colorectal cancer in affected women, many agree that a mutation-positive or known affected female might wish to consider prophylactic hysterectomy and bilateral salpingo-oophorectomy even before considering subtotal colectomy, after childbearing is complete.

MUIR-TORRE SYNDROME

Muir-Torre syndrome [MTS (MIM 158320)] is a variant of HNPCC characterized by sebaceous adenomas, especially of the face and scalp, in addition to the known HNPCC-associated cancers. The sebaceous adenomas may progress to sebaceous epitheliomas or sebaceous carcinomas. Keratoacanthomas and basal-cell carcinomas of the skin have been reported in MTS. Hepatobiliary and breast cancers may be more common among HNPCC families with the Muir-Torre phenotype. Mutations in the *MSH2* gene are more common among individuals with MTS, but mutations have been reported in *MLH1* as well.

TURCOT SYNDROME

Turcot syndrome (MIM 276300) can represent a variant of either HNPCC or familial adenomatous polyposis (FAP) and is characterized by the combination of colorectal cancer and brain tumors. Medulloblastomas and multiple adenomatous polyps seem to be associated with FAP and account for two thirds of Turcot syndrome cases, whereas glioblastoma is associated with HNPCC. Both the brain and colon tumors from patients with HNPCC-associated Turcot syndrome exhibit MSI. The proper diagnosis is critical for determining whether family members should be managed following the FAP or HNPCC screening guidelines.

FAMILIAL ADENOMATOUS POLYPOSIS

Clinical Aspects

FAP (MIM 175100) is rare, accounting for well under 1% of all cases of colon cancer. FAP is characterized by hundreds to thousands of adenomatous polyps throughout the colon and rectum. Nearly 100% of individuals with classic FAP

will develop colon cancer (most by age 40) if they do not undergo prophylactic colectomy. The adenomatous polyps can also occur in the upper gastrointestinal tract and can lead to an increased risk (5%–8%) for duodenal cancer (especially in the Ampulla of Vater). Individuals with FAP also have an increased risk for developing hepatoblastoma in childhood, medulloblastoma (with the Turcot variant), and papillary thyroid carcinoma (especially in young women with FAP) (58). Individuals with FAP may have osteomas of the mandible (>90%), congenital hypertrophy of the retinal pigment epithelium (CHRPE) (58%–88%), epidermoid cysts (most notably on the scalp) (66%), and supernumerary and/or unerupted teeth (33%). Desmoid tumors occur in 5%–10% of FAP patients, are more common in women, and are a major cause of morbidity and mortality. There is a high degree of variability with this syndrome, even within families, so that affected individuals may have any combination of the associated features at different degrees of severity. Gardner syndrome is a variant of FAP characterized by osteomas and desmoids.

Genetics

Germline mutations in the *APC* gene located on chromosome 5q21 cause FAP, an autosomal dominant condition (reviewed in 59). About one third of FAP patients have de novo *APC* mutations, and 70%–80% have germline *APC* mutations. Extensive work has been done on the genotype-phenotype correlations in this syndrome.

Clinical Cancer Genetic Management

Once a diagnosis of FAP is made, all first-degree relatives of an affected individual have a 50% chance of having inherited the family-specific *APC* mutation. As with MEN 2, if the family's mutation can be identified, genetic testing is the standard of care for reliably identifying which relatives did or did not inherit FAP (12). It is recommended that at-risk children undergo genetic testing by age 10–11, since this is the age at which clinical screening begins. For families in which the mutation is not detectable, endoscopic examination and/or opthalmologic examination for CHRPEs can help diagnose at-risk relatives (60).

Individuals with FAP begin annual flexible sigmoidoscopy beginning at age 10–11. Prophylactic colectomy is generally performed between ages 17 and 20 (60). A proctocolectomy with an ileoanal anastomosis may be the most medically prudent surgery owing to the risk of rectal cancer (32% in the 20 years following colectomy) (60). This is especially true for FAP patients with severe rectal polyposis (often with mutations between codons 1250 and 1440 of the *APC* gene). FAP patients who do not undergo a proctocolectomy require proctoscopy screening of the rectal stump every 6 months. Ileal or pouch polyps have been increasingly recognized, so ileoscopy is now recommended every 3–5 years after colectomy. Chemoprevention trials are under way to determine whether polyp

formation can be slowed both before and after proctocolectomy through the use of nonsteroidal anti-inflammatory drugs. It is also recommended that individuals with FAP undergo extended upper endoscopy and side-view examination of the papilla by age 25 (and continuing every 1–5 years depending on the severity of duodenal polyposis) to assess the presence of adenomas in the stomach and duodenum. Recommendations regarding thyroid and liver screening differ from center to center. More aggressive centers will add routine thyroid sonography in addition to neck palpation and annual liver palpation, serum α-fetoprotein measurement, and even ultrasounds in at-risk children up to age 6 because of the risk of developing hepatoblastoma.

In families without a detectable *APC* mutation, at-risk relatives should undergo sigmoidoscopy annually at ages 11–24, every 2 years at 25–34, every 3 years at 35–44, and every 3–5 years after age 45. If polyps develop, the screening then follows the guidelines for affected individuals.

ATTENUATED FAMILIAL ADENOMATOUS POLYPOSIS

A milder form of FAP, known as attenuated FAP, is caused primarily by mutations in the first four exons (prior to codon 158) and those 3′ of codon 1440 of the *APC* gene. Individuals with attenuated FAP develop fewer polyps (on average 40–50), tend to develop them in the ascending colon, and may not begin developing them until the third decade of life. These individuals usually do not have CHRPEs. Clinicians may have difficulty distinguishing between attenuated FAP and a subset of HNPCC. Cases of attenuated FAP can be managed with annual colonoscopy beginning around age 20, since attenuated FAP is milder than classical FAP. Colectomy is considered on a case-by-case basis.

PEUTZ-JEGHERS SYNDROME

Clinical Aspects

Peutz-Jeghers syndrome [PJS (MIM 175200)] is a rare condition. PJS is characterized by pathognomonic hyperpigmented macules that can occur on the lips, buccal mucosa, hands, feet, and genitalia, and around the eyes and anus. PJS spots usually appear in infancy and fade at puberty; however, they have been reported to appear as late as age 70. PJS causes multiple hamartomatous polyps in the small bowel (78%), stomach (38%), colon (42%), and rectum (28%) (61). Rarely, the hyperpigmented macules may be present without polyposis. The main complication of the hamartomatous polyps is intussuseption and intestinal obstruction, with onset ranging from a few weeks of age to 82 years (average, 29 years). It now appears that the hamartomatous polyps can occasionally become malignant

through loss of the wild-type *LKB1* gene in the hamartoma-adenoma-carcinoma sequence.

PJS patients are 10–18 times more likely than the general population to develop intestinal and other PJS-associated cancers during their lifetime (58, 62). In addition, one study found that 48% of individuals with PJS died of cancer by age 57, although this is probably an overestimate due to ascertainment. The most common locations for cancer to occur are the colon, small intestine, stomach, and pancreas. Ovarian sex cord tumors, granulosa cell tumors, dysgerminoma, and Brenner tumors occur in ~10%–14% of female patients, and Sertoli cell tumors of the gonads are more common in male patients. Breast cancer and cervical cancers have been reported in women with PJS.

Genetics

PJS is an autosomal dominant disorder whose major susceptibility gene is *LKB1/STK11*, located on chromosome arm 19p (63, 64). The mutation frequency ranges from 50% to 70% (reviewed in 63, 64). Half of all isolated PJS cases have been found to carry germline *LKB1* mutations. Genotype-phenotype association studies have yet to be reported.

Clinical Cancer Genetic Management

It is unclear whether routine *LKB1* mutation analysis is clinically useful at this time. It might have some use as a molecular diagnostic tool in cases where a mutation-positive result would be informative but a mutation-negative result would be nondiagnostic, given that an average of 50% of PJS cases have a germline *LKB1* mutation and some investigators believe that there is at least one other susceptibility gene, perhaps on 19q.

First-degree relatives of patients with PJS should be carefully evaluated for features of the syndrome, since it is quite variable. Individuals with PJS should receive colonoscopy every 1–2 years beginning in adolescence, since the colon is the most frequent site for cancer development in PJS. They should also have upper gastrointestinal endoscopy and small-intestinal double-contrast radiology or push enteroscopy performed every two years due to the risk for small bowel cancers. The frequency and efficacy of screening for small bowel cancers are unknown.

Part of the surveillance includes annual hemoglobin measurements. Women with PJS should have increased breast cancer surveillance and should also receive annual abdominal and transvaginal ultrasound to screen for the ovarian tumors associated with PJS. Men with PJS should undergo annual testicular examination with ultrasound if clinical symptoms appear. It should be pointed out, however, that these surveillance recommendations are not based on careful case-control studies, which would be impossible in this relatively rare syndrome, but on the best practice of experts.

JUVENILE POLYPOSIS

Clinical Aspects

Juvenile polyposis [JP (MIM 174900)] is a disorder of hamartomatous polyps in the large bowel and stomach. JP polyps have a characteristic smooth histological appearance, prominent stroma, cystic spaces, and no smooth muscle core. Individuals with JP have a lifetime risk for colorectal cancer of 9%–68% and are considered at increased risk for gastric, duodenal, and pancreatic cancers as well. Extracolonic abnormalities such as congenital heart defects, cleft lip or palate, microcephaly, and malrotations have been described in 11%–20% of individuals with JP.

Genetics

A major susceptibility gene for JP, an autosomal dominant disorder, is the *SMAD4/DPC4* tumor suppressor gene located in 18q21.1 (65). The mutation frequency varies widely, 3%–50% depending on the study. There is little doubt that at least one other JP susceptibility gene exists.

Clinical Cancer Genetic Management

Given the variable mutation frequency found to date, a genetic test for JP may not be useful in the routine clinical setting. Especially in the setting of intestinal hamartoses and a few other features, the triad of *PTEN, LKB1,* and *SMAD4* gene testing might help differentiate, at a molecular level, the three syndromes, which carry very different risks of various cancers.

Once a diagnosis of JP is made, all first-degree relatives should undergo colonoscopy for the assessment of JP. Since the JP cancer risks are primarily to the digestive tract, surveillance involves endoscopy. Individuals with JP need annual colonoscopy and upper gastrointestinal endoscopy beginning in adolescence or after the diagnosis is made. Unfortunately, there is no proven method of screening for pancreatic cancers or cancers of the small bowel beyond the duodenum.

HEREDITARY MALIGNANT MELANOMA

Clinical Aspects

Around 8%–12% of melanoma patients have a family history of the disease (reviewed in 66). Hereditary melanoma can occur either with or without a family history of multiple dysplastic nevi. Families with both melanoma and dysplastic nevi have been referred to as having familial atypical multiple mole and melanoma syndrome and dysplastic nevus syndrome. This phenotype is difficult to define, since there is disagreement regarding the size, number, and histology of

dysplastic lesions and since dysplastic nevi occur in up to 50% of the general population (reviewed in 67). In general, individuals with multiple primary melanomas and individuals with >2 relatives affected with melanoma should be evaluated in formal clinical cancer genetics consultation.

Genetics

Germline mutations in the *CDKN2A* gene (also known as *p16, MTS1, CDKN2,* and *INK4A*) are found in ~40% of melanoma-prone families (reviewed in 68). The likelihood of finding a mutation increases if there are >2 relatives affected with melanoma or if there are family members with more than one primary melanoma (69). Based on linkage data to the *CDKN2A* locus on chromosome 9p, it was estimated that the penetrance of this gene is 53% by age 80 (70). Another study found that the penetrance ranged from 55% to 100% depending on the particular mutation in *CDKN2A* (71). A second melanoma susceptibility gene, known as *CDK4* (12q14), has been identified. Mutations in *CDK4* have been found in three melanoma kindreds; therefore, this gene is responsible for a small fraction of hereditary malignant melanoma cases (reviewed in 72). However, *CDK4* is important in that it represents the third oncogene proven to confer a hereditary cancer predisposition. There is also epidemiologic evidence that the *RB1* gene may confer an increased risk for melanoma, based on follow-up studies of patients who have survived hereditary retinoblastoma (73). Although this would account for a very small proportion of hereditary malignant melanoma kindreds, it is possible that *RB1* mutations account for an increased risk for melanoma in patients with hereditary retinoblastoma. It is likely that there are other, as yet unidentified melanoma-susceptibility genes. Finally, a rare syndrome of melanoma and astrocytomas has been shown to be caused by a contiguous gene deletion on chromosome arm 9p, which includes the *CDKN2A* and the *p15* genes.

Clinical Cancer Genetic Management

Genetic testing for the *CDKN2A* and *CDK4* genes is clinically available, but it is still advised that testing occur in a research setting (12) because the gene test results cannot be adequately interpreted at present and the results do not alter clinical management. Therefore, many clinical cancer geneticists advise that all affected and unaffected members of melanoma-prone kindreds should receive increased surveillance for melanoma. This should include self-examination, clinical examinations with close follow-up, and sun avoidance. For individuals with multiple dysplastic nevi, full-body photography is sometimes indicated to assist in following their many lesions. There is some evidence that families with *CDKN2A* mutations have an increased risk for pancreatic cancer; however, this finding is controversial and since there is no proven method of screening for pancreatic cancer this does not currently alter clinical management.

PENETRANCE AND THE PRACTICE OF CLINICAL CANCER GENETICS

Penetrance refers to the percentage of individuals harboring germline-disease–associated mutations in a certain gene who actually manifest a syndromic feature at some point in their life. The inherited cancer syndromes discussed so far have a relatively high penetrance, which makes mutation-based prediction highly accurate. However, some variants in genes confer low-level susceptibility to certain cancers, so-called low-penetrance alleles. Because we cannot predict who among those who have inherited low-penetrance alleles of predisposition will actually get cancer, this issue is a challenge to clinical cancer genetics.

One of the first examples of a low-penetrance allele for colorectal cancer susceptibility is *APC* I1307K, which is a founder variant among the Ashkenazi Jews and can be found in 6% of all Ashkenazim. Among the Ashkenazim, 10% of those with colorectal cancer carry this variant, 16% of cases diagnosed at a young age and 28% of those with familial colorectal cancer (74). Given the frequency of this founding low-penetrance allele, the *APC* I1307K variant might account for more colon cancer in the Ashkenazi Jewish population than even the HNPCC-predisposing genes. The relative risk of colorectal cancer in carriers of this variant has been calculated to be twofold. Given our current state of knowledge, knowing whether someone carries *APC* I1307K does not alter medical management. Colorectal surveillance decisions are based on clinical parameters such as family history.

Other apparently low-penetrance alleles of susceptibility have been described but are not well understood. For example, a polymorphic variant that does not change the amino acid in PPAR-γ, which is involved in the differentiation of fat, is overrepresented in individuals with glioblastoma multiforme (75). Other polymorphisms in other genes seem to be associated with age of onset as well, such as *cyclin D1* and HNPCC, and *PTEN* and familial breast cancer. Alleles of anonymous repeat sequences, minisatellites, have also been associated with an increased risk for various cancers, including those of the ovary, breast, and colon. Specific alleles affecting enzymes that interact with environmental exposures, e.g. *NAT2* and the *CYP* genes, are also interesting. Nonetheless, it should be emphasized that all these low-penetrance alleles are still being intensively investigated and should not be used in clinical cancer genetic management yet.

CONCLUSIONS

The premise of clinical cancer genetics is to be able to prevent or reduce the likelihood of death from heritable cancer. In this setting, genetic testing is a tool to identify those at risk, preferably before the disease phenotype manifests. It has already been shown that, at least for a subset of the inherited cancer syndromes, the strategy of genetic testing followed by targeted surveillance and/or prophylactic maneuvers reduces morbidity and mortality.

With the discovery of germline *RET* mutations in MEN 2 and its rapid translation to routine clinical practice, the era of molecular oncology was born. As illustrated in this review, not all inherited cancer syndromes are as amenable to the practice of molecular oncology as MEN 2. The next challenge is to ensure that genetic testing for all inherited cancer syndromes becomes equally useful in guiding clinical management. Equally important, the new field of molecular oncology and clinical cancer genetics means that the primary physician in all specialities and subspecialities must be able to recognize cancer that might have a genetic basis and to know when to refer such patients and their families for clinical cancer genetic consultation. No genetic testing should be performed without the input of cancer genetics professionals.

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