Concise Handbook of Familial Cancer Susceptibility Syndromes

Second Edition

Noralane M. Lindor, Mary L. McMaster, Carl J. Lindor, Mark H. Greene

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Affiliations of authors: Department of Medical Genetics, Mayo Clinic, Rochester, MN (NML); Genetic Epidemiology Branch (MLM) and Clinical Genetics Branch (MHG), Division of Cancer Epidemiology and Genetics, National Cancer Institute, Bethesda, MD.

Correspondence to: Noralane M. Lindor, MD, Mayo E7B, Department of Medical Genetics, Mayo Clinic, Rochester, MN 55902 (e-mail: nlindor@mayo.edu).

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Introduction

More than 10 years have passed since we first attempted to develop a clinically accessible catalog of recognizable family cancer syndromes (1). Our sense at that time was that we were on the brink of an avalanche of information regarding the inherited basis of human neoplasia and that the clinical consequences of these novel molecular insights threatened to overwhelm both health-care providers and their patients. We attempted to distill currently available data related to the most common genetically determined cancer susceptibility syndromes into a format that would make this arcane knowledge more readily accessible to busy clinicians who only occasionally needed this information. It seemed inevitable that, as the number of disorders for which germline mutation testing for cancer susceptibility increased, the need for a better understanding of how to approach these challenging clinical problems would follow.

And so it has. It is now increasingly routine to undertake a cancer genetics risk assessment, which includes the option of germline mutation testing for one or more relevant genes, for an astonishing array of disorders.

Experience over the past several decades has demonstrated, unequivocally, that the study of rare familial clusters is a remarkably productive scientific and clinical enterprise. These data have identified multiple new susceptibility genes, defined the clinical phenotype of specific disorders more precisely, and have informed our understanding of the pathogenesis of hereditary and nonhereditary cancers at the individual, population, and laboratory levels. For example, recognition of the Li–Fraumeni syndrome provides a vivid illustration of how the identification of familial clusters of childhood sarcomas and breast cancer ultimately led to the identification of germline mutations in the p53 tumor suppressor gene as the genetic basis for this disorder, thereby providing seminal insights from clinical cancer genetics to the molecular biology of both inherited and sporadic cancers (2–6).

Progress begets new challenges. Previously unfamiliar concepts related to clinical genetics are now being integrated into the information base used by diverse health-care providers, most of whom have no formal training in genetics. The need has never been greater for clinicians to be well grounded in the biological and molecular bases of the diseases which they encounter and to become familiar with related new clinical issues, including predictive risk assessment, genetic counseling, germline mutation testing for clinical decision making, the duty to warn at-risk relatives vs their high-risk patients' right to privacy and confidentiality and, most importantly, the need for evidence-based, safe, and effective management recommendations for high-risk individuals. Proposed elements of informed consent related to testing for inherited cancer susceptibility are set forth in Table 1.

The advent of syndrome-specific germline mutation testing represents a major advance in the care of cancer-prone individuals. But, in the process of focusing on the molecular biology of human cancer susceptibility, the importance of taking a thoughtful family history cannot be emphasized sufficiently. Because the pace, complexity, and sophistication of medical practice have accelerated, the decidedly low-tech but nonetheless invaluable family history often receives short shrift, depriving both the patient and the health-care provider of information that might have a substantial impact on clinical decisions and patient outcome. In one survey of 100 unselected colorectal cancer patients, the medical record contained a family history in only 46% of subjects and, of those, only 80% were accurate (8). Taking an appropriately focused family history must receive increased emphasis in the course of daily practice. The Family History Public Health Initiative of the US Center for Disease Control and Prevention (http://www.cdc.gov/genomics/activities/famhx.htm) recognizes and promotes this need (9).

Table 1. Basic elements of informed consent for cancer susceptibility testing (7)

1. Information on the specific genetic test being performed.
2. Implications of a positive and negative result.
3. Possibility that the test will not be informative.
4. Options for risk estimation without genetic testing.
5. Risk of passing a mutation to children.
6. Technical accuracy of the test.
7. Fees involved in testing and counseling.
8. Psychological implications of test results (benefits and risks).
9. Risks of insurance or employer discrimination.
10. Confidentiality issues.
11. Options and limitations of medical cancer risk management and strategies for prevention following testing.
12. Importance of sharing genetic test results with at-risk relatives so that they may benefit from this information in making their own health-care decisions.

Learning the clinical features that suggest the possibility of an underlying genetic predisposition to cancer is another, easily mastered diagnostic tool (Table 2). These guidelines are not infallible but, when used to guide the collection of family history data, they have been proven to be clinically useful.

Because much of our risk assessment and clinical decision making rests on empirical studies of self-reported, unverified family history, a brief comment regarding these data is warranted. Diagnosis accuracy varies considerably, depending on the age, gender, and cancer status of the respondent, the primary site of cancer origin, the degree of relatedness between the respondent and the relative of interest, the vital status of the affected relative, and the recentness of the reported cancer diagnosis (11,12). In general, reported breast and colorectal cancer diagnoses are quite accurate, whereas cancer "sites" that are vaguely defined (eg, organs in the female pelvis) or which represent tissues commonly involved with metastatic disease (eg, brain, liver, bone, and lung) are often incorrect (13). The predictive value of a *negative* cancer report (eg, "my mother did NOT have cancer") is very high. The accuracy of reports from first-degree relatives is substantially better than for second-degree relatives; information from more distant relatives is of such poor quality that it is of questionable value in routine practice.

Genetic risk assessment in the context of childhood cancer represents another specific setting in which a meticulous clinical evaluation often provides essential information upon which to base a syndromic diagnosis. An elegant and detailed evaluation of the prevalence and patterns of morphological abnormalities in nearly

Table 2. Features that suggest the presence of a hereditary cancer predisposition [modified from Weber et al. (10)]

In the individual patient	In the patient's family
• Multiple primary tumors in the same organ • Multiple primary tumors in different organs • Bilateral primary tumors in paired organs • Multifocality within a single organ • Younger-than-usual age at tumor diagnosis • Rare histology • In the sex not usually affected • Associated with other genetic traits • Associated with congenital defects • Associated with an inherited precursor lesion • Associated with another rare disease • Associated with cutaneous lesions known to be related to cancer susceptibility disorders (eg, the genodermatoses)	• One first-degree relative with the same or a related tumor and one of the individual features listed • ≥ two first-degree relatives with tumors of the same site • ≥ two first-degree relatives with tumor types belonging to a known familial cancer syndrome • ≥ two first-degree relatives with rare tumors • ≥ two relatives in two generations with tumors of the same site or etiologically related sites

1100 consecutive pediatric cancer patients resulted in the identification of confirmed cancer susceptibility syndromes in 42 (3.9%) patients and suspected syndromes in an additional 35 (3.3%). Half of the proven disorders had been missed before the study-related physical examination, leading the authors to recommend that *all* children with cancer should be examined by either a clinical geneticist or a pediatrician skilled in the clinical dysmorphology examination (14,15). Thus, even in this postgenomic world, the need for input from a skilled clinician remains essential to the cancer risk assessment enterprise.

Much of the data that form the basis of our understanding of hereditary cancer syndromes are derived from evaluation of highly selected families. The inability to characterize the population from which such families are ascertained imposes major constraints on one's ability to generalize these observations, particularly in estimating cancer risk. Alternatively, population-based analyses may produce results that are generalizable to the population that was studied, as well as being large enough to produce statistically reliable risk estimates, even for relatively rare cancers. Population-based registries are particularly useful in assessing magnitude of familial risk, as opposed to risks associated with specific hereditary cancer syndromes, and for most patients with a "family history of cancer," these risks are most relevant in clinical decision making. Single-gene hereditary syndromes account for only a small fraction of familial clustering on a population basis. The Utah Population Database (16) and the Swedish Family-Cancer Registry (17) have been explored systematically in an effort to improve the level of evidence related to the magnitude of familial cancer risk. A sample of the data available from these two registries is shown in Table 3, which summarizes the familial relative risk (FRR) of selected cancers among first-degree relatives of probands with a specified malignancy. The pattern of risks by site is similar between the Utah and the Swedish data, with FRRs in the range of 2.0–3.0.

The Utah data were analyzed by age at cancer diagnosis in the proband, and they show substantially increased FRRs among relatives of probands with early-onset cancer, consistent with the clinical clues to an inherited cancer susceptibility disorder. For example, the FRR for breast cancer is 1.8 overall but 3.7 among the relatives of women whose breast cancer was diagnosed at age younger than 50 (Table 3). The Swedish Family-Cancer Registry has generated data regarding the population-attributable fraction (PAF) related to site-specific familial cancer susceptibility in Sweden (see the final column in Table 3) (19). The PAF is the proportion of cases that is exposed to the risk factor of interest (here, positive family history of a particular cancer), and it represents that fraction of cases that could be prevented if the risk factor were completely eliminated. These data provide substantial support for the claim that familial and inherited factors account for a relatively small proportion of any specific malignancy. For most sites, the PAF is between

Table 3. Familial relative risks and population attributable fraction of the same cancer among first-degree relatives of cancer probands by primary cancer site [modified from Risch (18)][a]

	Utah (16)		Sweden (17,19)		
Site	FRR (total)	FRR[b] (early onset)	FRR (child)	FRR (sibling)	PAF (%)
Prostate	2.2	4.1	2.8	9.4	20.5
Breast	1.8	3.7	1.9	2.0	10.6
Colorectal	2.5	4.5	1.9	4.4	6.9
Lung	2.6	2.5	1.7	3.2	3.8
Uterine Corpus	1.3	1.8	–	–	3.9
Melanoma	2.1	6.4	2.5	3.4	1.4
Urinary bladder	1.5	5.0	1.5	3.3	2.0
Non-Hodgkin lymphoma	1.7	2.4	1.7	2.4	1.2
Brain and/or CNS	2.0	9.0	1.7	2.4	1.2
Ovary	2.0	–	2.9	2.5	4.9
Stomach	2.1	–	1.7	8.8	1.5
Pancreas	1.2	–	–	–	1.0
Kidney	2.5	–	1.6	5.3	1.9
Thyroid	8.5	–	9.5	12.4	3.6
Multiple myeloma	4.3	–	4.2	5.6	1.0
Hodgkin lymphoma	1.2	–	–	–	0.9
Soft tissue sarcoma	2.0	–	–	–	0.1
Testicular	8.6	–	4.3	8.5	2.7
Total, mean	2.1	3.8	2.1	3.4	–
Total, median	2.2	4.1	1.9	3.5	–

[a]FRR = familial relative risk; PAF = population attributable risk; CNS = central nervous system. Cancers listed in order of decreasing population prevalence in Utah.

[b]Early onset: age <50 for melanoma, breast, and brain; age <60 for all others.

1% and 3%. Interestingly, prostate, breast, and colorectal cancer have substantially higher PAFs: 20.5%, 10.6%, and 6.9%, respectively.

One final issue warrants general comment before proceeding on to consideration of the specific cancer susceptibility syndromes, and that is population screening for germline mutations in cancer susceptibility genes. It is commonly (and mistakenly) assumed that the availability of clinical testing for deleterious mutations in rare, high-penetrance genes such as *BRCA1*, *BRCA2*, *MLH1*, *MSH2*, and *CDKN2A* means that such testing can and should be routinely applied to anyone who has a concern about their familial cancer risk. However, the rarity of these mutations in the general population typically results in test performance characteristics (sensitivity, specificity, positive predictive value, etc) that are unacceptable (20,21). Genetic testing appears to be most efficient when performed on an individual with a reasonable prior probability of having the disorder for which the testing is performed, although a recent report has highlighted the difficulties encountered when family size is small (22).

The clinical and molecular advances of the past decade, catalyzed by the enthusiasm with which our original publication was received and used, have led us to offer this updated version of the *Concise Handbook of Family Cancer Syndromes*. The 1998 publication included 35 disorders; the current revision has been expanded to 54, and the familial hematopoietic and lymphoproliferative disorders are now included. The syndromes are listed in alphabetical order, and for each a templated capsule summary is provided, using the following subtopics:

Disorder
OMIM number (syndrome; gene(s))
Inheritance pattern
Gene and chromosomal location
Mutations
Incidence
Diagnosis
Laboratory features
Associated malignant neoplasms
Associated benign neoplasms
Cancer risk management
Comments
References.

We have again attempted to capture the major malignant manifestations of the 54 hereditary cancer syndromes in Table 4 to facilitate formulation of a differential diagnosis based upon the cancers that are present in a family. For example, a family history of breast cancer could be a sign of several different hereditary cancer syndromes, but the constellation of other tumors in the family tree likely would help guide risk assessment discussions. In addition, we have now added tables summarizing the nonmalignant neoplasms (Table 5) and additional nonneoplastic clinical signs (Table 6) that may provide clues to a familial cancer syndrome diagnosis.

Finally, the reader should note that there are now a number of additional online resources that provide more comprehensive information about these conditions than is appropriate for a document intended to be concise. These resources are listed in Appendix 1. Of particular use for identification of genetic testing resources and regularly updated clinical management information for many of these disorders, we refer readers to the GeneTests website, a resource that has become indispensable to those seeing individuals with genetic disorders: http://www.genetests.org/

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Table 4. Malignancies associated with specific familial cancer syndromes[a]

Cancer/tumor site	Ataxia telangiectasia	Basal cell nevus	Beckwith–Wiedemann	Birt–Hogg–Dubè	Bloom	Breast/ovarian-BRCA1	Breast/ovarian-BRCA2	Carney	Chordoma	Colon (HNPCC/Lynch)	Costello	Cowden	Dyskeratosis congenita	Exostoses, hereditary multiple	Fanconi	Gastric, diffuse	Gastrointestinal stromal tumor	Hyperparathyroidism	Leukemia, Chronic Lymphocytic
Adrenal cortical carcinoma			■																
APUdoma[b]																			
Biliary							▒			■									
Bladder, urinary											■	▒							
Breast—female	■				■	■	■					■							
Breast—male						▒	■					■							
Carcinoid																			
Chondrosarcoma														■					
Chordoma									■										
Choroid plexus																			
Colon/rectum					■	▒	▒			■		▒	▒			▒			
Cervix					■	▒									■				
Endolymphatic sac tumor																			
Endometrium	▒					▒				■		■							
Ependymoma																			
Esophagus[e]					■								■						
Fallopian tube						■	■												
Fibrosarcoma		f																	
Gastric	■						▒			■			▒			■			
Gastrointestinal stromal tumor																	■		
Germ cell/gonadal	▒		g					h											
Glioma	▒								i	■		▒			▒				
Head/Neck (squamous cell cancer)													■						
Hepatoblastoma			■								▒								
Hepatocellular							▒			▒		▒			■				
Hodgkin disease					▒								▒						■
Larynx					■		▒												
Leukemia[e]	l				m		n			ii			o		o				l
Lung					▒		▒												
Lymphoma, NH	■				■					ii									▒
Medulloblastoma/PNET[q]	▒	■								ii					n				
Meningioma																			
Multiple myeloma																			
Neuroblastoma[e]			▒								▒								
Neurofibrosarcoma/MPNST[s]																			
Oncocytoma				■															
Osteosarcoma																			
Ovarian		f				t	t			■		▒	▒			▒			
Pancreas—adenocarcinoma[e]						▒	■	▒		■		▒	▒						
Pancreas—islet cell																			
Paraganglioma																			
Parathyroid																		■	
Peritoneal, primary, carcinoma						■	■												
Pheochromocytoma																			
Pinealoblastoma																			
Prostate						■	■									▒			
Renal: clear cell, other[e]				■								▒							

(Table continues)

Table 4 (continued).

Cancer/tumor site	Ataxia telangiectasia	Basal cell nevus	Beckwith–Wiedemann	Birt–Hogg–Dubè	Bloom	Breast/ovarian-BRCA1	Breast/ovarian-BRCA2	Carney	Chordoma	Colon (HNPCC/Lynch)	Costello	Cowden	Dyskeratosis congenita	Exostoses, hereditary multiple	Fanconi	Gastric, diffuse	Gastrointestinal stromal tumor	Hyperparathyroidism	Leukemia, Chronic Lymphocytic
Renal, transitional										■									
Renal, papillary				■															
Retinoblastoma																			
Rhabdomysarcoma			▒								■								
Schwannoma/MPNST[s]								■			▒								
Sebaceous gland										■									
Small bowel										■									
Sarcoma, other														■					
Skin, basal cell	▒	■			■														
Skin, melanoma							▒					▒							
Skin, squamous cell					■										▒				
Testicle[e]								h											
Thyroid, non-medullary								■				ff							
Thyroid, medullary												▒							
Tongue					■								■						
Ureter										■									
Vulva															■				
Wilms[e]			■		■		n								n			■	■

[a]black fill = definitely or strongly associated; cross-hatched fill = reported; significance not established. This table is designed to assist clinicians in considering whether the constellation of cancers reported in the family history suggests a hereditary cancer syndrome. Most associations have *not* been subjected to rigorous statistical analysis.

[b]Amine precursor uptake and decarboxylation tumors: can secrete pancreatic polypeptide, gastrin, insulin, vasoactive intestinal peptide, glucagon, somatostatin, growth hormone–releasing peptide, parathyroid hormone–related protein, and adrenocorticotrophic hormone.

[c]Adenoma malignum (80%).

[d]Benign or malignant.

[e]See chapter for site-specific syndrome; for space reasons, not included on this table.

[f]Ovarian fibrosarcoma.

[g]Gonadoblastoma.

[h]Large cell calcifying Sertoli cell tumors and Leydig cell tumors.

[i]Pilocytic astrocytoma reported twice.

[j]Subependymal giant cell astrocytoma.

[k]Carcinoma of the nasal cavity.

[l]Chronic lymphocytic leukemia.

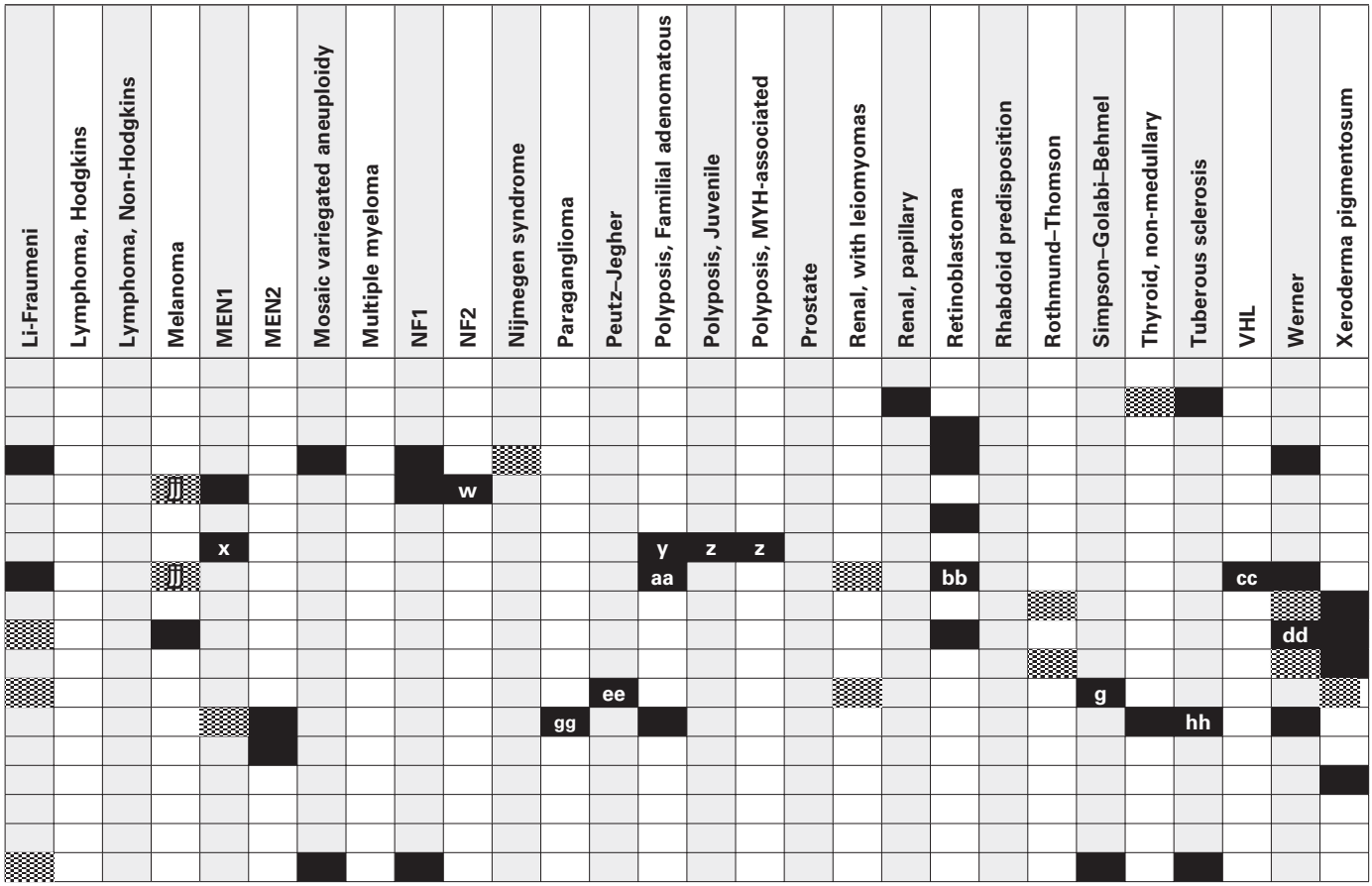
[m]Both acute myeloid and acute lymphocytic leukemia.

[n]Biallelic mutations in *FANCD1/BRCA2* only.

[o]Acute myeloid leukemia.

[p]Juvenile chronic myelomonocytic leukemia.

[q]Primitive neuroectodermal tumor.



[r]Primitive neuroectodermal tumors (PNET) of the central nervous system and kidneys.

[s]MPNST: malignant peripheral nerve sheath tumor, now the preferred name for neurofibrosarcoma or malignant Schwannoma.

[t]Includes primary peritoneal carcinoma; restricted to epithelial carcinomas.

[u]Sex cord tumor with annular tubules or granulosa cell tumors.

[v]Renal and extrarenal atypical teratoid/rhabdoid tumors.

[w]Spinal cord schwannoma.

[x]Carcinoid tumors.

[y]Especially carcinoma of the ampulla of Vater (duodenum).

[z]Duodenal carcinoma.

[aa]Desmoid tumors (technically benign, clinically aggressive).

[bb]Leiomyosarcoma of the uterus, Ewing's sarcoma.

[cc]Hemangioblastoma (benign).

[dd]Melanomas of the nasal mucosa and plantar surface of the foot.

[ee]Sertoli cell tumors.

[ff]Primarily follicular carcinoma.

[gg]Papillary thyroid cancer.

[hh]Hurthle cell carcinoma (rare reports).

[ii]Biallelic mutations in mismatch repair genes.

[jj]Mutations disrupting the p14 transcript of *CDKN2A*.

Table 5. Benign neoplasms associated with specific familial cancer syndromes[a]

Benign neoplasm	Basal cell nevus	Beckwith–Wiedemann	Birt–Hogg–Dubé	Carney	Colon (HNPCC/Lynch)	Costello	Cowden	Dyskeratosis congenita	Esophagus, with tylosis	Exostoses, hereditary multiple	Fanconi anemia	Gastrointestinal stromal tumor	Hyperparathyroidism	Melanoma
Adenoma, broad ligament or epididymal														
Adenoma, hepatic														
Adenoma, hyperplasia: adrenal cortex/medulla		■		b										
Adenoma, hyperplasia: parathyroid													■	
Adenoma, hyperplasia: pituitary				■										
Adenoma, hyperplasia: pancreatic														
Adenoma, hyperplasia: sebaceous					■									
Adenoma or cysts: thyroid				■			■							
Angiomyolipoma														
Cysts: cutaneous, epidermoid	■													
Cysts: cutaneous, sebaceous	■													
Cysts: dentigerous, odontogenic	■													
Cysts: epididymal						■								
Cysts: hepatic,pancreatic,splenic														
Cysts: ovarian, calcified	■													
Cysts: renal													d	
Desmoid tumor														
Exostoses										■				
Fibroadenoma, breast	■			■			f							
Fibroma, cardiac	■													
Fibroma, jaw													g	
Fibroma, hyperkeratotic papules of gingiva							■							
Fibroma, peri-ungual														
Gangliocytoma/ganglioglioma, brain							■							
Ganglioneuroma, peripheral or enteral	■													
Gastrointestinal stromal tumor	■											■		
Glial hamartoma (tubers; subependymal nodules)														
Glomus tumor														
Gonadoblastoma		■												
Hemangioblastoma, central nervous system/retinal														
Hemangioma		■					■							
Lisch nodules (iris hamartomas)					l									aa
Leiomyoma, skin														
Leiomyoma, uterus				i			j						■	
Leukoplakia, intraoral								■	■		■			
Lipoma	■		■				■							
Lymphangiolyomatosis, lung														
Meningioma														
Myelodysplasia, bone marrow								■			■			
Myxoma: cardiac, skin, or other				■										
Nasopharyngeal angiofibroma, juvenile														
Neurofibroma, simple	■			k	l									aa
Neurofibroma, plexiform					m									aa
Neuroma, muco-cutaneous	■						■							
Nevi: numerous or dysplastic	■			■										■
Oncocytoma, oncocytosis			■											

(Table continues)

Table 5 (continued).

Benign neoplasm	Basal cell nevus	Beckwith–Wiedemann	Birt–Hogg–Dubé	Carney	Colon (HNPCC/Lynch)	Costello	Cowden	Dyskeratosis congenita	Esophagus, with tylosis	Exostoses, hereditary multiple	Fanconi anemia	Gastrointestinal stromal tumor	Hyperparathyroidism	Melanoma
Osteochondroma, osteomas														
Ovarian tumor	m													
Papilloma						p								
Paraganglioma														
Pheochromocytoma														
Pilomatricoma														
Polyps, adenomatous, large/small bowel														
Polyps, juvenile, large/small bowel							q							
Polyps, gastric, non-adenomatous							q							
Retinal hamartomas														
Retinoma														
Rhabdomyoma		u				v								
Schwannoma, vestibular														
Schwannoma, non-vestibular				x										aa
Sertoli cell tumor, large cell calcifying														
Skin, acrochordons														
Skin: angiofibroma														
Skin, fibrofolliculoma or trichodiscoma														
Skin, trichilemmoma														
Skin: warty or papillomatous lesions						y								

[a]This table is designed to assist clinicians in considering whether the constellation of benign findings reported in the family history suggests a hereditary cancer syndrome. Most associations have *not* been subjected to rigorous statistical analysis. This table includes both strong associations and associations that are still speculative, both of which as shown as black fill.

[b]Primary pigmented nodular adrenocortical hyperplasia.

[c]Intraductal papillary mucinous neoplasm.

[d]Renal failure also reported.

[e]Not yet reported, but biologically plausible (see text).

[f]Giant or multiple fibroadenomas.

[g]Resemble ossifying/cementifying fibroma.

[h]May occur in a segmental pattern, suggesting somatic mosaicism.

[i]Myxoid leiomyoma.

[j]Early-onset leiomyoma.

[k]Myxoid neurofibroma.

[l]Only associated with biallelic gene carriers.

[m]Fibromas or dermoid tumors.

Disorders

1. Ataxia Telangiectasia (includes Ataxia Telangiectasia Complementation Groups A, C, D, E, Louis–Barr Syndrome)

OMIM number: 208920; 208900; 607585.

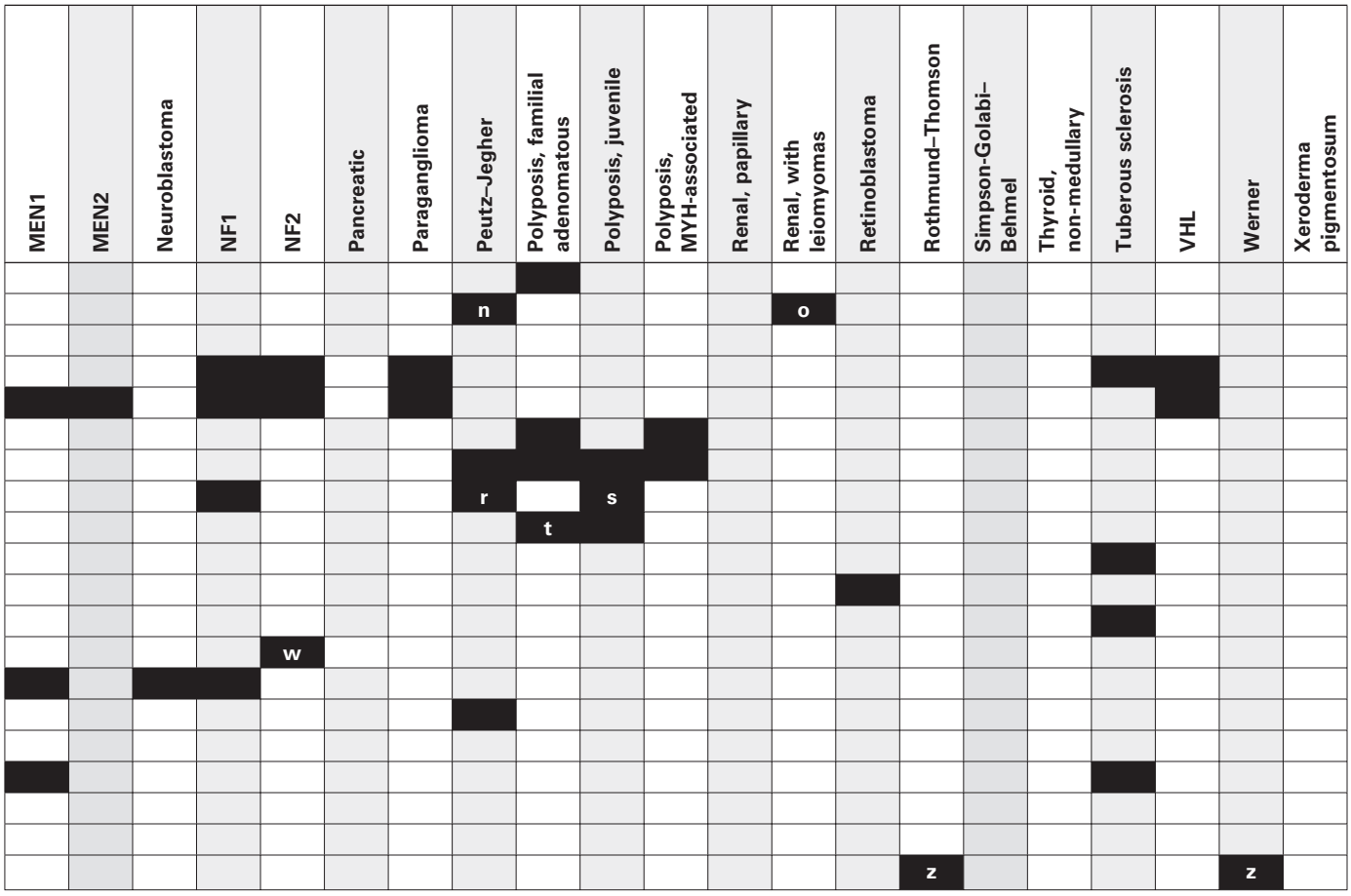
Inheritance pattern: Autosomal recessive.

Gene and chromosomal location: *ATM* at 11q22.3. Complementation groups are defined on the basis of a characteristic radioresistant DNA replication phenotype as a marker in cultured cells. Four complementation groups—A, C, D, and E—map to the same locus and show the following distribution worldwide: A = 55%, C = 28%, D = 14%, and E = 3%.

Mutations: A variety of *ATM* mutations have been reported, with 70%–85% resulting in a truncated protein.

Incidence: One in 30 000 to one in 100 000 live births; heterozygotes in the general population are estimated at about 0.2%–1.0%.

Diagnosis: Cerebellar ataxia (present in 100% of cases) becomes evident around the time a child learns to walk. Initially truncal, the ataxia evolves to include gait, intention tremor, choreoathetosis and/or dystonia (in 90% of cases), slurred speech, apraxia of eye movements, nystagmus, and strabismus.



[n]Sex cord tumor with annular tubules (almost always).

[o]Ovarian adenoma.

[p]Perioral and perianal.

[q]Similar to polyps of juvenile polyposis; dissimilar to Peutz–Jegher polyps.

[r]Distinctive Peutz—Jehger histology– —can be found in other sites, too.

[s]Massive gastric polyposis occurs in those with SMAD4 mutations.

[t]Cystic fundic gland polyps.

[u]Rhabdomyoma, multiple locations.

[v]Rhabdomyoma, cardiac .

[w]Vestibular schwannoma was formerly known as "acoustic neuroma."

[x]Psammomatous melanotic schwannoma is characteristic and distinctive for Carney complex.

[y]Warty lesions of the perioral and perianal area; intraductal breast papillomas.

[z]Warty dyskeratosis, actinic keratoses.

[aa]Mutations disrupting p14 transcript of *CDKN2A*.

Most affected individuals are wheelchair-bound by the age of 10 years and develop a progressive spinal muscular atrophy in their 20s and 30s. The cerebellum is visibly atrophic on magnetic resonance imaging (MRI) by age 7 or 8 years. Dementia is not a feature of most ataxia telangiectasia (AT) patients, although severe impairment of short-term memory has been noted in adults.

Telangiectasiae generally begin in sun-exposed areas of the skin and conjunctivae and occur later than the onset of ataxia symptoms. Other cutaneous features include vitiligo, café-au-lait macules, and premature graying of the hair.

Fifty percent of affected individuals experience endocrine dysfunction, including glucose intolerance, hypogonadism, and impaired fertility.

Frequent sinopulmonary infections are related to a variable degree of immunodeficiency, with decreased levels of immunoglobulins IgG2, IgA, and IgE reported in most patients. No single immunodeficiency is present in all AT patients; the most consistent are IgE and IgA deficiency, detected in 85% and 75% of patients, respectively. Cellular immunodeficiency is also found in 30%.

Laboratory features: Alpha-fetoprotein levels are elevated in about 90% of cases, but this can be elevated in normal children

Table 6. Clinical signs associated with specific familial cancer syndromes[a]

Nonneoplastic abnormality	Ataxia telangiectasia	Basal cell nevus	Beckwith–Wiedemann	Birt–Hogg–Dubé	Bloom	Carney	Colon (HNPCC/Lynch)	Costello	Cowden	Dyskeratosis Congenita	Esophagus, with tylosis	Exostoses, hereditary multiple
Calcification, ectopic		b										
Cardiovascular: arterial dysplasia/aneurysms												
Cardiovascular: atherosclerosis, premature												
Cardiovascular: heart anomalies												
Cardiovascular: pseudoaneurysm												
Cutaneous: café-au-lait spots							e					
Cutaneous: freckles, lentigines							e					
Cutaneous: diffuse hyperpigmentation or patches										h		
Cutaneous: hypomelanotic macules												
Cutaneous: keratosis, palmar/plantar												
Cutaneous: nail abnormalities												
Cutaneous: pits, palmar/plantar												
Cutaneous: scleroderma-like												
Cutaneous: shagreen patch												
Cutaneous: telangiectasiae	k											
Dental: anomalies of teeth												
Ear: external anomalies or low set												
Ear: hearing loss												
Endocrine: diabetes mellitus, type 2												
Endocrine: fetal adrenocortical cytomegaly												
Esophagus: stenosis												
Eye: aniridia												
Eye: cataract												
Eye: CHRPE[p]												
Eye: microophthalmia												
Eye: strabismus												
Face: dysmorphic features												
Gastrointestinal: anomalies			v									
Genitourinary: genital anomalies												
Genitourinary: cryptorchidism												
Genitourinary: reduced fertility												
Genitourinary: renal malformations												
Growth: birth weight, low												
Growth: deficiency												
Growth: hemihypertrophy									aa			
Growth: macrocephaly												
Oral: macroglossia												
Growth: macrosomia (overgrowth)												
Growth: marfanoid phenotype												
Growth: microcephaly												
Growth: short stature												
Growth: visceromegaly								g				
Hair: loss, brittle, or sparse												
Hair:graying, premature												
Hematologic: bone marrow failure												
Immunologic: cellular deficiency												
Immunologic: humoral deficiency												
Neurologic: ataxia									dd			
Neurologic: brain anomalies												
Neurologic: cerebellar atrophy or hypoplasia												
Neurologic: cognitive impairment[ff]												

(Table continues)

Table 6 (continued).

Nonneoplastic abnormality	Ataxia telangiectasia	Basal cell nevus	Beckwith–Wiedemann	Birt–Hogg–Dubé	Bloom	Carney	Colon (HNPCC/Lynch)	Costello	Cowden	Dyskeratosis Congenita	Esophagus, with tylosis	Exostoses, hereditary multiple
Neurologic: altered quality of voice		■			■			■				
Neurologic: neuropathy												
Neurological: seizures	■							■				
Neurological: spinal muscle atrophy	■											
Pulmonary: pneumothorax				■								
Pulmonary: pulmonary fibrosis										■		
Sensitivity: chemotherapy										■		
Sensitivity: ionizing radiation or radiomimetics	■	■								■		
Sensitivity: sun (UV)					■							
Skeletal: anomalous bones		■			■							
Skeletal: radial ray abnormalities					■							
Urethral stenosis										■		

[a]This table is designed to assist clinicians in considering whether non neoplastic signs reported in a family history might be clues to a hereditary cancer syndrome. This table includes signs clearly associated with certain syndromes as well as some that are only occasionally reported to be associated with a specific syndrome, both of which are shown as black fill.

[b]Calcification of falx cerebri, falx cerebelli, petroclinoid ligament, dura, pia, choroid plexus.

[c]Cardiomyopathy, conduction abnormalities, pulmonic stenosis.

[d]Mucocutaneous hyperpigmentation.

[e]Only in biallelic carriers of gene mutations.

[f]Inguinal and axillary freckling.

[g]Pigmented macules of the buccal muscosa, lips, fingers, toes, and external genitalia.

[h]Lacey, reticulated pigmentation.

[i]Marbleized pigmentation (poikiloderma).

[j]Shagreen patch: nodular cutaneous plaques that resemble shark or pig skin.

[k]Telangiectasiae involve bulbar conjunctiva, bridge of nose, ears.

[l]Include supernumerary or congenitally absent teeth, dentigerous cysts, jaw osteomas.

[m]Multiple dental enamel pits in secondary teeth.

[n]Include conductive hearing loss, external auditory canal stenosis, and auricular malformation.

[o]Cataracts in NF2 are early onset and posterior subcapsular in location.

[p]Congenital hypertrophy of the retinal pigment epithelium.

[q]CHRPE = congenital hypertrophy of the retinal pigment epithelium.

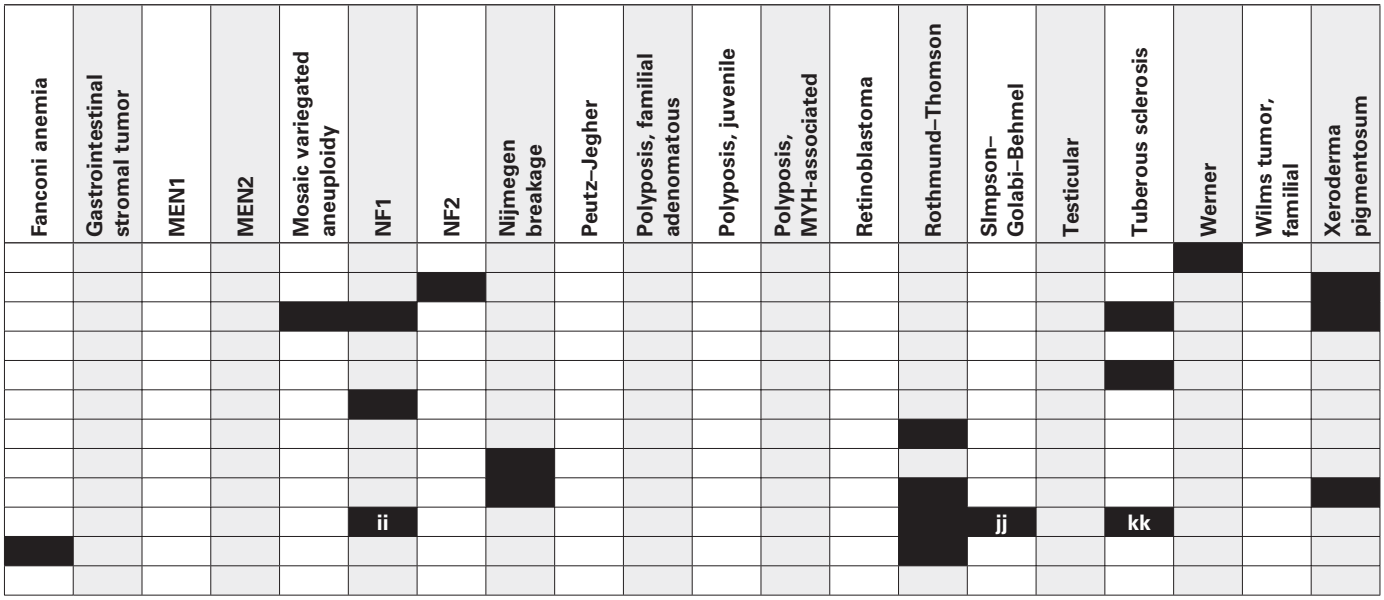
[r]Hypertelorism, down-slanted palpebral fissures, strabismus, sparse hair, short nose, small/asymmetric/pointed ears, microretrognathia, short neck, tapered/bent second fingers.

through 24 months of age. Radiosensitivity, as measured by a colony survival assay of lymphoblastoid cell lines, is reported to have 99% sensitivity and 93% specificity as a diagnostic test for AT (1). Characteristic cytogenetic features include acquired aberrations involving 10% of mitoses, commonly (approximately 80%) with chromosome breakpoints at loci for T-cell and B-cell receptors (7p14, 7q35, 14q11, 14q32, 2p11, 22q11). A 7;14 translocation is found in 5%–15% of routine AT patient karyotypes.

Associated malignant neoplasms: One-third of all AT patients will develop cancer, and 15% will die of cancer. Milder, clinically atypical forms of AT have been identified. Eighty-five percent of the associated malignant neoplasms involve lymphoreticular tissue, especially non-Hodgkin lymphoma (usually B-cell), a feature shared by other disorders exhibiting immunodeficiency, and leukemias (usually acute or chronic lymphocytic leukemia). Adult male patients, particularly those who are IgA deficient, have a 70-fold increased risk of gastric cancer. Increased rates of medulloblastomas, basal cell carcinomas, gliomas, and uterine cancer have been reported. Ovarian dysgerminomas have been reported six times; relative risk is unknown [reviewed by Koksal et al. (2)]. Most people with AT live into their 30s with cancer and infection accounting for 90% of mortality (3).

Associated benign neoplasms: None known.

Associated risks of heterozygous carriers of AT: Swift et al. (4) reported that heterozygous men and women from AT families have relative risks of 2.3 and 3.1 of developing cancer, all sites combined, with excess risks of cancer mortality of 3.0 and 2.6, respectively. In addition, heterozygotes for *ATM* mutations were reported to have a 6.8-fold increased risk of breast cancer compared with control subjects. Multiple studies have confirmed increased risks of



[s]Deletions of the whole gene are associated with facial dysmorphism.

[t]Facial dysmorphic features: sloping forehead, prominent midface, retrognathia.

[u]Coarse facies, hypertelorism, downslanting palpebral fissures, large jaw, broad nasal bridge, short/upturned nasal tip, midline groove of tongue and/or lower lip.

[v]Omphalocele.

[w]Hirschsprung aganglionic megacolon.

[x]Denys–Drash syndrome: severe genitourinary malformations, pseudohermaphrodism and mesangial sclerosis of the kidney, early childhood renal failure.

[y]Females only.

[z]Renal aplasia, duplication, ectopia, and horseshoe kidney.

[aa]Asymmetric breast hypertrophy.

[bb]Hemihypertrophy.

[cc]*MEN2B* only.

[dd]Cerebellar gangliocytoma.

[ee]Dandy–Walker malformation (cerebellum, fourth ventricle), +/-quadriparesis.

[ff]Variable in penetrance and severity.

[gg]Mental retardation only seen in patients with cytogenetically visible deletions at chromosome 22q12.2.

[hh]Organic brain syndrome.

[ii]Sphenoid wing dysplasia or congenital bowing or thinning of the long bone cortex (+/-pseudoarthrosis).

[jj]Broad/short hands, hypoplasia of distal index finger.

[kk]Periosteal "sclerosis."

breast cancer in heterozygote carriers of AT mutations, findings which are most consistent when the cohort is defined through an affected proband. Olsen et al. (5) analyzed 1445 relatives of 75 Nordic AT patients. The standardized incidence ratio (SIR) for breast cancer was 1.7 (95% CI = 1.2 to 2.4); in women younger than age 55, the SIR was 2.9 (95% CI = 1.8 to 4.5). In a study of 169 AT patients and their 1160 relatives in the United Kingdom, overall relative risk of breast cancer was 2.2, but the relative risk was 4.9 (95% CI = 1.9 to 12.9) in women younger than age 50. This study also provided evidence for increased risks of colorectal cancer and stomach cancer (6). Liberzon et al. (7) found an association between *ATM* germline mutation and T-cell acute lymphoblastoid leukemia, with both reports adding further evidence in support of the hypothesis of increased cancer risk among *ATM* heterozygotes.

Most studies that analyzed *ATM* mutations in cohorts of women with breast cancer have yielded insignificant results. However, 443 probands from *BRCA* mutation-negative families with three or more breast cancers and 521 controls were recently screened for *ATM* mutations. Mutations that are known to cause AT in biallelic carriers were associated with a 2.4-fold (95% CI = 1.5 to 3.8) increase in familial breast cancer risk among monoallelic carriers, whereas other *ATM* variants not known to cause AT conferred no increase in risk (8). This is the strongest evidence to date that heterozygous carriers of specific *ATM* mutations are at increased risk of breast cancer outside the setting of AT families. The role of Finnish *ATM* founder mutations in familial (n = 541) and sporadic (n = 1124) breast cancer vs controls (n = 1107) revealed breast cancer odds ratios (ORs) of 12.4 (95% CI = 1.5 to 103) and 6.9 (95% CI = 0.9 to 56), respectively (9). In a population-based study of 3743 breast cancer cases and 1268 controls, the cumulative breast cancer risk to age 70 for carriers of the c.7271T>G *ATM* variant was 52%, with an OR of 8.6 (95% CI = 3.9 to 18.9). No

breast cancer risk was observed for the c.1066-6T>G allele (10). It has been suggested that, while individual variants in specific DNA repair-related genes (*ATM*, *BRCA1*, and *BRCA2*) may be associated with undetectable levels of breast cancer risk even in adequately powered studies, increasing total numbers of SNPs in these genes might, in the aggregate, make a substantial contribution to cancer risk (P_{trend} = 0.0004; OR for ≥3 SNPs = 3.2, P = 0.001) (11).

Cancer risk management: There is no proven cancer reduction strategy for those with AT. The role of intensive mammographic surveillance for breast cancer in heterozygotes is unclear, in light of the demonstrated clinical sensitivity to ionizing radiation in this disorder. Breast MRI offers a theoretically attractive alternative screening strategy in this setting, but there are no data yet available to support its use.

Comments: AT patients are unusually sensitive to ionizing radiation and some radiomimetic chemotherapy agents. Treatment of cancer with conventional doses of radiation can be fatal.

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2. Basal Cell Nevus Syndrome, Nevoid Basal Cell Carcinoma Syndrome, or Gorlin Syndrome

OMIM number: 109400; 601309.

Inheritance pattern: Autosomal dominant.

Gene and chromosomal location: Basal cell nevus syndrome (BCNS) is caused by mutations in *PTCH* at 9q22.3.

Mutations: Multiple unique *PTCH* mutations have been reported, but no clinically significant genotype–phenotype correlations were noted. Mutations are detected in 60%–85% of individuals meeting diagnostic criteria. Twenty to forty percent of cases represent de novo germline mutations. Rarely, cytogenetically detectable deletions of chromosome 9q have been reported.

Incidence: Incidence is estimated at one in 40 000–57 000 live births. In children diagnosed with basal cell skin cancer (BCC) younger than age 19 years, 26% had features of BCNS. Among BCC cases diagnosed younger than age 45, at least 2% have unequivocal BCNS. Among individuals with more than one odontogenic keratocyst, a minimum estimate is that 2.5% have BCNS.

Diagnosis: Evans et al. (1) provided diagnostic criteria for BCNS (Table 7). Note that a full orthopantogram of the jaw, chest, and skull radiographs are required to adequately evaluate for BCNS, and pelvic ultrasound seeking ovarian fibromas may also be helpful. Ectopic calcification of the falx cerebri is seen in more than 90% of patients older than age 20. More than 50% of patients with BCNS manifest enlarged occipitofrontal circumference, mild ocular hypertelorism, palmar and/or plantar pits, calcified ovarian cysts, rib anomalies (splayed, fused, partially missing, bifid, etc), spina bifida occulta of cervical or thoracic vertebrae, calcified diaphragma sellae, or hyperpneumatization of paranasal sinuses. A recent report suggests that the occurrence of discrete patches of unusually long pigmented hair on the skin may represent a novel physical sign associated with BCNS (3).

Laboratory features: No specific findings.

Associated malignant neoplasms: Multiple BCCs usually appear in the third decade, but have been reported as young as age 2 years, with a median age at diagnosis of 25 years. Only 40% of African Americans with BCNS manifest BCC and, even when present, the number of lesions may be small. Ten percent of gene mutation carriers may never develop BCC. Up to 5% of children develop medulloblastoma (a type of primitive neuroectodermal tumor) with a peak incidence around age 2 years, compared with 7 years in sporadic medulloblastomas (4). Ovarian fibrosarcoma may develop.

Associated benign neoplasms: Odontogenic keratocysts of the jaw (mean number = 5) in over 90% of individuals with BCNS, often developing in the second decade, and epidermal cysts and palmoplantar pits reportedly occur in the majority of cases. In a minority of cases, meningioma or ovarian fibromas (20%) and cardiac fibromas (2%) may occur. Fetal rhabdomyomas have been

Table 7. Diagnostic criteria for basal cell nevus syndrome (1)[a]

Diagnosis is established if two major or one major and two minor criteria are met.

Major criteria:
- Multiple (>2) basal cell carcinomas or one <30 years or >10 basal cell nevi.
- Any odontogenic keratocyst (proven on histology) or polyostotic bone cyst.
- Palmar or plantar pits (≥3).
- Ectopic calcification; lamellar or early (<20 years) falx calcification.
- Family history of BCNS.

Minor criteria:
- Congenital skeletal anomaly: bifid, fused, splayed, or missing rib, or bifid, wedged, or fused vertebrae.
- Head circumference >97th centile, with frontal bossing.
- Cardiac or ovarian fibroma.
- Medulloblastoma (PNET, most often of desmoplastic histology) (2).
- Lymphomesenteric or pleural cysts.
- Congenital malformation: cleft lip and/or palate, polydactyly, eye anomaly (cataract, coloboma, microphthalmia).

[a]BCNS = basal cell nevus syndrome; PNET = primitive neuroectodermal tumor.

reported now in five cases. More than 100 other manifestations have been recorded in BNCN (5). Radiographic features were studied in new series of 82 patients (6).

Cancer risk management: The risks and benefits of cancer screening in patients with BCNS have not been established. Affected individuals should be carefully instructed on how to minimize sun exposure of the skin throughout life. In infancy, head circumference should be monitored for rapid enlargement that could indicate developing hydrocephalus. A jaw radiograph has been advised in individuals older than age 8, and every 12–18 months thereafter, because keratocysts usually require surgical excision. Skin examination by a dermatologist experienced with BCNS should be conducted every 4–12 months, from adolescence onward. BCC has been reported before puberty, albeit rarely. Surgical excision, laser therapy, and use of systemic retinoid are among the options now available for management of BCC. Careful annual gynecologic examination in adulthood is advised, and periodic ovarian ultrasound may be useful. If excision of large or symptomatic ovarian fibroma is required, attempts should be made to preserve ovarian tissue (and fertility), as malignant degeneration is uncommon. Echocardiogram in the first year of life has been suggested, and if fibromas are present but asymptomatic, regular evaluation by a cardiologist is suggested. Although there is a risk of medulloblastoma, no evidence exists to support routine brain imaging as a screening strategy. Exposure to radiation should be avoided in this condition when possible, based upon reports of thousands of BCCs developing within the radiation field of those receiving therapeutic radiation (7). A recent report suggests that BCNS patients are at risk of radiation-induced brain tumors (8).

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3. Beckwith–Wiedemann Syndrome (Exomphalos–Macroglossia–Gigantism Syndrome)

OMIM number: 130650.

Inheritance pattern: Autosomal dominant pattern seen in 15% of cases. Of individuals with Beckwith–Wiedemann Syndrome (BWS), 85% have no family history of BWS.

Genes and chromosomal location: A variety of genetic alterations are reported in BWS. Most are epigenetic in nature, involving a differentially imprinted region of chromosomal band 11p15. The molecular basis of this enormously complex disorder is described and diagramed clearly by Weksberg et al. (1).

Mutations: Paternal segmental isodisomy or isodisomy of the whole chromosome [92% vs 8%, respectively (2)], sometimes with somatic mosaicism, for a region including chromosomal band 11p15 is found in 10%–20% of all cases; at least five different genes in this region have been implicated in the etiology of BWS. *IGF2* is normally paternally expressed. Disruption of *IGF2* imprinting resulting in biallelic expression of this gene has been found in some BWS patients. *H19* is a maternally expressed gene. Imprinting of *IGF2* and *H19* is controlled by the imprinting center locus (*IC1*) at 11p15.5. This is a methylation-sensitive chromatin insulator that binds zinc-finger protein, *CTCF*, in a parent-of-origin–specific manner. Microdeletions of the *CTCF* target sites of *IC1* are associated with BWS by disrupting normal imprinting of the *IGF2* and *H19* loci (3). Rarely, changes in *H19* expression have been reported in BWS. $p57^{KIP2}$ (*CDKN1C*) has preferential maternal expression (incomplete paternal imprinting), and 5%–10% of BWS cases have $p57^{KIP2}$ mutations; these are found more commonly in cases with a positive BWS family history, omphalocele, and cleft palate. *KVLQT1* is maternally expressed. Loss of imprinting of an antisense transcript (*LIT1;KCNQ1OT1*) that is expressed by the paternal allele and lies within the *KVLQT1* gene has been reported in some BWS cases, and maternally derived deletions of *LIT1* can also cause BWS. Less than 1% of BWS cases have a cytogenetically visible abnormality involving the 11p15 region (4,5).

Incidence: One in 13 700 live births.

Diagnosis: No consensus criteria exist, but it has been suggested that a diagnosis requires the presence of three findings (at least two major and one minor). Major findings include previously diagnosed family members, height and/or weight greater than 97th percentile, anterior linear ear lobe creases or posterior helical ear pits, macroglossia, omphalocele, visceromegaly involving one or more intra-abdominal organ (liver, spleen, kidneys, adrenals, pancreas), embryonal tumor in childhood, hemihyperplasia, adrenocortical cytomegaly, renal abnormalities, and cleft palate (rarely). Minor findings include polyhydramnios, prematurity, neonatal hypoglycemia, facial nevus flammeus, hemangioma, characteristic facies (midfacial hypoplasia, infraorbital creases), cardiomegaly or structural cardiac lesions, diastasis recti, advanced bone age, and monozygotic twinning (usually female and discordant for BWS).

Associated malignant neoplasms: Children with BWS have a 7.5% risk of tumors (all sites combined) in the first 8 years of life; development of cancer above that age is uncommon (6). The most common is Wilms tumor (60% of malignancies in BWS; conversely, about 1%–2% of all Wilms tumors arise in the context of BWS). Mean age at Wilms tumor diagnosis in BWS is 28 months, with 89% of cases diagnosed younger than age 5 years. The contralateral kidney is also affected in 21% of BWS-related Wilms tumor. Other BWS-associated tumors include hepatoblastoma, neuroblastoma, adrenocortical carcinoma, rhabdomyosarcoma, and gonadoblastoma. Patients with uniparental disomy or

mutations in imprinting center 1 of the BWS region (involving the *IGF2* and *H19* genes) may be more likely to develop cancer than those with mutations elsewhere in the gene. Patients with mutations in imprinting center 2 (involves *LIT1* and $p57^{KIP2}$) generally do not develop Wilms tumor but are at risk of other BWS-related embryonal neoplasms (6), whereas loss of *H19* gene imprinting, including that associated with uniparental disomy involving chromosome band 11p15, is associated with increased cancer risk, particularly for Wilms tumor (7).

Associated benign neoplasms: Pancreatic islet cell hyperplasia (leading to neonatal hypoglycemia), adrenal cytomegaly (which may or may not result in adrenal overactivity), hyperplasia of pituitary, hamartomas, adenomas, myxomas, ganglioneuromas, and fibroadenomas.

Cancer risk management: Surveillance for neoplasia includes ultrasound abdominal imaging to screen for embryonal tumors and is recommended every 3–4 months until age 8 years. Serum alpha-fetoprotein every 6 months may also be reasonable. Periodic chest radiograph and urinary screening for neuroblastoma have been suggested but are not often used in screening protocols because evidence of efficacy is lacking (8). For specific recommendations related to screening for Wilms tumor in BWS, see "Wilms Tumor."

Comments: A multidisciplinary team is required to address issues such as neonatal hypoglycemia, correction of omphalocele, management of hemihypertrophy, and more. Several recent reports suggest increased risk of BWS and Angelman Syndrome in pregnancies conceived using assisted reproductive technology, raising the possibility that genomic imprinting can be altered by the process of in vitro fertilization (9). However, Doornbos et al. (10) present evidence that the increased risk of these syndromes is related to parental infertility rather than the assisted reproductive technology itself. Surgical correction of macroglossia is technically challenging because patients often fail to achieve completely normal tongue function and appearance as adults (11).

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4. Birt–Hogg–Dubé Syndrome

OMIM number: 135150; 607273.

Inheritance pattern: Autosomal dominant.

Gene and chromosomal location: *FLCN* (folliculin) at 17p11.2, encoding a novel protein of the same name. It is involved in AMPK and mTOR signaling (1).

Mutations: About 50% of mutations involve an insertion/deletion of a C-8 hypermutable tract in exon 11; other mutations are found throughout the gene—10 of 61 families studied to date have no identifiable mutation (2). Overall, *FLCN* sequence analysis has an 84% detection rate in Birt–Hogg–Dubé Syndrome (BHDS).

Incidence: Unknown.

Diagnosis: The BHDS is first manifest by the cutaneous triad of multiple fibrofolliculomas (FFs), trichodiscomas (TD; both of which are fibroepithelial hamartomas of the hair follicle), and acrochordons (skin tags) appearing in the third to fourth decade of life. These asymptomatic lesions primarily appear on the head, face, neck, upper chest, back, arms, and inner thighs. In addition to various cutaneous manifestations, affected individuals are at risk of pulmonary cysts, spontaneous pneumothorax, and kidney tumors, and diagnostic evaluation includes screening for these skin, lung, and kidney features. The development of renal tumors may lead to syndrome recognition, particularly if they present with chromophobe or oncocytic histology, both of which are uncommon in the general population but typical for BHDS. A family history of multiple FFs may indicate BHDS. Ninety percent of BHDS patients studied in a familial kidney cancer program have pulmonary cysts, and pneumothorax develops in 20%. Pneumothorax has been reported as the presenting sign in a BHDS family (3). In contrast, families ascertained through a dermatology genetics unit seemed to have lower risks of both kidney cancer and pneumothorax (4).

Laboratory features: No specific laboratory findings. Skin biopsy is required to confirm the diagnosis of FF. Collins et al. (5) studied the histology of BHDS-related FFs and TDs and found them to be similar to their sporadic counterparts.

Associated malignant neoplasms: BHDS is associated with multiple bilateral renal tumors of various types, including oncocytoma, chromophobe renal cell carcinoma, clear cell carcinoma, and papillary renal carcinoma, as well as hybrid oncocytic neoplasms. Zbar et al. (6) demonstrated that BHDS patients were 6.9 times more likely to develop renal tumors compared with unaffected family members. Pavlovich et al. (7) reviewed 130 solid renal tumors resected from 30 patients with BHDS in 19 different families. Preoperative computed tomography (CT) scans showed a mean of 5.3 tumors per patient (range = 1–28 tumors), the largest averaging 5.7 centimeters in diameter. Multifocal tumors were noted at a mean age of 50.7 years and consisted of chromophobe

renal cell carcinomas (34%) or of hybrid oncocytic neoplasms with areas suggestive of chromophobe renal cell carcinoma and oncocytoma (50%). Nine percent were clear cell renal carcinomas. Microscopic oncocytosis was found in the renal parenchyma of most patients, including five patients with clear cell renal cell carcinoma. This suggests that microscopic oncocytic lesions may be precursors of hybrid oncocytic tumors, chromophobe renal cell carcinomas, and perhaps clear cell renal cell carcinomas in BHDS. Nonrenal malignancies are not known to be part of this syndrome.

Associated benign neoplasms: Benign tumors of the hair follicle, including FFs, perifollicular fibromas (PFFs), TDs, and acrochordons. Several findings suggest that FF and TD represent a spectrum of a single process. The diagnosis of FF and TD may depend merely on the topographic location of the hair follicle within the biopsy specimen. Most likely, PFFs represent a part of the spectrum from FF to TD. Other features of BHDS include pulmonary cysts and, rarely, deforming lipomas and collagenomas (8).

Colonic polyps have been noted in a number of case reports on BHDS; however, Zbar et al. (6) showed no increased prevalence of colonic polyps in BHDS families. They examined 83 BHD family members by colonoscopy. While eight of the 45 BHDS-affected individuals (18%) had colon polyps, seven of the 38 non-BHDS individuals (18%) did as well. Others have reported parotid oncocytoma, multinodular goiter, meningioma, and neurothekeoma occurring in individuals with BHDS; it is unclear if they are syndrome related or not.

Cancer risk management: No surveillance is indicated for the skin lesions because they are not precancerous. Annual imaging of the kidneys by magnetic resonance imaging (MRI) is suggested (avoiding radiation exposure on general principles), starting around age 35 or 10 years younger than the youngest case of renal tumor identified in that family. Abnormalities identified by MRI should be further evaluated by CT scan. Because BHD-related kidney cancer is often bilateral, renal-sparing surgery should be attempted if possible; given the multifocal nature of these tumors, surgery is generally reserved for masses greater than 3 cm in diameter (9).

Comment: Familial oncocytoma has been reported as a distinct entity. Some of the originally reported kindreds were later shown to have *FLCN* mutations, but other families may have a discrete new entity (gene unknown) [summarized by Cohen and Zhou (10)]. Individuals with BHDS should be counseled regarding the potential for spontaneous pneumothorax (which can occur as early as adolescence), and they should be made aware of pneumothorax-associated symptoms so as not to delay diagnosis, but no screening tests to detect cystic changes in the lungs seem indicated at this time.

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5. Bloom Syndrome

OMIM number: 210900.

Inheritance pattern: Autosomal recessive.

Gene and chromosomal location: *BLM* at 15q26.1, a RecQ-like DNA helicase.

Mutations: Multiple mutations identified including missense, nonsense, frameshift, exon skipping, and exonic deletions (1). In a registry-based study, 64 different mutations (54 truncating and 10 missense) were identified in 125 affected subjects (2). Seventy-five subjects were homozygous for their mutation; 15 were compound heterozygotes. A founder mutation in Ashkenazi Jews is designated BLM^{ash}, a 6 bp deletion/7 bp insertion. Overall, 19 different recurring (founder) mutations were reported.

Incidence: Actual incidence is unknown in general population. Among Ashkenazi Jews, Bloom syndrome (BS) is seen in one in 48 000 live births and is most common in those of Ukrainian or Polish ancestry. The Bloom Syndrome Registry represents the majority of people in the world diagnosed with BS between l960 and 2006. Currently, there are 238 persons in the registry. Approximately 30% report Ashkenazi ancestry. The reported frequency of the Ashkenazi founder mutation is 1/231 heterozygotes among New York Ashkenazim and 1/101 among Polish Ashkenazim.

Diagnosis: BS is characterized by growth deficiency (pre- and postnatal), with normal body proportion except for mild microcephaly, a sun-sensitive erythema or telangiectasia generally on the face and dorsa of the hands and forearms, and characteristic facies: malar hypoplasia, nasal prominence, small mandible, and dolichocephalic skull. Males are sterile and females, although sometimes fertile, have reduced fertility and a shortened reproductive span. An increased susceptibility to infection, with recurrent bronchitis and bronchiectasis; frequent occurrence of diabetes; infantile diarrhea and vomiting; café-au-lait or hypopigmented macules; and high-pitched voice are all reportedly syndrome related. Learning disabilities are frequent, but overall intellect is usually normal.

Specific diagnostic testing involves demonstration of increased frequency of sister chromatid exchange (SCE) in cultured peripheral blood lymphocytes; demonstration of this feature requires special analytic techniques and cannot be detected by routine chromosomal

analysis. Limited clinical genetic testing for founder mutations is now available.

Laboratory features: Strikingly elevated (10-fold greater than normal) SCE rate in all cell types examined. Other somatic hyperrecombination mutations that give rise to chromosomal quadraradials and excess breakage are also seen, all of which may lead to loss of heterozygosity due to homologous recombination, duplications, and deletions from unequal SCEs between repetitive elements or syntenic members of gene families. BS is the only disorder with evidence of hyperrecombination of this type.

Associated malignant neoplasms: Cancers show increased frequency at all ages, with acute leukemia, lymphoid neoplasms, and Wilms tumor predominating before the age of 25; after age 20, carcinomas of the tongue, larynx, lung, esophagus, colon, skin, breast, and cervix are most frequent (summarized in Table 8), with the age at diagnosis often 20 or more years younger than that generally expected for each tumor type. German (1) reported that the two oldest persons known to have BS both died of cancer, one at age 46 and the other at 49.

Somatic mutations in BS cells are not inherited through the germline but are far more likely to arise spontaneously compared with cells in healthy individuals. In BS patients, every cell in the body capable of further division is at high risk of neoplastic transformation. The spectrum of BS-related malignancies is very heterogeneous, a pattern quite distinct from the usual cancer susceptibility disorder, in which cancer risk is generally restricted to one or a limited number of cancers.

Until recently, obligatory heterozygotes have been said to lack any increased cancer risk. Gruber et al. (4) have now reported that Ashkenazi Jews with colorectal cancer were more than twice as likely to carry the *BLM* founder mutation than Ashkenazi Jewish controls without colorectal cancer. This was true in both an Israeli population and a New York City cohort. On the other hand, the founder mutation was not overrepresented among Ashkenazim with cancers of the breast, prostate, ovary, uterus, or in lymphomas.

Table 8. Malignancies reported by the Bloom Syndrome Registry through 2005 [adapted from Sanz and German (3)]

	No.	Age at diagnosis, y (range)
Persons under cancer risk management	238	
Carcinomas		
Lower enteric	25	34 (16–47)
Skin	22	32 (18–42)
Upper enteric or respiratory	12	35 (25–48)
Breast	9	32 (21–42)
Genitals or urinary tract	8	28 (19–43)
Lower respiratory	6	33 (26–40)
Lymphoreticular		
Lymphoma	32	20 (4–45)
Acute lymphocytic leukemia	11	20 (5–40)
Other acute leukemia	18	17 (2–40)
Sarcoma	3	16 (4–30)
Germ cell	2	24 (22–26)
Nervous	1	3
Other—Wilms tumor	6	4 (1–8)

Associated benign neoplasms: Multiple adenomatous colon polyps have been reported in one individual with BS.

Cancer risk management: The risks and benefits of cancer screening in BS have not been established. In infancy, one could consider offering semiannual ultrasonographic screening through age 8 years for Wilms tumor. As colorectal cancer is the single most common carcinoma, we suggest colonoscopy every 3–5 years, starting in late adolescence. Meticulous annual physical examination is suggested from age 18 onward, with initiation of upper gastrointestinal endoscopic and mammographic surveillance beginning in early adulthood. Before adulthood, hematologic malignancies predominate, and no screening for these beyond a careful history and physical examination is specifically suggested.

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6. Breast/Ovarian Cancer, Hereditary (*BRCA1*)

OMIM number: 113705.

Inheritance pattern: Autosomal dominant.

Gene and chromosomal location: *BRCA1*, a tumor suppressor gene at 17q21, is central to the maintenance of genome stability. It is a multifunction E3 ubiquitin ligase involved in DNA damage signaling, DNA repair (homologous recombination repair of double-stranded DNA breaks), chromatin remodeling and transcription (1). It is not homologous to *BRCA2*; each has its own distinctive mechanisms of action. Mutations in other genes that also play a role in protecting genomic integrity, for example, *CHEK2*, *ATM*, *NBS1*, *RAD51*, *BRIP1*, and *PALB2* are all associated with approximately twofold increases in sporadic breast cancer risk (2). These genetic variants are relatively uncommon. The international CIMBA (Consortium of Investigators of Modifiers of *BRCA1/2*) collaboration is systematically searching for genetic modifiers of *BRCA*-related breast cancer, having assembled a cohort of more than 10 000 mutation carriers. To date, they have corroborated the reported increase in *BRCA2*-related breast cancer risk observed with a functional promoter variant in the *RAD51* gene (3) and published definitive negative reports of the putative associations with the *AIB1* polyglutamine repeat (4) and F31I variant of *AURKA* (5). A functional promoter SNP in the *MDM2* gene has been reported to accelerate the rate of breast and ovarian carcinogenesis in Ashkenazi Jewish *BRCA1* and *BRCA2* mutation carriers (6).

Mutations: More than 1643 distinct mutations, polymorphisms, and variants have been identified (Breast Cancer Information Core: http://research.nhgri.nih.gov/bic/). The diagnostic accuracy of various methods for detecting mutations in *BRCA1/2* has been reviewed (7).

Incidence: Overall, *BRCA1* and *BRCA2* account for a small proportion of all breast cancers, a fraction that varies according to the population; most studies have been limited to early-onset cancer. The Anglican Breast Cancer Study Group (8) reported mutations in either *BRCA1* or *BRCA2* in 2% of women in a population-based series of 1220 breast cancers diagnosed younger than age 55 years. Among Australian women diagnosed with breast cancer before age 40 years, 3.8% were found to have *BRCA1* mutations (9). In the United Kingdom, *BRCA1* or *BRCA2* mutations were found in 5.9% of women diagnosed younger than age 36 and in 4.1% of women diagnosed from ages 36 through 45 years (10). In the United States, *BRCA1* mutations were found in 3.3% of women diagnosed with breast cancer between the ages of 20 and 74 (11). (This age range accounts for about 70% of all breast cancer in the United States.) *BRCA1* and *BRCA2* mutations occur in 10%–15% of all ovarian cancer in patients unselected for family history (12,13). One estimate of *BRCA1* mutation prevalence in the general US non-Hispanic white non-Ashkenazi population is 0.24%, or one in 416, in a study of women with breast cancer diagnosed between ages 20 and 64 years (14). In general, about two-thirds of families with three or more cases of female breast and/or ovarian cancer had either a *BRCA1* or a *BRCA2* mutation (15). The cause of cancer in the remaining third of families is unknown, and attempts to find novel, highly penetrant genes (eg, "*BRCA3*") through genome-wide linkage analysis of *BRCA1/2*-negative families have been unsuccessful (16). Estimates of *BRCA1* carrier frequencies have ranged from 0.056% to 0.24%, with a recent population-based Canadian study finding the highest rate yet reported, 0.32%, or one in 312 (17).

Compared with non-Hispanic, non-Jewish Caucasian women in the United States, African American women have a lower rate of deleterious *BRCA1* and *BRCA2* clinical mutations but a much higher rate of genetic variants of unknown clinical significance (18). Methods aimed at clarifying the cancer risks associated with sequence variants of unknown clinical significance are being developed (19). A survey of the prevalence of pathogenic *BRCA1* mutations in women younger than age 65 years at diagnosis in different US racial/ethnic groups revealed the following: Hispanic = 3.5%, African American = 1.3%, Asian American = 0.5%, Ashkenazi Jewish = 8.3%, and non-Hispanic whites = 2.2%. Note, however, that in African American women diagnosed under age 35 years, BRCA1 mutations were particularly common (16.7%) (20).

Founder mutations in *BRCA1/2* have been reported in multiple populations [reviewed by Ferla et al. (21)]; in the United States, the focus has been on individuals of Ashkenazi (central European) Jewish ancestry. Three founder mutations *(BRCA1* 185delAG, *BRCA1* 5382insC, and *BRCA2* 6174delT) account for 80%–90% of the identifiable *BRCA1/2* mutations in Ashkenazi hereditary breast/ovarian cancer families; these mutations have population frequencies of 1.1%, 0.1%, and 1.5%, respectively, or approximately one per 40 in the aggregate.

It has recently been demonstrated that genomic rearrangements may account for up to 25% of all *BRCA1* mutations (22). This class of genetic lesion is missed by conventional sequencing technologies; the commercial *BRCA* testing algorithm was modified initially in 2002 and revised a second time in 2006 to include detection of some of these mutations. *BRCA*-negative subjects who were tested before these modifications may benefit from additional testing.

Diagnosis: Suspected on the basis of premenopausal breast cancer diagnosis or a pedigree suggestive of dominant inheritance of a predisposition to breast and/or ovarian cancer. Larger numbers of early-onset breast cancer (particularly, if bilateral) and the presence of ovarian cancer increase the likelihood of finding a *BRCA1* mutation. Genetic testing is required to confirm that an individual carries a *BRCA* mutation. Several mutation carrier prediction models are available, aimed at identifying individuals who are likely to carry *BRCA1* and *BRCA2* mutations (23–30). A validation study comparing seven different models suggested that BRCAPRO had the best performance statistic, although all models were adequate for clinical use (31). BRCAPRO also appears to perform satisfactorily in Hispanic populations (32). In small families, these models are less useful (33). Genetic testing for germline mutations in *BRCA1* and *BRCA2* as a basis for clinical decision making has become a routine part of clinical practice. The US Preventive Services Task Force has published a systematic evidence review (34), and there are formal recommendations for selecting individuals in whom genetic evaluation is warranted (35,36).

Associated malignant neoplasms: Breast and ovarian cancer are the defining features of this syndrome. Ductal carcinoma in situ is part of the spectrum of breast neoplasia in *BRCA* mutation carriers though mutations were somewhat less frequent than in comparable families with invasive cancer (37,38).

Estimates of cancer penetrance by age vary considerably. A pooled analysis of 22 studies in which cases were unselected for family history provides the best average *BRCA1* risk estimates to age 70: breast cancer = 65% (95% CI = 51% to 75%) and ovarian cancer = 39% (95% CI = 22% to 51%) (39). A recent, large, population-based analysis in Ontario, Canada, yielded *BRCA1*-related breast and ovarian cancer risk estimates to age 80 of 90% and 24%, respectively (17). The carrier frequency for *BRCA1* and *BRCA2* combined in this latter series was one in 100, a much higher rate than the generally cited one in 800. Chen and Parmigiani (40) conducted a meta-analysis of 10 studies that used methods to correct for ascertainment and reported cumulative cancer risks to age 70 for breast and ovarian cancer as 57% and 40%, respectively, for *BRCA1* mutation carriers.

The penetrance of the two Ashkenazi *BRCA1* mutations—185delAG and 5382insC—for breast cancer by age 70 are 64% (95% CI = 34% to 80%) and 67% (95% CI = 36% to 83%), respectively (41). The corresponding values for ovarian cancer are 14% (95% CI = 2% to 24%) and 33% (95% CI = 8% to 50%), respectively. In the US population, Chen et al. (42) estimated cumulative breast cancer risk in *BRCA1* mutation carriers to age 70 as 46% (95% CI = 0.39% to 0.54%) and 39% (95% CI = 0.30% to 0.50%) for ovarian cancer, based on 676 Ashkenazi families and 1272 families of other ethnicities.

The risk of *BRCA*-related breast and ovarian cancer appears to be confined to *epithelial* malignancies of both organs. *BRCA1*-related breast cancer tends to be of high histological grade, lymph node positive, estrogen receptor negative, progesterone receptor negative, HER2/neu negative, with expression of basal or myoepithelial markers by immunohistochemistry ("basal phenotype") (43). Recent data indicate that the dearth of estrogen receptors in *BRCA1*-related breast cancer is a direct result of the mutation

itself; *BRCA1* regulates the expression of estrogen receptors (44). Whereas the clinical features of *BRCA2*-related breast cancer are indistinguishable from those of sporadic breast cancer, these two entities do appear to have distinctive molecular characteristics by mRNA expression profiles. In general, the clinical differences between *BRCA1*- and *BRCA2*-related breast cancers are associated with differences in prognosis, such that the former (but not the latter) have a worse prognosis than their sporadic counterparts (45–47), although outcome has been reported to be similar between these two breast cancer subgroups by some investigators (48). The primary difference between *BRCA*-related ovarian cancer and sporadic ovarian cancer is the rarity of mucinous and borderline neoplasms in the former. Although hereditary ovarian cancers tend to be of higher stage and grade than their sporadic counterparts, their clinical prognosis seems to be better (49,50).

Fallopian tube carcinoma is now a well-established component of the *BRCA*-related cancer spectrum, with relative risks (RRs) as high as 120 reported (51). Carriers of *BRCA1* mutations are at risk of primary papillary serous carcinoma of the peritoneum, a malignancy that is indistinguishable from serous epithelial ovarian carcinoma. The cumulative risk has been reported as 3.9%–4.3% at 20 years after oophorectomy (52,53). Candidate morphological (tubal intraepithelial carcinoma) and molecular (p53 overexpression colocalized with γ-H2AX, a marker of DNA damage) precursor lesions have been described in the tubal fimbriae, providing novel targets for early detection and prevention research (54). These findings have suggested that a substantial fraction of what has, in the past, been classified as "ovarian cancer" may actually represent primary fallopian tube carcinoma (55). Prostate cancer (RR = approximately 3) also occurs in male carriers of *BRCA1* mutations (56), although such cancers do not typically demonstrate a younger-than-usual age at diagnosis (57). It has been suggested that this risk of prostate cancer may vary substantially, depending on the location of the *BRCA1* mutation (58). A variety of other cancers have been inconsistently implicated as part of the *BRCA1* cancer susceptibility syndromes (59). The most convincing associations are increased risks of pancreatic cancer (60) and male breast cancer (61,62). The latter investigators report that the cumulative breast cancer risks to age 70 among male mutation carriers are 1.2% and 6.8% for *BRCA1* and *BRCA2*, respectively. Initial reports of increased colorectal cancer risk have generally not been replicated. The Breast Cancer Linkage Consortium reported statistically significantly elevated relative risks for cancers of the pancreas, uterine body, cervix, and prostate (only in carriers younger than age 65), with RRs of 2.3, 2.6, 3.7, and 1.8, respectively (63). The possibility that endometrial cancer might be a BRCA-related malignancy has been plausibly explained as related to tamoxifen exposure (64). Cancer risks in *BRCA1* mutation carriers have recently been reviewed (65).

Associated benign neoplasms: None known.

Cancer risk management: Management options for women with *BRCA1/2* mutations include training in breast self-examination (BSE), regular monthly BSE (starting at age 18), clinical breast examination twice yearly (starting at age 25), annual mammogram and breast magnetic resonance imaging (MRI; starting at age 25 or earlier in families with very early-onset breast cancer), individualized discussion of risk-reducing mastectomy, recommendation for risk-reducing salpingo-oophorectomy (ideally between ages 35 and 40 or upon completion of childbearing), and twice-yearly transvaginal ultrasound and CA-125 screening for women with intact ovaries (the latter despite the absence of proven clinical benefit). Male mutation carriers are recommended to learn and perform BSE (monthly); undergo twice-yearly clinical breast examination; and consider baseline mammogram, with annual repeat in the presence of gynecomastia or glandular breast density on the baseline examination. All patients should be advised regarding the genetic risk to relatives, urged to alert family members to the potential value of genetic risk assessment, and be educated regarding the signs and symptoms of BRCA-related cancers (adapted from National Comprehensive Cancer Network) (66). The management of hereditary breast cancer has been reviewed (67).

There is great interest in determining whether the breast and ovarian cancer risk factors that have been identified in analytic epidemiology studies targeting unselected cases of these cancers within the general population also exert similar effects in *BRCA1/2* mutation carriers [for reviews, see Narod (68) and Levy-Lahad and Friedman (65)]. In general, the data are inconsistent from study to study. However, analyses from a large international cohort of mutation carriers have suggested that early age at first birth does not confer the same reduction in breast cancer risk among mutation carriers as that seen in the general population (69), whereas parity (associated with reduced ovarian cancer risk in the general population) may be associated with an increased risk of hereditary ovarian cancer (70).

Additional considerations include the following:

- MRI of the breasts is substantially more sensitive as a breast cancer screening tool in young, high-risk women than mammography, ultrasound, or clinical breast examination, while maintaining high specificity as well (71). Breast MRI, in conjunction with mammography, is emerging as the screening strategy of choice for *BRCA1/2* mutation carriers. Based on evidence from nonrandomized screening trials and observational studies, the American Cancer Society has issued guidelines for breast screening with MRI and has recommended annual MRI (as an adjunct to mammography) in women 1) who have a *BRCA* mutation, 2) who are untested but who have a first-degree relative with a *BRCA* mutation, or 3) with an estimated lifetime risk of breast cancer that exceeds 20%–25% (72). Breast MRI screening is reported to be more cost-effective in *BRCA1* vs *BRCA2* carriers (73).
- There remains no proven benefit to *any* ovarian cancer screening strategy in either low- or high-risk women, and the very high false-positive rate inherent in standard screening techniques incurs substantial morbidity and economic cost. However, a single study of 424 women at high risk of hereditary ovarian cancer reported that both the absolute value and the serial change in CA-125 tumor marker levels were statistically correlated with ovarian cancer, although the absolute differences in CA-125 appeared to be quite small and of uncertain clinical utility (74); preliminary results using a panel of 6 biomarkers

suggests that a more sensitive clinical tool will be available in the future (75).

- Tamoxifen represents the first chemopreventive agent that might reduce the risk of breast cancer in *BRCA* mutation carriers. The value of chemoprevention as an alternative to risk-reducing mastectomy is unclear, although a gonadotropin-releasing hormone agonist–based regimen has been shown to significantly reduce mammographic density (a widely accepted breast cancer risk factor) in *BRCA1* mutation carriers (33). Although definitive data are not yet available, the evidence to date derives from the observed 50% reduction in the risk of contralateral breast cancer among *BRCA* mutation carriers receiving adjuvant therapy with tamoxifen for treatment of an initial breast cancer (76). This protective effect was observed in *BRCA1* as well as *BRCA2* carriers despite the predilection of the former to develop hormone receptor–negative breast cancer. As yet, there is no experience using raloxifene as a chemoprevention option in *BRCA* mutation carriers.
- Oral contraceptives appear to confer upon *BRCA* mutation carriers the same 50% reduction in ovarian cancer risk observed in the general population (77,70). Although preliminary evidence suggested that this effect can be achieved without increasing the risk of breast cancer (78), a subsequent analysis has demonstrated some increased risk of breast cancer in both *BRCA1* and *BRCA2* mutation carriers related to duration of oral contraceptive use, especially before the first full-term pregnancy (79).
- Bilateral risk-reducing mastectomy lowers the risk of breast cancer among *BRCA* mutation carriers by 90%–95% (80a), but this management option is selected by a minority of gene carriers. Approximately 20% of risk-reducing mastectomy surgical specimens will contain invasive or in situ carcinoma that was not apparent on preoperative imaging. Bilateral oophorectomy offers an alternative strategy as this procedure has been shown to reduce the risk of breast cancer by 50%–60% (80b, 81).
- In a series of 72 *BRCA* mutation carriers undergoing preventive removal of the ovaries and fallopian tubes, premalignant adnexal lesions were identified in 50% of women older than 40 years and 14% of women 40 years or younger at surgery (82). Bilateral risk-reducing salpingo-oophorectomy decreases the risk of developing ovarian cancer by 71%–96% among *BRCA* mutation carriers (53). This procedure must include removal of the fallopian tubes, given their increased cancer risk in this setting (83).
- Preliminary evidence suggests that bilateral oophorectomy may improve both overall survival and cancer-specific survival among *BRCA* mutation carriers (84).
- Neither late toxicity related to breast radiotherapy (85) nor acute toxicity related to breast cancer adjuvant chemotherapy (86) appear to be increased among *BRCA1/2* mutation carriers compared with sporadic breast cancer controls.
- A report from the United Kingdom raised the disturbing possibility that mutation-negative women from *BRCA* mutation-positive families could be as much as five times more likely to develop breast cancer than women from the general population (87). If correct, this observation raises major concerns regarding how to counsel women from high-risk families who are true negatives on genetic testing. Of note, the methodologically most appropriate subset in this study, that is, mutation-negative women who had not developed breast cancer before study entry, and who were then followed prospectively for breast cancer development, showed only a twofold increase in breast cancer risk, which was *not* statistically significant. The data related to this important question have been reviewed (88). The authors suggest that these women may, in fact, have a twofold increase in breast cancer risk and propose that being a mutation-negative member of a mutation-positive family may not exempt women from the usual risks associated with a positive family history of breast cancer. However, the data to support a modification of breast cancer screening guidelines for such patients are not yet in hand. There is evidence that these women tend to overutilize both breast and ovarian screening procedures despite their mutation-negative status (89).
- Kauff et al. (90) prospectively studied the risk of ovarian cancer in probands from 165 *BRCA1/2* mutation-negative site-specific breast cancer kindreds (ie, no relative had ovarian cancer). The standardized incidence ratio of ovarian cancer in the proband was not increased relative to the Surveillance, Epidemiology, and End Results population, suggesting that women from such families are not at increased risk of ovarian cancer. Further validation of this important observation is awaited.

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7. Breast/Ovarian Cancer, Hereditary (*BRCA2*)

OMIM number: 600185.

Inheritance pattern: Autosomal dominant.

Gene and chromosomal location: *BRCA2*, a tumor suppressor gene at 13q12.3, is central to the maintenance of genome stability through repair of double-stranded DNA breaks by homologous recombination (1). It is not genetically related to *BRCA1*; each has its own distinctive mechanisms of action.

Mutations: Nearly 1900 distinct mutations, polymorphisms, and variants have been reported (Breast Cancer Information Core: http://research.nhgri.nih.gov/bic/). The central portion of the *BRCA2* gene has been designated the Ovarian Cancer Cluster Region (nucleotides 3035–6629) because mutations located here (eg, the Ashkenazi founder mutation 6174delT) are twice as likely to be associated with ovarian cancer as are mutations at the 5′ or 3′ ends of the gene (2). The risk of breast cancer associated with mutations in this region is lower.

Incidence: (See *BRCA1* chapter for additional details.) In most clinical series, *BRCA2* mutations are outnumbered by *BRCA1* mutations two to one. *BRCA2* mutations have been identified in 25% of American families with three or more cases of female breast and/or ovarian cancer (values range from a low of 8% in Finland to a high of 64% in Iceland). In families with male and female breast cancer, *BRCA2* mutations were found in 19% of American families and in 90% of Icelandic families (3). *BRCA2* 999del5 is a founder mutation that has been detected in 38% of Icelandic men with breast cancer (n = 34) and in 10.4% of Icelandic women with breast cancer (n = 541) (4). In Ashkenazi Jewish women, the *BRCA2* 6174delT founder mutation is present in 8% of women diagnosed with breast cancer before the age of 42 years and in 1.5% of unselected Ashkenazi (5,6). Estimates of *BRCA2* carrier frequencies include 0.072% (7), and a recent population-based Canadian study finding the highest rate yet reported, 0.69%, or one in 145 (8). The carrier frequency for *BRCA1* and *BRCA2* combined in this latter series was one in 100, a much higher rate than the generally cited one in 800.

Diagnosis: (See *BRCA1* chapter for additional details.) Suspected on the basis of premenopausal breast cancer or a pedigree showing a constellation of *BRCA2*-associated cancers with possible dominant inheritance. The presence of male breast cancer or pancreatic cancer may be a clue pointing toward the involvement of *BRCA2*. Ovarian cancer is observed less frequently than in *BRCA1* carriers. Genetic testing is required to confirm that an individual carries a *BRCA* mutation. Several mutation carrier prediction models are available, aimed at identifying individuals who are likely to carry *BRCA1* and *BRCA2* mutations (see *BRCA1* Diagnosis section). In small families, these models are less useful.

Associated malignant neoplasms: (See *BRCA1* chapter for additional details.) Adenocarcinoma of the female breast (generally estrogen receptor positive, moderately differentiated) is the hallmark of *BRCA2*-related cancer. *BRCA2*-associated breast cancers are more likely to be high grade, of no special histological subtype, have pushing tumor margins, be estrogen receptor positive, and exhibit a luminal phenotype and less likely to express basal keratin or overexpress HER2/neu protein compared with sporadic breast cancers (9). A pooled analysis of 22 studies in which cases were unselected for family history provides the best average *BRCA2*-related risk estimates to age 70: breast cancer = 45% (95% CI = 33% to 54%) and ovarian cancer = 11% (95% CI = 4% to 18%) (10). Chen and Parmigiani (11) also conducted a meta-analysis of 10 studies that used methods to correct for ascertainment and reported cumulative cancer risks to age 70 for breast and ovarian cancers as 49% and 18%, respectively, for *BRCA2* mutation carriers. The penetrance of the Ashkenazi *BRCA2* 6174delT mutation for breast cancer by age 70 is 43% (95% CI = 14% to 62%), and the corresponding value for ovarian cancer is 20% (95% CI = 2% to 35%) (12). The breast cancer penetrance of the *Icelandic BRCA2* 999del5 mutation was 17% by age 50 and 37% by age 70, which is lower than other *BRCA2* reports (4). The risk of a contralateral breast cancer by age 70 was 52.3% (95% CI = 41.7% to 61.0%). Male breast cancer is more common in *BRCA2* than in *BRCA1* families. The cumulative probability to age 70 of male breast cancer in *BRCA2* mutation carriers has been reported as 6% (13) and 6.8% (14).

The risk of ovarian cancer, although lower than that observed in *BRCA1* mutation carriers, is still greatly increased compared with the rates in the general population. Ovarian cancer in *BRCA2* carriers is more likely to occur after age 50 than those found in *BRCA1* carriers (15). Fallopian tube carcinoma has also been associated with *BRCA2* mutations (16), as has primary papillary serous carcinoma of the peritoneum, a malignancy that is indistinguishable from serous epithelial ovarian carcinoma; like ovarian cancer, this malignancy occurs less frequently among *BRCA2* than *BRCA1* carriers (17). Prostate cancer (relative risks (RRs) = approximately 3) also occurs excessively in male carriers of *BRCA2* mutations (18), although *BRCA*-related prostate cancers do not typically demonstrate a younger-than-usual age at diagnosis (19). A recent, large, population-based analysis in Ontario, Canada, yielded *BRCA2*-related breast and ovarian cancer risk estimates to age 80 of 41% and 8.4%, respectively (8). The latter is the lowest ovarian cancer penetrance estimate yet reported.

The presence of pancreatic cancer in a breast cancer family may be a statistically significant predictor of a *BRCA2* mutation (20), although *BRCA1* carriers also have an increased risk. The Breast Cancer Linkage Consortium (21) reported statistically increased risks of cancers of the prostate (RR = 4.6), pancreas (RR = 3.5), gallbladder and bile duct (RR = 5.0), stomach (RR = 2.6), and melanoma (RR = 2.6). The latter three sites are inconsistently associated with *BRCA2* (22), and initial reports of increased colorectal cancer risk have generally not been replicated. Cancer risks in *BRCA2* mutation carriers have recently been reviewed (23).

Associated benign neoplasms: None known.

Cancer risk management: (See *BRCA1* chapter for additional details.) Management options for women with *BRCA1/2* mutations include training in breast self-examination (BSE), regular monthly BSE (starting at age 18), clinical breast examination twice yearly (starting at age 25), annual mammogram and breast magnetic resonance imaging (starting at age 25 or earlier in families with very early-onset breast cancer), individualized discussion of risk-reducing mastectomy, recommendation for risk-reducing salpingo-oophorectomy (ideally between ages 35 and 40 or upon completion of childbearing), and twice-yearly transvaginal ultrasound and CA-125 screening for women with intact ovaries (the latter despite the absence of proven clinical benefit). It is suggested that male mutation carriers learn and perform BSE (monthly), undergo twice-yearly clinical breast examination, and consider baseline mammogram, with annual repeat in the presence of gynecomastia or glandular breast density on the baseline examination. All patients should be advised regarding the genetic risk to relatives, urged to alert family members to the potential value of genetic risk

assessment, and be educated regarding the signs and symptoms of BRCA-related cancers [adapted from National Comprehensive Cancer Network (24)].

See the Management section in the *BRCA1* module for additional pertinent information about BRCA-related cancers. The fact that *BRCA2* carriers are substantially less common in most research studies has resulted in the evidence regarding the effectiveness of various intervention strategies (eg, oral contraceptives, tubal ligation, tamoxifen, etc) being substantially weaker than that for *BRCA1*.

Comment: Biallelic mutations in *BRCA2* have been shown to cause the D1 subtype of Fanconi Anemia [reviewed in Alter et al. (25,26)]. Affected individuals have extreme sensitivity to chemotherapy and therapeutic irradiation; full-dose treatment can be lethal. FANC-D1 patients have very high rates of spontaneous chromosomal instability and are at risk of Wilms tumor and medulloblastoma as well as the more typical acute leukemia [(26); reviewed by 27,28]. Biallelic mutations in *PALB2*, which encodes a BRCA2-interacting protein, have also been shown to cause a Fanconi anemia phenotype (FANC-N). Monoallelic truncating mutations in *PALB2* appear to function as a low-penetrance breast cancer susceptibility allele, conferring a 2.3-fold increase in breast cancer risk (29,30).

There is strong evidence to suggest substantial increases in *BRCA2*-related breast cancer penetrance over calendar time. In Iceland, the cumulative risk of breast cancer to age 70 rose nearly fourfold among patients diagnosed in 2002 (72%) vs those diagnosed in 1920 (18.6%) (31). This, and similar observations in *BRCA1* carriers (32), suggests that important environmental or lifestyle factors influence the underlying genetic predisposition to cancer.

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8. Carney Complex, Types I and II (formerly known as NAME Syndrome [Nevi, Atrial Myxoma, Myxoid Neurofibromata, and Ephelides] and LAMB Syndrome [Lentigines, Atrial Myxomata, Mucocutaneous Myxoma, Blue Nevi])

OMIM number: 160980, 605244, 188830, 610489.

Inheritance pattern: Autosomal dominant.

Gene and chromosomal location: Carney complex type 1 (CNC1) is due to mutations in *PRKAR1A* at 17q22–q24, detected in about 50%–65% of CNC cases and in a subset of patients with isolated primary pigmented nodular adrenocortical dysplasia (PPNAD) (see below) (1). A subset of families (approximately 30%) with CNC have been linked to chromosomal band 2p16 (CNC2), but the gene has not been identified.

Mutations: Kirschner et al. (2000) identified 15 distinct *PRKAR1A* mutations, most of which were truncating mutations, in 22 of 54 families. Large deletions were recently reported. About 70% of individuals diagnosed with CNC have an affected parent (1).

Incidence: Rare. Incidence is unknown.

Diagnosis: Stratakis et al. (2) established criteria for a clinical diagnosis of Carney complex (Table 9).

Laboratory features: Histological features of CNC-related cutaneous myxomas are similar to sporadic lesions.

Associated malignant neoplasms: Testicular tumors occur in one-third of boys with CNC and nearly all adult males. The tumors are large cell calcifying Sertoli cell tumors (LCCSTs) and Leydig cell tumors. In one series of 53 affected patients from 12 CNC families, two patients had thyroid carcinomas (one papillary and one follicular), one had colorectal carcinoma, and one had pancreatic cancer (3). Additional patients with CNC and pancreatic cancer have been identified since that report, so a syndrome-related predisposition to this malignancy now seems more likely.

Associated benign neoplasms: The skin is the most commonly affected organ, with about 80% of patients presenting one or more skin lesions: lentigines, compound nevi, blue nevi, café-au-lait macules, or cutaneous myxoma. The pigmented lesions may be present at birth and typically increase in number around puberty. Spotty cutaneous pigmentation is common, especially involving the face, eyelids, vermillion border of lips, conjunctiva, sclera, vulva, glans penis, back of hands, and feet. Buccal mucosa is uncommonly involved, unlike the pigmentation seen in Peutz–Jeghers syndrome. In CNC, the pigmented lesions include tiny black–brown macules, cafe-au-lait macules, blue nevi, and other pigmented lesions. In some individuals, pigmented lesions have been observed to fade with age. Pedunculated cutaneous myxomas were reported in 62% of CNC patients; these myxomas appear at a mean age of 18 years and are multicentric in 71% of patients (4).

In CNC patients who develop cardiac myxomas, cutaneous findings precede development of cardiac myxomas in 81% of patients (5). Cardiac myxomas (87% atrial and 13% ventricular) affect 72% of patients, are multiple in half of cases, and are recurrent in 18%.

Myxoid uterine leiomyomas also occur. PPNAD, with or without overt Cushing syndrome, is the most common endocrine manifestation of CNC, reported in 31%–40% of recognized patients. Pituitary adenomas are found in 10% of patients and were found to secrete growth hormone in 8%. Prolactin may be secreted, but isolated prolactinomas are not reported (6). Stratakis et al. (1997) studied the thyroid in Carney syndrome and found follicular thyroid adenomas in three of 53 patients. Thyroid sonography on five adults and six children, all of whom were clinically and biochemically euthyroid, detected hypoechoic, cystic, solid, or mixed lesions in 60% (3).

The presence of a calcifying pigmented neuroectodermal tumor (psammomatous melanotic schwannoma) is highly characteristic of CNC; it occurs in about 10% of patients. Breast duct adenomas, breast myxomas, and osteochondromyxomas of bone also occur. Carney complex has been recently reviewed (7).

Cancer risk management: For children with CNC, the following have been recommended: 1) echocardiography during the first 6 months of life and annually thereafter and 2) monitoring for aromatase excess resulting in increased estrogen levels among children with testicular calcification or known LCCSCT. For individuals with CNC after puberty, the following have been recommended: 1) annual echocardiogram; 2) annual determination of urinary free

Table 9. Diagnostic criteria for Carney complex (2)[a]

The patient must have at least two of the following:

- Spotty skin pigmentation with a typical distribution (often vermillion border of lips, conjunctiva and ocular canthi, vaginal or penile mucosa).
- Myxoma (cutaneous—often on the eyelid, external ear, nipple).
- Cardiac myxoma.
- Breast myxomatosis or fat-suppressed MRI findings suggestive of this diagnosis.
- PPNAD or paradoxical positive response of urinary glucocorticosteroids to dexamethasone administration during Liddle's diagnostic test for Cushing syndrome.
- Acromegaly due to GH-producing adenoma (somatotropinomas).
- LCCSCT of testis or characteristic calcification on testicular ultrasonography.
- Thyroid carcinoma or multiple hypoechoic nodules on thyroid ultrasonography in a young patient.
- Psammomatous melanotic schwannoma.
- Blue nevus, epithelioid blue nevus (multiple).
- Breast ductal adenoma (multiple) (or mammary tumor with intraductal papilloma).
- Osteochondromyxoma of bone (a histological diagnosis).

Additionally, a patient meeting only one of these criteria, but having either 1) an affected first-degree relative or 2) an inactivating mutation of the *PRKAR1A* gene, satisfies the diagnostic criteria (4).

[a]MRI = magnetic resonance imaging; PPNAD = primary pigmented nodular adrenocortical dysplasia; LCCSCT = large cell calcifying Sertoli cell tumor; GH = growth hormone.

cortisol or overnight 1 mg dexamethasone suppression test; 3) annual measurement of plasma IGF-1; 4) baseline thyroid ultrasound, with repeat as needed (this may be of less value in older individuals); 5) baseline testicular ultrasound (minute calcifications may be followed annually); 6) ovarian ultrasound at baseline, with repeat not indicated unless abnormality detected, as risk of malignancy is judged to be low. Additional biochemical studies and imaging studies may be needed to adequately evaluate adrenal and pituitary function and as an aid in establishing the diagnosis in the first place. The risks and benefits of screening in this disorder are unknown. It has been suggested recently that male infertility should be considered a component of CNC (8).

Comments: Dr. Aidan Carney is also known for the identification of a clinical triad called Carney triad, which is *unrelated* to Carney complex. It is characterized by gastrointestinal stromal tumor, functioning extra-adrenal paraganglioma, and pulmonary chondroma. Any two of these three findings are considered sufficient for diagnosis. No gene has yet been implicated in its etiology. In a series of 79 patients with Carney triad, only two had relatives with features of the triad. These two had only paraganglioma and gastointestinal stromal tumors (GIST). Stratakis and Carney designated this a "dyad" (Stratakis-Carney Dyad), and it is now known to be distinct from the triad; [(9) see Paraganglioma chapter for details]. Thirty-seven Carney triad patients were studied for mutations in other genes related to risk of paraganglioma (*SDHB*, *SDHC*, *SDHD*) and GIST (*C-KIT*, *PDGFRA*) seeking a genetic basis for this disorder; no germline mutations were detected in any of these genes (10).

Mutations disrupting a phosphodiesterase gene called *PDE11A* were found in individuals with adrenal cortical hyperplasia and Cushing syndrome, as well as PPNAD; population studies suggest this is a low-penetrance predisposition gene. Mutations in *PDE11* have not been associated with Carney complex (11).

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9. Chordoma, Familial

OMIM number: 215400.

Inheritance pattern: Stepanek et al. (1) reported a multigeneration family with male-to-male transmission suggesting autosomal dominant inheritance with reduced penetrance.

Gene and chromosomal location: Using the extended pedigree of this family, Kelley et al. (2) identified a putative familial chordoma susceptibility locus on chromosome 7q33. This observation has been confirmed by Yang et al. (3), who also described a new family *not* linked to this locus, suggesting locus heterogeneity. Interphase fluorescent *in situ* hybridization studies have suggested that an as-yet-unidentified gene on chromosome 6p12 may be responsible for some instances of familial chordoma (4).

Mutations: Unknown.

Incidence: Overall age-adjusted incidence of all chordomas is 0.08 per 100 000 in the United States; it is more common in males than in females (5). Incidence of inherited disease is unknown.

Diagnosis: Diagnosis is based on family and medical history. In the initial family, several clinically normal individuals in their 60s had lesions detected by magnetic resonance imaging (MRI). Tumors may become symptomatic in the second decade of life or much later. Chordomas are very difficult to diagnose because they grow slowly and may present ambiguous symptoms (eg, headaches and facial pain, dysphagia, extremity weakness, bowel or bladder symptoms) as well as localizing symptoms [eg, diplopia, painful sacral mass, altered sacral sensation (6)]. Because it arises from notochordal remnants, chordoma is found almost exclusively along the axial skeleton.

Laboratory features: Juliao et al. (7) reported that galectin-3 immunohistochemistry staining of tumor tissue was 75% sensitive and 92% accurate in confirming the diagnosis. Rich et al. (8) reported that reticulin staining helped differentiate chordoma from other tumors, particularly adenocarcinoma.

Associated malignant neoplasms: Chordomas; recently two cases with pilocytic astrocytoma (one patient in each of two families) have been presented at scientific meetings, suggesting that this rare tumor may be part of the familial chordoma syndrome.

Associated benign neoplasms: Rich et al. (8) reported that two of 50 chordoma cases were benign (4%) and cited a 2% incidence from the literature.

Cancer risk management: None has been defined. Based on the reported family, we suggest that MRI of the entire craniospinal axis be performed at the time the familial aggregation is identified. A baseline examination is advised in childhood, with the frequency of repeated examinations uncertain (perhaps every 3–5 years in asymptomatic individuals).

Comments: Chordoma, presenting in infancy, is also part of the tuberous sclerosis complex (see Tuberous Sclerosis chapter).

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10. Colon Cancer, Hereditary Nonpolyposis–Lynch Syndrome (includes Lynch Syndrome, Hereditary Mismatch Repair Deficiency Syndrome, Muir–Torre Syndrome, and a subset of Turcot Syndrome)

OMIM numbers: 609310, 276300, 608089, 158320, 120436, 120435, 609309, 600258, 600259, 600678, 600887.

Inheritance pattern: Autosomal dominant; mutation homozygosity has been reported (see "Comments").

Gene and chromosomal location: *MLH1* at 3p21.3, *MSH2* at 2p21–p22, *PMS1* at 2q31–q33, *PMS2* at 7p22, *MSH6* at 2p16, *MSH3* at 5q11–q12. The products of these genes participate in a multimeric DNA mismatch repair complex. Syndrome-related deleterious germline mutations have clearly been documented for *MLH1*, *MSH2*, *MSH6*, and *PMS2*. The role of *MSH3* and *PMS1* in hereditary disease remains unclear.

Mutations: Mutations in *MLH1* and *MSH2* account for more than 90% of the 448 mutations in Lynch syndrome families in the database of the International Collaborative Group on Hereditary Non Polyposis Colon Cancer (1), with MSH6 accounting for 7%. In the largest population study in the United States, Hampel et al. (2) found the following distribution of mutations among 23 probands identified among 1066 individuals with colorectal cancer (CRC): *MLH1* (22%), *MSH2* (56%), *MSH6* (13%), and *PMS2* (9%). Large deletions and/or duplications account for 5%–10% of *MLH1* mutations and more than 20% of *MSH2* mutations. A database of mismatch repair gene variants of all types is available (http://www.med.mun.ca/MMRvariants/default.aspx) (3).

Incidence: HNPCC specifically due to deleterious mutations in DNA mismatch repair genes, hereafter called Lynch syndrome (to distinguish from a pedigree-defined or genetically uncharacterized cluster), accounts for 2%–3% of all CRCs (2,4). Approximately 2% of all endometrial cancer patients are also reported to have Lynch syndrome (5). Genetic modifiers of cancer risk in Lynch syndrome have been described. Short *IGF1* CA repeats were associated with a 2.4-fold increase in CRC risk and a 10–12 year earlier age at CRC diagnosis (6). An *RNASEL* gene variant was also associated with earlier age at diagnosis among CRC cases (7).

Diagnosis: In the past, diagnosis was based on pedigree assessment. The Amsterdam I criteria (AC-I) were developed in 1991 to assist in defining a subset of families for *research* purposes (8). These criteria have proven to be overly restrictive for *clinical* purposes because up to 39% of mutation-positive Lynch syndrome families do not meet AC-I criteria. Conversely, up to half the families that *do* fulfill the AC-I criteria do *not* have a detectable DNA mismatch repair defect and therefore do not have Lynch syndrome. Such families have been called familial CRC type X (9). AC-I criteria require all four of the following: 1) three or more cases of CRC, in which two of the affected individuals are first-degree relatives of the third; 2) CRCs occurring in two generations; 3) one CRC diagnosed before the age of 50 years; and 4) exclusion of familial adenomatous polyposis (FAP).

The Bethesda Guidelines [updated Umar et al. (10)] were developed to improve identification of individuals with Lynch syndrome. Patients meeting the Bethesda Guidelines were to be offered tumor testing for microsatellite instability (MSI). A high level of MSI, or loss of expression of a DNA mismatch repair protein by immunohistochemistry (IHC), comprise tumor phenotypes that indicate defective DNA mismatch repair. The likelihood of detecting a germline mutation in *MLH1* or *MSH2* is low if the colorectal tumor does not have this tumor phenotype. The tumor phenotype from *MSH6*-positive patients is more variable (MSI-stable, -low, or -high). The updated 2004 Bethesda Guidelines state that colorectal tumor MSI testing should be offered if any of the following criteria are met: 1) CRC diagnosed younger than age 50; 2) synchronous or metachronous CRC or other "HNPCC-associated" tumor (see below), regardless of age at diagnosis; 3) CRC diagnosed in a patient younger than age 60 with characteristic histology indicative of an MSI-high tumor (no consensus on this age cutoff); 4) a patient with CRC who has one or more first-degree relative with CRC or other "HNPCC-related tumor," with one of the cancers in the relative diagnosed younger than age 50; or 5) a patient with CRC who has two or more first- or second-degree relatives with CRC or other "HNPCC-related" tumor, regardless of age. For this guideline, "HNPCC-related" tumors included colorectal, endometrial, gastric, ovarian, pancreas, ureter, renal pelvis, biliary tract, and small bowel carcinoma, as well as brain and sebaceous skin tumors. Several mathematical models have now been published that predict the likelihood of carrying a mismatch repair gene mutation (11–13). In addition, a pathology-based model also demonstrated the usefulness of the histological features of MSI for selection of cases for further evaluation for possible Lynch syndrome (14).

Laboratory features: Clinical germline mutation analysis is available for *MLH1*, *MSH2*, *MSH6*, and *PMS2*. The presence of an MSI-high phenotype can be suggested by the histological appearance of the CRCs in Lynch syndrome (eg, poorly differentiated, presence of tumor-infiltrating lymphocytes, mucinous histology). Most colorectal tumors due to hereditary mismatch repair deficiency show a high level of MSI. However, this tumor phenotype is not specific for germline mutations in the DNA mismatch repair genes because age-related methylation of *MLH1* also leads

to the MSI-high phenotype; in unselected series of CRC patients, the latter accounted for the majority of MSI-high tumors. Clinical selection for MSI/IHC testing may be limited to patients with a presentation suggestive of Lynch syndrome, as suggested by the Bethesda Guidelines (10,15).

Immunohistochemistry stains (IHC) for expression of DNA mismatch repair proteins are complementary to MSI testing: loss of expression of *MLH1*, *MSH2*, *MSH6*, or *PMS2* can provide both a rapid method for evaluating possible Lynch syndrome as well as suggesting which gene may be mutated in a given family. Loss of expression of one of the four mismatch repair (MMR) proteins nearly always means that the tumor will be MSI high (ie, predictive value of approximately 100%); however, normal expression does not completely exclude an MSI-high tumor (16). Loss of *MSH2* expression has high specificity for presence of a germline mutation in that gene, but loss of *MLH1* is far less specific. Further tumor testing for *MLH1* methylation or somatic *BRAF* mutations can help in interpreting loss of *MLH1* expression by IHC (17). Muller et al. (18) reported that in 58 of 71 cases, the MMR-deficient phenotype was detectable in colorectal adenomas from Lynch syndrome patients, consistent with impressions that polyp testing may be specific but is not as sensitive as CRC MSI testing.

Associated malignant neoplasms: CRC, two-thirds of which are located in the right side of the colon, with average age at diagnosis in the mid 40s, is the hallmark of Lynch syndrome. The risk of colon cancer appears to be greater in carriers of *MLH1* vs other MMR genes, but the overall risk of all cancers combined may be greatest with *MSH2* mutations. The lifetime risk of CRC is about 70% by age 70 in high-risk clinic series. The lifetime risk of endometrial adenocarcinoma is 30%–60%, with an average age at diagnosis also in the 40s. Aarnio et al. (19) reported lifetime risks of gastric, biliary tract, urinary tract, and ovarian carcinoma as 19%, 18%, 10%, and 9%, respectively. Mean ages at diagnosis of gastric cancer and ovarian cancer are 56 and 42.5 years, respectively. A trend toward increased risk of pancreatic cancer has been noted in some (but not all) studies. Small bowel carcinoma is also a syndrome-related malignancy, having been reported in mutation carriers of each of the four susceptibility genes (20). In one-third of this series of 85 HNPCC patients with MMR mutations and small bowel cancer, the latter was the first HNPCC-associated malignancy identified. Small bowel cancer–associated *MSH2* mutations clustered in codons 626–733.

MSH6 appears to have later age at diagnosis of CRCs (mean range = 49–64) and endometrial cancer (mean range = 53–61); *MSH6* germline mutations have been reported to result in higher risk of endometrial cancer (lifetime risk of approximately 70%) and lower penetrance for the other Lynch syndrome–related tumors (21–25). In a North American population, cumulative risks to age 70 for CRC in males were 25% (95% CI = 18% to 34%); female CRC, 19% (95% CI = 14% to 26%); endometrial cancer, 39% (95% CI = 27% to 54%); male other-Lynch cancers, 3% (95% CI = 0% to 18%) and female other-Lynch cancers, 11% (95% CI = 6% to 20%). The risk to age 70 of any Lynch cancer was 26% in males and 49% in female carriers of deleterious mutations in *MSH6* (26).

Describing the phenotype of germline *PMS2* carriers has been hampered by its rarity and technical issues involving a pseudogene. Recently, Senter et al. (27) studied 99 individuals with Lynch-associated cancers in which tumors showed isolated loss of *PMS2* by IHC. Germline mutations were found in 62% (55 monoallelic; six biallelic). Of the monoallelic carriers, 9% met Amsterdam I or II criteria and 65.5% met Bethesda Guidelines. Penetrance for CRC to age 70 was 15% for men and 21% for women. Mean ages at CRC diagnosis were 61 and 64 years for male and female carriers, respectively, in population-based registries, compared with 47 and 63 years in clinic-based registries. *PMS2*-related CRCs tended to be right-sided and to have an MSI-high phenotype, like other Lynch syndrome genes. Penetrance for endometrial cancer was 8%–16% at mean ages of 49 and 52 in population-based vs clinic-based registries.

PMS2 mutations, particularly biallelic, have been reported in families with the Turcot syndrome variant of HNPCC (see "Comments").

Sebaceous neoplasms of the skin are a feature in a subset of Lynch syndrome families. Benign or malignant (carcinomas) sebaceous skin tumors in combination with Lynch syndrome–related internal cancer have been called Muir–Torre syndrome; linkage and mutational analysis of *MSH2* (most common), *MLH1*, and *MSH6* have proven that Muir–Torre syndrome is a variant of Lynch syndrome. Glioblastoma is also associated with Lynch syndrome. Brain tumor in combination with colorectal carcinoma is also called Turcot syndrome. Patients with Familial Adenomatous Polyposis have an increased risk of medulloblastoma, and this, confusingly, has also been called Turcot syndrome.

Associated benign neoplasms: Colonic adenomas, keratoacanthomas, sebaceous adenomas, Fordyce granules (intraoral ectopic sebaceous glands), and epitheliomas.

Cancer risk management: Consensus recommendations from experts (28–31) advise colonoscopy with removal of polyps every 1–2 years, beginning between ages 20–25, or 10 years before the earliest age of CRC diagnosis in the family, whichever is younger. Periodic removal of polyps reduces the incidence of CRC in individuals with Lynch syndrome (32). Prophylactic surgery has not been routinely recommended for individuals at risk of CRC because colonoscopy is an effective preventive measure. Subtotal colectomy with ileorectal anastamosis has been advised by some experts if a colon cancer is detected because of the very high rate of metachronous CRC (up to 30% in some series). Patient preferences and likely compliance with medical recommendations are very important in decisions regarding the choice of prophylactic surgery vs screening. The nonsteroidal anti-inflammatory drug celecoxib has been shown to reduce the prevalence of adenomatous polyps in FAP and in patients who have undergone a prior polypectomy in the absence of cancer (33). Small pilot studies have suggested that celecoxib (34) may reduce polyp prevalence in HNPCC, whereas sulindac does not (35). Its use does *not* replace colonoscopic screening.

Endometrial and ovarian cancer surveillance could include annual Pap smear, pelvic examination, annual transvaginal ultrasound, and/or endometrial biopsy and CA-125 blood test beginning between 25 and 30 years of age. Two prospective observational screening studies have shown that clinically unsuspected endometrial cancer can be diagnosed in women from HNPCC families using transvaginal ultrasound with endometrial biopsy and/or

flexible hysteroscopy, although a survival advantage has not yet been demonstrated (36,37). Both direct visualization of the endometrium and endometrial biopsy seemed superior to transvaginal ultrasound in these nonrandomized studies. Oral contraceptives are associated with substantial reductions in the risk of both endometrial and ovarian cancer risks in the general population, but this has not been demonstrated in Lynch syndrome. New evidence from a retrospective study of 315 women documents that prophylactic removal of uterus and ovaries after childbearing is completed essentially eliminated the risk of cancer in these organs during the 10 years of follow-up and therefore is a reasonable option for women with Lynch syndrome to consider (38). The value of screening for ovarian cancer in Lynch syndrome has not been proven.

Upper gastrointestinal endoscopy could be used to screen for gastric and ampullary neoplasms and has been advised by some experts, although one study reported no benefit because of the lack of precursor lesions (39). Annual urinalysis and cytology for screening to detect cancer of the renal pelvis is inexpensive, noninvasive, and therefore generally advised, but evidence of efficacy is lacking. Presently, no specific screening for cancers of the pancreas, hepatobiliary tract, or brain is recommended. Small bowel carcinoma has been diagnosed in this setting with capsule endoscopy (40). A careful examination of the skin should be included in the annual examination. Reviews of Lynch syndrome and suggested management have recently been published (41,42,30,31).

Comment: Rare patients who have biallelic germline MMR mutations have been reported, involving *MSH2*, *MLH1*, and, most frequently, *PMS2*. Affected individuals have café-au-lait macules, like those seen in neurofibromatosis, and early-onset hematologic and/or brain malignancies, in addition to very early-onset Lynch syndrome spectrum tumors (43).

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11. Costello Syndrome; Facio–Cutaneous–Skeletal Syndrome

OMIM number: 218040, 190020.

Inheritance pattern: Autosomal dominant, with more than 80% due to de novo mutations. Rare reports of affected sibs and/or mild features reported in parent are likely due to gonadal and/or somatic mosaicism.

Gene and chromosomal location: *HRAS* at 11p15. This gene is in the *Ras/MAPK* pathway, explaining the notable phenotypic overlap with other disorders caused by mutations in genes that affect this pathway, including cardiofaciocutaneous syndrome (OMIM #115150; *KRAS*, *BRAF.MEK2*, and *MEK1* genes), Noonan syndrome (OMIM #163950; *PTPN11*, *BRAF*, *RAF1*, *KRAS*, *SOS1* genes), neurofibromatosis type 1 (OMIM #162200; *NF1* and *SPRED1* genes), and LEOPARD syndrome (OMIM #151100; *PTPN11* and *RAF1* genes) (1–3). The relationship between these complex disorders has recently been reviewed (3).

Mutations: Mutations found in about 80%–90% of patients with Costello syndrome, of which a specific 34G→A transition in codon 12 (G12S) accounts for about 90% (4–6). In nine informative families, de novo mutations were inherited from the father in all cases, which were also associated with advanced paternal age (7). Prior studies have suggested a predominance of paternal origin of point mutations in numerous autosomal dominant disorders, presumably due to greater opportunity for mitotic errors in spermatogonia.

Incidence: Unknown. One hundred fifteen cases reported through 2003.

Diagnosis: The prenatal phenotype includes overgrowth, edema, and polyhydramnios. Postnatal features include mild-to-severe developmental delay, feeding difficulty often requiring feeding tubes, failure to thrive, hypotonia, hoarse voice, macrocephaly, coarse facies, prominent forehead, epicanthal folds, nystagmus, downslanting palpebral fissures, short nose with depressed nasal bridge, thick lips, low-set ears with thick helices, curly, sparse hair, soft loose skin, hyperkeratotic palms and soles with deep creases, and hyperpigmentation. Cardiac findings may include structural defects (especially pulmonic stenosis), hypertrophic cardiomyopathy, and conduction abnormalities. Musculoskeletal findings may include incomplete range of motion at the elbow, tight heel cords, ulnar deviation of the hands, small joint laxity, and broad distal phalanges. Warts in unusual locations are one of the defining features of the syndrome (8). Hennekam (9) reviewed all described cases through 2003. Costello syndrome has been recently reviewed (10).

Laboratory features: Elevated catecholamine metabolites in serum and urine have been reported in a number of Costello patients in whom no tumor could be identified. Thus, caution is needed in interpretation of catecholamine tests in this population (11).

Associated malignant neoplasms: Seventeen percent of 100 known patients with Costello syndrome have had solid tumors (12). Rhabdomyosarcoma (usually embryonal) is the most common, accounting for more than half of those reported; 80% occurred in the abdomen, pelvis, or urogenital area. Transitional cell carcinomas of the bladder are also reported in childhood (often before puberty) and are now accepted as part of the tumor predisposition spectrum. Among two adults with Costello syndrome, both had bladder tumors. No other cancers have been reported in affected adults (13). Neuroblastoma, hepatoblastoma, ganglioneuroblastoma, and vestibular schwannoma have also been reported. A genotype–phenotype correlation has been suggested, with the risk of cancer appearing greater in carriers of the gly12-to-ala (G12A) substitution (four of seven; 57%) vs the common gly12-to-ser (G12S) mutation (four of 57; 7%) (8). There is a mutational hotspot in *HRAS* involving codons 12 and 13 (6).

Associated benign neoplasms: Papillomata develop throughout childhood in the perioral and perianal areas. Benign bladder tumors and multiple intraductal papillomas of the breast have been reported.

Cancer risk management: The issues related to cancer surveillance in this rare syndrome have been reviewed (14). Screening the abdomen and pelvis with ultrasound for rhabdomyosarcoma and abdominal neuroblastoma is suggested every 3–6 months from infancy until age 8–10 years; urine catecholamine metabolite analysis is indicated only if clinical symptoms or imaging studies suggest possible neuroblastoma because current evidence suggests a very high rate of false-positive tests in Costello syndrome. Annual urinalysis to screen for bladder carcinoma after age 8 years is suggested,

with aggressive follow-up of any abnormal finding. Urine fluorescent in situ hybridization for aneuploidy detection in exfoliated urothelial cells may also be considered for screening for urinary tract tumors. The efficacy of these screening strategies is unknown.

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12. Cowden Syndrome (Multiple Hamartoma Syndrome; PTEN Hamartoma Tumor Syndrome)

OMIM number: 158350, 601728.

Inheritance pattern: Autosomal dominant.

Gene and chromosomal location: *PTEN* at 10q23.3.

Mutations: Mutations in *PTEN* have been found in 80% of Cowden syndrome (CS) patients who meet the clinical diagnostic criteria reported by Liaw et al. (1). Haplotype analysis suggests that mutation-negative patients may harbor deleterious *PTEN* mutations that are not detected by standard genetic testing methods (4). In *PTEN* sequencing-negative, clinically positive CS, approximately 10% have large deletions and approximately 10% have promoter mutations, which require alternate analytic techniques for their detection (2). Only 10%–50% of individuals have an affected parent (3).

Incidence: Nelen et al. (5) estimated incidence of approximately one in 200 000 to one in 250 000 live births in The Netherlands.

Diagnosis: The International Cowden Syndrome Consortium Operational Criteria are provided in Table 10 (6). CS is probably most often recognized clinically on the basis of skin lesions and intestinal hamartomas (7).

Table 10. Diagnostic criteria for Cowden syndrome (6)[a]

Pathognomonic criteria	Major criteria	Minor criteria
• Mucocutaneous lesions • Trichilemmomas, facial • Acral keratoses • Papillomatous papules • Mucosal lesions	• Breast carcinoma • Thyroid carcinoma (non-medullary), especially follicular • Macrocephaly (megalencephaly) (≥97th centile) • LDD[b]—a glial cerebellar mass • Endometrial carcinoma	• Other thyroid lesions (eg, adenoma or multinodular goiter) • Mental retardation (IQ ≤ 75) • Gastrointestinal hamartomas • Fibrocystic disease of the breast • Lipomas • Fibromas • GU[b] tumors (eg, renal cell carcinoma, uterine fibroids) or malformation
Operational diagnosis in an individual	1. Mucocutaneous lesions alone if: • There are six or more facial papules, of which three must be trichilemmomas or • cutaneous facial papules and oral mucosal papillomatosis or • oral mucosal papillomatosis and acral keratoses or • palmoplantar keratoses, six or more 2. Two major criteria but one must include macrocephaly or LDD 3. One major and three minor criteria 4. Four minor criteria	
Operational diagnosis in a family where one person is diagnostic for Cowden syndrome	1. The pathognomonic criterion or criteria 2. Any one major criterion with or without minor criteria 3. Two minor criteria	

[a]Operational diagnostic criteria are reviewed and revised on a continuous basis as new clinical and genetic information becomes available.

[b]LDD = Lhermitte–Duclos disease, GU = genitourinary.

Laboratory features: None specific to CS.

Associated malignant neoplasms: Studies have convincingly demonstrated an increased risk of female breast cancer (30%–50% lifetime risk; age range = 14–65 years), occurring about 10 years younger than in the general population. Male breast cancer also can occur. An elevated lifetime risk of thyroid cancer (5%–10%) has also been identified for both male and females. Follicular histology predominates, but papillary carcinomas have been reported. Experts cite a 5%–10% risk of endometrial cancer and an increased but unquantified risk of renal cancer (8,9). A much longer list of cancers has been reported in the context of CS, but the rarity of CS makes it difficult to prove that specific risks are different from those in the general population. The list includes glioblastoma, melanoma, Merkel cell cancer, lung cancer, retinal glioma, liposarcoma, and cancers of the colorectum, liver, pancreas, ovary, and bladder (10). Single case reports also note ependymoma, medullary thyroid cancer, granulosa cell tumor of the ovary, and lipoblastoma (11–13).

Associated benign neoplasms: Verrucous skin lesions of the face and limbs and cobblestone-like hyperkeratotic papules of the gingiva and buccal mucosa. In a series of patients with clinical diagnosis of CS, examination of more than half of biopsied skin lesions revealed facial trichilemmomas; all oral mucosal lesions were fibromas, and all hand and foot lesions were hyperkeratoses (14). Sixty percent of affected individuals had hamartomatous polyps of the stomach, small bowel, and colon. The polyps resemble those found in juvenile polyposis but are dissimilar from those observed in Peutz–Jegher syndrome. Sweet et al. (15) studied 49 unrelated patients with unexplained hamartomatous or hyperplastic and/or mixed polyposis and reported finding three *PTEN* mutations. Lipomas, cerebellar gangliocytomatosis, hemangiomas, and multiple early-onset uterine leiomyomas are common in CS. An intradural ganglioneuroma, inverted follicular keratosis, a pulmonary sclerosing hemangioma, multiple vertebral hemangiomas, and eccrine angiomatous hamartoma have each recently been reported. Tan et al. (11) reported on the spectrum of vascular abnormalities in 26 patients with PTEN mutations and concluded that they are typically multifocal intramuscular combinations of fast-flow channels and ectopic fat. Cerebral developmental venous anomalies are quite common.

Schrager et al. (16) examined breast tissue from 19 symptomatic women with CS and demonstrated a spectrum of benign histopathological findings including ductal hyperplasia, intraductal papillomatosis, adenosis, lobular atrophy, hamartomas, fibroadenomas, and fibrocystic change. A common benign breast lesion in this series was a densely fibrotic hyalinized nodule, whereas the most frequent breast malignancy was ductal carcinoma.

A recent report has suggested that, like Multiple Endocrine Neoplasia Type 2B, CS may manifest mucocutaneous neuromas (17).

Cancer risk management: The efficacy, risk, and benefits of cancer screening in CS are unknown. Monthly breast self-examination and annual clinical breast examination starting at age 18 years have been suggested. Annual mammography is recommended to begin at age 30 or 5 years younger than the earliest breast cancer in the family. No studies have assessed efficacy of breast magnetic resonance imaging (MRI), chemoprevention (eg, tamoxifen), or prophylactic mastectomy in CS. Nonetheless, based on expert consensus opinion, the American Cancer Society currently recommends annual MRI screening of the breasts as an adjunct to mammography in women with Cowden and Bannayan–Riley–Ruvalcaba syndromes and their first-degree relatives (18). Careful palpation of the thyroid gland on an annual basis beginning in adolesence has been suggested. The role of thyroid ultrasound is unclear, but a baseline examination in the early 20s may be considered, with periodic reexamination as guided by family history or physical examination. Surveillance for endometrial cancer by ultrasound and/or endometrial biopsy has been suggested to begin at age 35–40 or 5 years before the earliest endometrial cancer in the family. An annual urinalysis has been suggested, supplemented by cytology and renal ultrasound if there is a family history of renal cell cancer. At present, screening of other organs is advised as per standard American Cancer Society guidelines. Guidelines are regularly updated at http://www.genetests.org/.

Comments: Marsh et al. (19) showed CS to be allelic with Bannayan–Riley–Ruvalcaba syndrome (OMIM #153480: BRR syndrome; macrocephaly, multiple lipomas, speckled penis, and hemangiomata) (19). Approximately 60% with patients with BRR have detectable *PTEN* mutations. Current data suggest that CS and BRR represent one condition with variable expression and age-related penetrance (20). Germline mutations in *PTEN* are also present in some cases of Proteus syndrome and in individuals with the combination of autism and macrocephaly (OMIM 605309) (21–23). It has been suggested that *PTEN* Hamartoma Tumor Syndrome is an apt term encompassing CS, BRR, Proteus, and Proteus-like syndromes (24).

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13. Dyskeratosis Congenita

OMIM number: 127550, 300126, 300240, 305000, 224230, 187270, 602322, 606471, 604319.

Inheritance pattern: Predominantly X-linked recessive (>50%); autosomal dominant (5%), recessive (10%), or undetermined inheritance also occur.

Gene and chromosomal location: X-linked recessive dyskeratosis congenita (DC) is due to mutations in *DKC1*, Xq28, which encodes the protein, dyskerin, a small nucleolar RNA functionally associated with the RNA component of *TERC*. Autosomal dominant DC is due to telomerase RNA component, *hTR/TERC*, 3q21–q28 or to telomerase reverse transcriptase, *TERT*, 5p15.33. Biallelic mutations in *TERT* have been associated with an autosomal recessive or apparently sporadic pattern of DC (1,2). *NOP10* (*NOLA3*), 15q14–q15, has been implicated as the etiologic basis of DC in one large consanguineous family (3). It produces a protein component of H/ACA snoRNP complexes that include telomerase and dyskerin. *TINF2*, chromosome 14q11.2, a component of the telomere-related shelterin complex, has been identified as the newest DC gene (autosomal dominant) (4). Thus, the five genes identified as predisposing to DC are all members of the telomere maintenance pathway and together account for approximately 75% of all DC families.

Mutations: In families with X-linked DC, the majority of mutations in *DKC1* result in single amino acid substitutions in the dyskerin protein. One mutation, causing an alanine-to-valine substitution at position 353, accounts for 30% of X-linked DC, and it can arise as a de novo event. No genotype–phenotype correlations have been observed with specific mutations. Mutations in *TERC* include large intragenic and terminal deletions, a small frameshift mutation, and point mutations often resulting in haploinsufficiency for functional telomerase. These mutations do not account for all autosomal dominant DC. *TERC* deletions are associated with progressive telomere shortening, resulting in clinical anticipation with more severe disease presenting at an earlier age in successive generations (5–7). A single kindred with clinical DC and a germline mutation in *TERT* in an affected mother and her identical twin sons has recently been reported (8).

Incidence: Rare.

Diagnosis: Clinical gene testing is available for mutations in *DKC1* and *TERC*. DC is a multisystem disorder characterized by the classic triad of nail dystrophy, lacey reticular skin hyperpigmentation or generalized hyperpigmentation, and mucosal leukoplakia. Bone marrow failure is frequent and is the principal cause of death. Other abnormalities include short stature, premature loss of hair and teeth, hyperhidrosis of palms and soles, telangiectasiae, hair tufts with hyperkeratotic plugs, keratinized basal cell papillomas, pulmonary fibrosis, esophageal stricture, urethral stricture, liver disease, gastrointestinal abnormalities, and increased predisposition to cancer, particularly squamous cell carcinomas of the head and neck and acute myelogenous leukemia [recently reviewed by Kirwan and Dokal (9)]. Because most of the affected tissues are characterized by rapidly dividing cells, DC shares features with premature aging syndromes (eg, Werner syndrome) and other bone marrow failure syndromes (eg, Fanconi anemia [FA]). In fact, DC may be mistaken for FA (10). Diagnosis may be difficult because of the clinical and genetic heterogeneity of DC [reviewed by Handley et al. (11)]. Age at onset and severity of the cutaneous and noncutaneous features are highly variable; in some cases, patients may present with noncutaneous manifestations, including aplastic anemia or solid tumors, before developing the characteristic integumental features. The diagnosis of squamous cell carcinoma of the head and neck in a young, nonsmoking, nondrinking adult warrants seeking the presence of an unrecognized cancer susceptibility disorder such as DC or FA.

Autosomal dominant DC appears to have milder manifestations compared with the X-linked and autosomal recessive forms, which may present with more frequent physical anomalies and earlier onset of aplastic anemia.

In vitro cellular sensitivity to clastogens will distinguish between DC (absent) and FA (present) patients (see "Fanconi Anemia"). Identification of skewed X-chromosome inactivation patterns in peripheral blood cells of women from DC families can differentiate X-linked from autosomal forms of the disease, distinguish inherited mutations from de novo events in sporadic male DC

cases, and establish carrier status for the purpose of risk counseling (12).

Mutations in *DKC1* and homozygous *TERT* mutations have been detected in patients with the Hoyeraal–Hreidarsson syndrome (OMIM 300240), a severe variant of DC characterized by severe growth failure, cerebellar hypoplasia, aplastic anemia, and progressive immunodeficiency. Mutations in *TERC* as well as *TERT* have been described in cases of familial aplastic anemia without other features suggestive of DC and also are reported in families with autosomal dominant idiopathic pulmonary fibrosis with no features of DC (13). Finally, *TINF2* mutations have now been described both in Hoyeraal–Hreidarsson (HH) and in Revesz syndrome (OMIM 268130) (4). The latter is characterized by bone marrow failure and exudative retinopathy and has long been suspected to be part of the DC disease spectrum.

Laboratory features: Chromosomes from DC lymphocytes have no increased breakage in the presence of DNA-damaging agents. White cells from DC patients have *very* short telomeres (5,7), and a clinical assay (Flow-FISH) for this parameter has recently become available (14). Very short telomere length (ie, below the first percentile for age) has been proposed as a diagnostic screening test, analogous to the chromosome breakage test in FA, to identify DC patients in families without detectable mutations in one of the three genes and to distinguish DC from other hereditary bone marrow failure disorders (15).

Associated malignant neoplasms: Reported in approximately 10% of patients. These are predominantly acute myelogenous leukemia (AML) and carcinomas of the upper aerodigestive tract, particularly squamous cell cancers of the head and neck and esophagus. Case reports of gastric, pancreatic, and rectal carcinoma, as well as malignant lymphoma, are of uncertain significance.

Associated benign neoplasms: Myelodysplasia occurs in DC patients with bone marrow failure; it may precede the development of AML. Leukoplakia commonly affects the oral mucosa and may evolve into squamous cell carcinoma. Leukoplakia occasionally is found in conjunctiva, urethra, or genital mucosa. Predisposition to fibrosis in DC may present as symptomatic esophageal or urethral stenosis.

Cancer risk management: No consensus. Hematopoietic stem cell transplantation is the only curative treatment for DC patients who develop severe bone marrow failure. However, conventional myeloablative conditioning regimens should be undertaken with extreme caution because DC patients are predisposed to frequent and severe early and late transplant-related complications, including sepsis, hepatic venoocclusive disease, and pulmonary fibrosis. The recognition that DC may occur without an obvious clinical phenotype, coupled with knowing that at least 25% of all families meeting the clinical criteria for DC do not have a detectable germline mutation in any of the five known genes, creates a potential dilemma when selecting bone marrow donors in such families. In this situation, measurement of telomere length by Flow-FISH may permit identification of clinically occult DC patients, who can then be excluded as potential marrow donors (15).

Comments: The HH syndrome (OMIM 300240) is considered a severe variant of DC. Most of the germline mutations reported to date involve *DKC1*, which explains the male predominance in this condition (16).

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14. Esophageal Cancer, Tylosis with; Keratosis Palmaris et Plantaris with Esophageal Cancer; Howel–Evans Syndrome

OMIM number: 148500.

Inheritance pattern: Autosomal dominant, with complete penetrance by puberty.

Gene and chromosomal location: "Tylosis with oesophageal cancer" (TOC) has been linked to chromosomal band 17q25, and this condition is distinct from the other forms of palmoplantar keratoderma (PPK) that have been linked to the keratin gene cluster on chromosome 17.

Mutations: Unknown. A series of increasingly sophisticated genetic studies have repeatedly confirmed the linkage between the TOC locus and the tylosis trait, but extensive testing of candidate genes in this region has failed to identify a causative gene (1).

Current research is targeting less traditional mechanisms (such as epigenetic silencing) as possible explanations for the inability to identify the responsible gene (2).

Incidence: Very rare; a limited number of large families have been reported (3–5).

Diagnosis: PPK is a complex group of inherited disorders, subdivided into diffuse, punctate, and focal types, as determined by the pattern of skin thickening (hyperkeratosis) on the palms and soles. The diffuse subtype occurs in epidermolytic and nonepidermolytic forms, the latter being known as tylosis (6). It is this specific subgroup of PPK patients that is associated with a high risk of squamous cell carcinomas of the middle and distal esophagus. The hyperkeratosis in patients with tylosis is "late onset"; that is, after 1 year of age, ranging from 5 to 15 years of age. In one large Liverpool family, 32 of the 89 members with tylosis had died; 21 of the 32 died from esophageal cancer (3). The average age at diagnosis of esophageal cancer was 45 years; 95% of affected individuals developed this cancer by age 65. There may be a synergistic interaction between tobacco smoking and the risk of tylosis-associated esophageal cancer (4).

Laboratory features: No specific findings.

Associated malignant neoplasms: Squamous cell carcinoma of the esophagus.

Associated benign neoplasms: Mucosal leukoplakia.

Cancer risk management: Although the mean age at esophageal cancer diagnosis is 45 years, cases as young as 20 have been reported (3). We suggest that annual upper gastrointestinal endoscopy commences between ages 15 and 20 years in family members with tylosis or 5–10 years younger than the youngest case of esophageal cancer diagnosis in the family, whichever is younger. On general grounds, it is recommended that at-risk family members be counseled to avoid environmental risk factors for esophageal cancer, especially alcohol, tobacco, and vitamin A deficiency. The risks and benefits of cancer screening in this syndrome are not established.

Comments: Abstinence from tobacco exposure may reduce the risk of esophageal cancer, although proof of this in TOC is lacking. Families with severe gastroesophageal reflux and related Barrett's esophagus may also present with more than one case of esophageal cancer in the family; this entity is in the differential diagnosis of a family history of esophageal cancer. Selected geographic populations at increased risk of esophageal cancer include those found in parts of Russia, Turkey, Iran, and China. Tylosis does not seem to account for these clusters. A segregation analysis done in Linxian, China, supported the presence of an autosomal recessive gene in 19% of the population, accounting for 4% of the esophageal cancer in that region (7).

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15. Exostosis, Hereditary Multiple (includes Type 1, Type 2, Type 3, and Multiple Osteochondromas (Enchondromatosis)

OMIM number: 133700 and 608177 (EXT1), 133701 and 608210 (EXT2), 600209 (EXT3), 166000 (enchondromatosis).

Inheritance pattern: Autosomal dominant with nearly complete penetrance, especially in males.

Gene and chromosomal location: *EXT1*, *EXT2*, and *EXT3* are located at 8q24.11–q24.13, 11p11–p12, and 19p, respectively.

Mutations: More than 80 different mutations have been reported in *EXT1*, which accounts for 50%–76% of families with hereditary multiple exostosis (HME). Twenty-one to fifty percent of families have mutations in *EXT2*. A few families link to the *EXT3* locus; the gene has not been cloned—and a few are not linked to any of these three loci. About 10% of affected individuals have a de novo mutation. Overall mutation detection rate is about 85%–90%.

Incidence: Estimated prevalence ranges from 0.9 to 2 per 100 000 live births (in white populations). Among all individuals with chondrosarcoma, about 5% have HME.

Diagnosis: HME is characterized by multiple exostoses (osteochondromas), which are cartilaginous excrescences near bony diaphyses of the extremities, ribs, or scapulae (but not skull), that undergo ossification and sometimes result in deformity, pain, nerve compression, arthritis, or bowing (1,2). This disorder can be associated with mild short stature, and its penetrance is 96%. HME may be detectable at birth, but the median age at diagnosis is 3 years; nearly all affected individuals are identified by age 12. Growth of new or existing lesions stops with skeletal maturation. The diagnosis is established in the presence of multiple exostoses in an individual (average number is six). By several different measures, the *EXT1*-related phenotype is more severe than that associated with *EXT2* (3). Patients with *EXT1* mutations have more exostoses, more limb malalignment with shorter limb segments and height, and more pelvic and flat-bone involvement than those with *EXT2* mutations (4). Skeletal surveys suggest that a solitary exostosis can be found in 1%–2% of the population; therefore, in the absence of a family history or other manifestations of HME, more than one exostosis must be present for the diagnosis to be made.

Schmale et al. (5) described 113 affected members of 46 families: the most commonly affected regions were humerus (50%), forearm (50%), knee (70%), and ankle (25%). In the HME series of Pierz et al. (6), the number of exostoses per patient ranged from

2 to 27 (mean 12). The following frequencies were observed: proximal humerus (64%), distal humerus (5%), scapula (30%), clavicle (2%), forearm (67%), metacarpals (26%), digits (44%), proximal femur (37%), distal femur (86%), proximal tibia (79%), proximal fibula (74%), locking of knees (16%), peroneal nerve involvement (28%), ankle (54%), metatarsals (14%), toes (9%), ribs (37%), spine (7%), and pelvis (19%).

Laboratory features: No specific findings.

Associated malignant neoplasms: Malignant transformation to chondrosarcoma or other sarcomas occurs in less than 5% of cases. Other reports suggest a 0.5%–2% risk of malignant degeneration per person, with a mean age at diagnosis of 31 years. Chondrosarcoma, which has a predilection for the proximal femur or axial skeleton (80%) in HME, seldom occurs before age 10 or after age 50. Neither the number of exostoses nor the severity of the overall phenotype was predictive for sarcomatous change (3). In this prospective study of 172 persons from 78 affected families, seven chondrosarcomas developed among 71 *EXT1* mutation carriers vs one chondrosarcoma among 72 *EXT2* carriers. Sarcoma risk was not formally quantified in this analysis.

Associated benign neoplasms: Osteochondromas and multiple exostoses, which may cause a variety of compressive problems. For example, there are more than 100 reports of pseudoaneurysm, primarily of the popliteal artery, in association with adjacent osteochondromas (7).

Cancer risk management: Asymptomatic osteochondromas do not require therapy, and the vast majority of symptomatic lesions can be treated successfully, with low morbidity (8). The treatment of osteochondromas involving the forearm in children is a particular challenge (9). Corrective osteotomy and/or lengthening of forearm bones have been suggested to be without clinical benefit, although excision of exostoses to improve forearm rotation or to improve appearance was reported as useful (10). It may be helpful to obtain baseline radiographs of the pelvis and shoulder girdle in young affected adults for the purposes of later comparison. Affected individuals should be instructed to report any rapidly enlarging exostosis or a new onset of pain in a preexisting lesion. A cartilage cap (as imaged by magnetic resonance imaging or computerized tomography) of more than 2–3 cm is suggestive of chondrosarcoma (11). The risks and benefits of radiographic screening for chondrosarcoma in this syndrome are not established.

Comments: The genes causing HME are also involved in several contiguous gene syndromes. The Langer–Giedion syndrome (lax skin in infancy, dysmorphic facies, mental deficiency, sparse hair, and multiple exostoses) is associated with a large deletion in the 8q24 region that contains *EXT1*. McGaughran et al. (12) reported a patient with the WAGR syndrome (see Wilms tumor) plus multiple exostoses, resulting from the deletion del(11)(p14.2p11.2). Potocki and Shaffer (13) described a syndrome with multiple exostoses, mental retardation, dysmorphic features, and parietal foramina, known as Catlin marks, in which a de novo 11(p12p11.2) deletion encompassing the *EXT2* gene was found. Multiple enchondromas (enchondromatosis) may be caused by mutations in *PTHR1* (OMIM 166000). This condition is also known as Ollier syndrome or, in the presence of hemangiomata, Maffucci syndrome.

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16. Fanconi Anemia

OMIM numbers: Thirteen complementation groups and their corresponding genes have been identified (Table 11). Complementation groups are defined based on determining which of the DNAs subcloned into retroviruses can correct the in vitro cell hypersensitivity to DNA interstrand cross-linking agents such as mitomycin C, a trait that is characteristic of Fanconi anemia (FA). Many of the FA genes interact in a nuclear complex that is involved with the monoubiquitination of FANCD2, which colocalizes with multiple proteins involved with genomic stability (1,2).

Inheritance pattern: Autosomal recessive except *FANCB*, which is X-linked recessive (3).

Genes and chromosomal locations: Listed in Table 11.

Mutations: *FANCA* mutations account for approximately 66% of all cases; *FANCC* and *FANCG* together account for approximately 9% each; *FANCD1*, *FANCD2*, *FANCE*, and *FANCF* each account for approximately 2%–3%; and the remaining groups, less than 1% each (4).

Incidence: Heterozygote frequency is estimated at one in 300, with one in 89 Ashkenazi Jewish carriers, one in 77 Afrikaners, and one in 100 Black Africans. One *FANCC* founder mutation has been described in Ashkenazi Jews, with a carrier frequency of

Table 11. Fanconi anemia genetics[a]

FA complementation group	Gene	Chromosome	OMIM number
A	*FANCA*	16q24.3	607139
B	*FANCB/FAAP95*	Xp22.31	300514, 300515
C	*FANCC*	9q22.3	227645
D1	*FANCD1/BRCA2*	13q12.3	600185, 605724
D2	*FANCD2*	3p25.3	227646
E	*FANCE*	6p21–p22	600901
F	*FANCF*	11p15	603467
G	*FANCG/XRCC9*	9p13	602956
I	*FANCI/KIAA1794*	15q25–q26	609053
J	*FANCJ/BACH1/BRIP1*	17q22–q24	609054, 605882
L	*FANCL/PHF9/FAAP43/POG*	2p16.1	608111
M	*FANCM/FAAP250/Hef*	14q21.3	609644
N	*FANCN/PALB2*	16p12.1	610335, 610832

[a]FA = Fanconi anemia; OMIM = online Mendelian inheritance in man.

1.1%, and a *FANCG* founder mutation is present in 1% of Black Afrikaners. FA is associated with approximately 20% of all cases of childhood aplastic anemia and an unknown proportion of adult cases as well (5,6).

Diagnosis: The diagnosis is usually established by chromosome breakage studies rather than by mutation testing or clinical features (see Laboratory section below). Most children present in early to middle childhood (median age at diagnosis is 8 years) with hematologic abnormalities, including anemia, bleeding, and easy bruising. Multiple congenital anomalies are seen (60% of affecteds), including low birth weight, abnormal skin pigmentation (75% with hyperpigmentation, café-au-lait spots, or both), skeletal deformities (50% with thumb anomalies, eg, aplasia, hypoplasia, and supernumerary, 10% with radial aplasia, and 30% with microcephaly), renal malformations (30% with aplasia, duplication, ectopia, and horseshoe), neurological abnormalities (25% with strabismus, 20% with hyperreflexia, and 20% with mental retardation), microphthalmia (20%), ear anomalies and/or deafness (10%), congenital heart disease (5%), and hypogonadism (20%). Note that 25%–40% of individuals with FA have no dysmorphic features. In approximately 25% of known FA patients with cancer or leukemia, the neoplasm was diagnosed before the recognition of the underlying susceptibility disorder (7). The enormous complexity of FA, with its severe malformations, profound cancer susceptibility, morbidity, and mortality, has now been linked with major, previously unappreciated psychosocial morbidity for the healthy siblings of FA patients (8).

FA is also characterized by the frequent occurrence of diverse endocrine abnormalities, including short stature (±growth hormone deficiency), hypothyroidism, infertility, glucose intolerance, and metabolic syndrome. Early-onset hyperlipidemia and osteoporosis are newly recognized components of FA-related endocrine dysfunction (9).

A recently published model uses a simple clinical scoring system to predict the risk of selected outcomes for FA patients, including bone marrow failure, need for transplant, development of malignancy (acute leukemia or solid tumor) and death (10). Abnormal radii were the strongest predictor of early marrow failure. A congenital anomaly score separated patients with normal radii into distinct prognostic groups. The differential diagnosis of inherited bone marrow failure syndromes, including FA, has been reviewed (11).

Regarding heterozygote carrier testing, the heterogeneity of FA mutations, combined with the high prevalence of compound heterozygotes, makes diagnostic screening for FA mutations difficult except in populations with specific founder mutations.

The observation that biallelic mutations in *BRCA2* are responsible for the phenotype in the *FANC-D1* complementation group represents an unexpected nexus between two seemingly distinct cancer susceptibility pathways. The phenotype of this subset of FA patients is unusually severe, with very early onset of syndromic complications and a 97% probability of developing malignancy by age 5 (12,13). There also appear to be genotype–phenotype correlations between specific mutations and the risk of AML and brain tumor. The recent discovery that biallelic mutations in *PALB2* (a molecular partner of *BRCA2*) are responsible for FANCN and that the clinical phenotype is very similar to that seen in biallelic *BRCA2* carriers solidifies this extraordinary intersection between FA and hereditary breast and/or ovarian cancer (14–16).

Laboratory features: Anemia, macrocytosis, poikilocytosis, anisocytosis, leukopenia, thrombocytopenia, reticulocytopenia on peripheral blood smear, and hypocellular marrow, aplastic anemia, myelodysplastic syndrome, or leukemia on bone marrow examination. None of these findings are diagnostic for FA; chromosome breakage studies are far more specific. Enhancement of chromosome breakage in cells cultured with clastogenic agents such as diepoxybutane or mitomycin C reliably identifies FA homozygotes but not heterozygotes. Aberrations include excess chromatid breaks, gaps, radial chromosomes, endoreduplications, and other types of nonhomologous recombination. The test is usually done using peripheral blood leukocytes cultured with a T-cell mitogen; cultured skin fibroblasts may need to be tested to identify the 10%–20% of FA patients who have hematopoietic somatic mosaicism. Standard karyotyping does not demonstrate these features.

Associated malignant neoplasms: Acute myeloid leukemia; hepatocellular carcinoma; squamous cell cancer of the head, neck, and esophagus; vulvar and cervical cancer in women; and brain tumors (17–19). All have been described in patients without a history of bone marrow transplant. FA patients' intrinsic predisposition to squamous cell cancers of the head and neck is further

amplified in bone marrow transplant recipients, particularly those who experience severe graft vs host disease (20).

Cancer risk in heterozygotes: Swift and colleagues suggested that FA heterozygotes might be at increased risk of developing cancer [reviewed in Heim et al. (21)]. The cancer risks recognized in *BRCA2* and *PALB2* mutation heterozygotes (*FANCD1* and *FANCN*, respectively) represent established instances of this phenomenon in FA, but these two FA variants are so rare that they cannot account for the magnitude of heterozygote risks that have been suggested. The increasing evidence that there might be a demonstratable susceptibility to cancer in the heterozygous carriers of other recessive disorders, such as ataxia telangiectasia, Nijmegen breakage syndrome, and Bloom syndrome, has lent new currency to this hypothesis. However, analysis of a cohort (n = 944) of grandparents and other FA heterozygotes from the International Fanconi Anemia registry revealed no overall excess cancer risk (all sites combined). But a statistically significant excess risk of breast cancer among carrier grandmothers (standardized incidence ratio [SIR] = 1.7; 95% confidence interval [CI] = 1.1 to 2.7) was reported; this risk seemed particularly high among carriers of FANC-C mutations (SIR = 2.4; 95% CI = 1.1 to 5.2) (22).

Associated benign neoplasms: Hepatic adenomas.

Cancer risk management: Increased index of suspicion for hematologic cancers, hepatic tumors, and squamous cell cancers. The risks and benefits of cancer screening in this syndrome have not been established. Alter (12) has suggested serial bone marrow aspirations, regular liver enzyme assessment and ultrasound examinations, and frequent oral examination including use of nasolaryngoscopy. Endoscopy of the esophagus can also be considered.

Comment: The average life expectancy is now 30 years, with most deaths due to complications of aplastic anemia, leukemia, or solid tumors. Bone marrow transplantation is a potential life-extending treatment but requires modified protocols because Fanconi anemia patients are unusually sensitive to chemotherapeutic agents and radiation, which can be lethal in FA patients if doses are not modified appropriately. Radiation-free preparative regimens and fludarabine-containing regimens offer hope for reduced toxicity and improved survival in FA patients undergoing bone marrow transplantation (23).

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17. Gastric Cancer, Hereditary Diffuse

OMIM number: 137215, 192090.

Inheritance pattern: Autosomal dominant.

Gene and chromosomal location: *CDH1* on chromosomal band 16q22.1, encoding e-cadherin, a calcium-dependent adhesion protein.

Mutations: As of 2004, 48 families with 45 different *CDH1* germline mutations had been reported. Seventy-six percent were loss-of-function mutations.

Incidence: Unknown. Among apparently sporadic cases of diffuse gastric cancer or mixed gastric cancer with diffuse component, *CDH1* mutations are seldom present. About one-third of families meeting criteria (below) for hereditary diffuse gastric cancer (HDGC) have identifiable germline *CDHI* mutations.

Diagnosis: The International Gastric Cancer Linkage Consortium (IGCLC) defined HDGC as any family that fits the following criteria: 1) two or more documented cases of diffuse gastric cancer in first and/or second-degree relatives, with at least one diagnosed before the age of 50, or 2) three or more cases of documented diffuse gastric cancer in first-/second-degree relatives, regardless of age. Families not meeting these criteria but in

which the index patient has diffuse gastric cancer are termed "familial diffuse gastric cancer" (1).

It has been suggested that genetic testing should be initiated at age 16, concurrent with initiation of annual endoscopic surveillance (2). The IGCLC recommended consideration of genetic diagnostic testing in the following circumstances in North America or other areas with low gastric cancer incidence (criteria not sufficiently stringent for regions with high gastric cancer rates): 1) two or more cases of gastric cancer in a family, with at least one diffuse gastric cancer diagnosed before age 50 years; 2) three or more cases of gastric cancer in a family, diagnosed at any age, with at least one documented case of diffuse gastric cancer; 3) an individual diagnosed with diffuse gastric cancer before 45 years of age; 4) an individual diagnosed with both diffuse gastric cancer and lobular breast cancer (no other criteria met); 5) one family member diagnosed with diffuse gastric cancer and another with lobular breast cancer (no other criteria met); and 6) one family member diagnosed with diffuse gastric cancer and another with signet ring colon cancer (no other criteria met). See recent review (3).

Laboratory features: Gastric cancers from individuals with *CDH1* mutations have consistently been the diffuse histological subtype ("linitis plastica"), rather than the more common "intestinal" type gastric carcinoma.

Associated malignant neoplasms: Diffuse gastric cancer, with average age at diagnosis of 40 years. Eleven IGCLC families with three or more cases of diffuse gastric cancer and one or more CDH1 mutation-positive cases were studied. The estimated cumulative risk of gastric cancer by age 80 years was 67% for men (95% confidence interval [CI] = 39% to 99%) and 83% for women (95% CI = 58% to 99%). Among women, the cumulative risk of breast cancer, often of the lobular type, was 39% (95% CI = 12% to 84%) by age 80. The combined risk of gastric cancer and breast cancer in women was 90% by age 80 years. Gastric cancer cumulative risks were also estimated in two large families and reported for men to be 1%, 3%, 6%, 9%, 14%, and 40% at ages 20, 30, 40, 50, 60, and 75 years, respectively. For women, gastric cancer risks were reported as 3%, 10%, 19%, 26%, 42%, and 63% for the same respective ages. In these two families, the risk of female breast cancer was estimated as 0%, 1%, 6%, 24%, 44%, and 52% at the same respective ages (4). These risks may not be generalizable to all gene-carrying families or those not stringently defined. Cancers of the colon, ovary, and prostate have been reported in mutation carriers, but it remains to be determined if their risks are substantially increased compared with the general population [reviewed by Oliviera et al. (5)]. Germline *CDH1* mutations have also been reported in women with invasive lobular carcinoma who present an early age at diagnosis and/or a positive family history of breast cancer, in the absence of a personal or family history of diffuse gastric cancer (6). This observation, if confirmed, would have clinically significant implications for women with lobular breast cancer.

Associated benign neoplasms: No benign precursor lesions have been defined. There are multiple reports of multifocal microscopic intramucosal signet ring cell adenocarcinoma in specimens from prophylactic gastrectomies on individuals with *CDH1* germline mutations (7,8). No information is available regarding the age at which carcinoma in situ lesions first appear, nor the natural history of these early neoplasms, although intramucosal foci of cancer cells have been reported to remain confined to the mucosa for many years (2).

Cancer risk management: Complete gastrectomy is effective in preventing gastric cancer. However, the high morbidity (nearly 100% of patients experience rapid gastrointestinal transit, dumping syndrome, and/or weight loss), potential post-operative mortality (1%–2%), and age-specific risks of cancer must be carefully balanced. Because the risk of gastric cancer in mutation carriers younger than age 20 is likely below 1%, some experts recommend that the morbidity of prophylactic surgery cannot be justified for younger family members (2). The risk of gastric carcinoma is estimated at 4% by age 30 years, so delaying prophylactic gastrectomy beyond this age carries substantial risk. If gastrectomy is performed, it is essential to document the complete removal of gastric tissue by histologically identifying esophageal and duodenal tissue at the resection margins.

For those not undergoing gastrectomy, surveillance endoscopy can be considered, recognizing the low likelihood that a lesion that spreads submucosally will be detected early. Endoscopy can be combined with other modalities including endoscopic ultrasound to search for areas of mucosal thickening, chromoendoscopy (a mucosal dye), which enhances detection of 4–10 mm carcinomas in HDGC and permits visualization of lesions not detectable on standard endoscopy (9), and obtaining multiple random biopsies in an effort to identify early intramucosal carcinomas. Standard white-light endoscopic examination of the stomach with either random or geographically targeted biopsies is reported to be insensitive in this setting, given the unpredictable distribution of mucosal abnormalities (10). Blair et al. (2) have suggested that annual gastroscopy using Congo red–methylene blue technique be offered to all gene carriers (or those at risk) who are 16 years or older. They caution that the long-term outcome of this strategy is unknown because the probability of missing a clinically significant lesion cannot be quantified.

Monthly breast self-examination and clinician examination every 6 months is suggested commencing at age 18, with annual breast ultrasound (because of the frequency of lobular carcinoma) and mammographic screening starting at age 35. Augmenting breast surveillance with magnetic resonance imaging may also be considered at the time mammography is initiated, though it is unknown if data obtained from *BRCA*-gene mutation carriers can be extrapolated to HDGC. Blair et al. (2) consider evidence insufficient to recommend prophylactic mastectomy in female mutation carriers. It is unclear if colorectal cancer risk is increased, so standard screening guidelines may be adequate. The genetics, pathology, and clinical management of familial gastric cancer have been recently reviewed (11).

Comment: Gastric cancer appears to be part of a number of other hereditary cancer syndromes, so these possibilities should be carefully considered in any family with two or more cases of gastric cancer, though histological type may help distinguish underlying causes (Table 4). Cleft lip and/or palate has been reported to be associated with *CDH1* mutations in two families with HDGC (12).

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18. Gastrointestinal Stromal Tumor; also Multiple Gastrointestinal Autonomic Nerve Tumors

OMIM number: 606764, 164920, 173490.

Inheritance pattern: Autosomal dominant.

Gene and chromosomal location: *C-KIT*, located at 4q12, and *PDGFRA*, also at 4q12.

Mutations: Seven families with five different activating germline mutations have now been reported [summarized in Robson et al. (1)], and several single-family case reports are now published. This is one of a few cancer susceptibility syndromes in which an oncogene (rather than a tumor suppressor gene) is pathogenic. The others include Multiple Endocrine Neoplasia type 2 (*RET*), hereditary papillary renal cancer (*MET*), hereditary melanoma (*CDK4*), hereditary pancreatic cancer (*PALLD*), and Costello syndrome (*HRAS*).

Chompret et al. (2) reported on a KIT mutation-negative family with five cases of gastrointestinal stromal tumors (GISTs), and found a germline mutation in *PDGFRA*, a gene known to have somatic mutations in many GISTs. No skin pigmentation was reported, but large hands were noted. de Raeft et al. (3) reported on a family with adult onset "intestinal neurofibromatosis" (OMIM #162220), which was phenotypically similar to GISTs; the tumors were negative for S-100, which is usually positive in neurofibromas and also negative for *KIT*, in contrast to the prior family. The affected family members had large hands and wrists. A germline mutation in *PDGFRA* was again found. The authors suggested these tumors are GISTs and that this entity be called familial *KIT*-negative GISTs. An additional family with a germline *PDGFRA* mutation was described by Pasini et al. (4).

Incidence: Frequency in the general population is unknown.

Diagnosis: Diagnosis is established by clinical phenotype gestalt, family history, tumor studies, and genetic tests, if available. GISTs are mesenchymal tumors of the gastrointestinal tract. They may originate from the interstitial cells of Cajal (ICCs), and activation of *KIT* by somatic point mutations is present in the vast majority of sporadic tumors. Familial GIST is characterized by multiple GISTs, cutaneous hyperpigmentation with multiple nevi and/or urticaria pigmentosum, and a family history of close relative diagnosed with GIST. The most common clinical symptoms are dysphagia (approximately 30%), upper GI pain, and GI bleeding. Hyperpigmentation, usually diffuse but sometimes speckled, was reported in 67% of presumed carriers and involved the digits, elbows, knees, perineum, and face. Pigmentation had a tendency to fade with age.

A second phenotype, also associated with activating mutations in *KIT*, involved a kindred with multiple gastrointestinal autonomic nerve tumors with hyperplasia of ICCs (5). Severe diverticulosis was reported in one such family and may be a consequence of the altered ICC (6).

Laboratory features: Historically, GISTs were not histologically distinguishable from leiomyosarcomas or epithelioid leiomyosarcomas. When it was discovered that GISTs typically did not express muscle or Schwann-cell markers (eg, S-100), the term GIST was adopted. Immunostaining can help distinguish GISTs from morphologically similar lesions. The gene expression and mechanisms of cytogenetic progression are indistinguishable between familial and sporadic GISTs (7). The *KIT* tyrosine kinase is activated in sporadic GISTs by somatic mutations (85%) and in hereditary tumors (nearly all) by germline mutations.

Associated malignant neoplasms: Rare malignant transformation of GISTs; indolent behavior is the rule. Approximately 10%–30% of all GISTs show malignant features histologically, although higher frequencies have been observed in some studies. Melanoma has been reported in one affected individual (7). Mastocytosis, known to be caused by activating somatic mutations in *KIT*, was reported in one GIST family with a novel *KIT* mutation (8).

Associated benign neoplasms: Benign GISTs. GISTs are most commonly found in the stomach (70%), small intestine (20%–30%) or, less commonly, in the esophagus, colon, or rectum (10%). In one large family with a germline *KIT* mutation, 68% of 22 presumed carriers were diagnosed with GIST at a median age of 47.5 years (range = 29–77), and the cumulative probability of being diagnosed with GIST was 91% by age 70 (1). Sporadic GISTs were diagnosed at a mean age of 67 years. One germline mutation carrier was reported to have an angioleiomyoma (7).

Cancer risk management: No consensus cancer screening guidelines have been developed for at-risk members in hereditary GIST families. Upper gastrointestinal endoscopic surveillance is suggested, along with small bowel contrast radiograph (or capsule endoscopy if available) and colonoscopy every 2 years starting at age 25–30 years or 5 years younger than the youngest case in a well-documented family.

Comments: Carney and Stratakis (9) reported a syndrome with paraganglioma and "gastric stromal sarcoma" or GIST (OMIM 606864), inherited in an autosomal dominant manner. Paragangliomas were observed in 92% of patients in this series, and GISTs were reported in 42%. This is now called the Carney–Stratakis syndrome, and germline mutations have been reported in *SDHB*, *SDHC*, and *SDHD* (see chapter on Hereditary Paraganglioma) (10).

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19. Hyperparathyroidism, Familial (includes Familial Isolated Hyperparathyroidism and Familial Hyperparathyroidism with Multiple Ossifying Jaw Fibromas (aka Hereditary Hyperparathyroidism-Jaw Tumor Syndrome); Familial Cystic Parathyroid Adenomatosis)

OMIM number: 145000, 145001.

Inheritance pattern: Autosomal dominant.

Gene and chromosomal location: Mutations in the parafibromin gene, *HRPT2*, on chromosome 1q25 have been found in more than half of families with hyperparathyroidism-jaw tumor (HPT-JT) syndrome, but they account for only a small proportion of familial isolated HPT (FIHPT) cases.

Mutations: As of 2006, 26 germline mutations had been reported, most of which were inactivating, suggesting a tumor suppressor role for *HRPT2* (1).

Incidence: Primary HPT is a common endocrine syndrome (eg, prevalence in postmenopausal women is 2%–3%). More than 90% of cases are sporadic. The other 10% of HPT is familial and includes FIHPT, Multiple Endocrine Neoplasia type 1, Multiple Endocrine Neoplasia type 2A, familial hypocalciuric hypercalcemia as well as HPT-JT syndrome. Some cases of FIHPT may be due to *HRPT2*, but for most cases of FIHPT, the genetic cause remains unknown despite thorough evaluation. *HRPT2* germline mutations were reported in two of seven patients with sporadic parathyroid cancer, an uncommon tumor, raising the possibility of underdiagnosis of familial HPT as a cause of parathyroid cancer (2).

Diagnosis: No other known endocrinopathy is associated with mutations in this gene. Thus, the diagnosis is suggested when a family shows autosomal dominant isolated HPT or HPT-JT syndrome; other syndromic causes must be carefully excluded.

Laboratory features: The parathyroid involvement may include parathyroid hyperplasia (either chief cell or oxyphil cell), parathyroid adenomas, or cystic parathyroid adenomas, with elevated parathyroid hormone levels. The latter causes renal stones, hypercalcemia, osteoporosis, and pancreatitis. Familial disease typically is multifocal, whereas sporadic HPT tends to be unifocal.

Associated malignant neoplasms: Parathyroid malignancy occurs in about 15% of neoplastic glands, so aggressive management has been advised (3). Wilms tumor has been reported three times in affected members from two families, including adults. The following tumors have been reported in *HRPT2* gene carriers, though their etiologic relationship to the syndrome remains undefined: pancreatic adenocarcinoma, papillary renal carcinoma, mixed epithelial–stromal tumor of kidney, testicular mixed germ cell tumor, Hurthle cell thyroid tumor, prostate cancer, and uterine adenosarcomas (4–8).

Associated benign neoplasms: Parathyroid adenomas affecting one or more gland are reported, with greater HPT penetrance in males than in females. Mean age at diagnosis of HPT is 32 years. Fibrous maxillary or mandibular tumors that resemble ossifying or cementifying fibromas (not the brown tumors of HPT) are present in about 30% of affected family members and are not known to have malignant predisposition. Several families have been reported that manifest renal disease including hamartomas, multiple cysts or polycystic renal disease, renal cortical adenomas, and development of renal failure. Benign uterine disease (hyperplasia, adenomyosis, leiomomas, fibromas) resulting in early or increased rate of hysterectomy has been noted (8).

Cancer risk management: There are no published guidelines on surveillance. Based upon the phenotype, annual screening with serum calcium, phosphorous, and parathyroid hormone levels and palpation of the thyroid and parathyroid glands are advised, beginning at age 10–12 years, as adenomas and carcinomas have been reported in adolescents. If tests are abnormal, imaging of the parathyroid glands is indicated with the aim of removing overactive parathyroid glands. Screening for subclinical jaw lesions is not indicated, except as an adjunct to determining who has inherited the HPT-JT syndrome. In individuals diagnosed with HPT-JT, baseline evaluation of renal function is suggested and baseline imaging to screen for renal masses or cysts should be performed. Reassessment of renal status every 1–2 years is suggested. Abnormal menstrual history should prompt evaluation for uterine pathology. Management of other HPT complications is beyond the scope of this review.

Comments: Isolated familial HPT was reported initially as a separate entity, but current studies of a few families suggest it may be accounted for by mutations in *MEN1* or *HPRT2*.

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20. Leukemia, Acute Myeloid, Familial

OMIM number: 601399, 151385 (familial platelet disorder with associated myeloid malignancy [FPD/AML]); 602439, 601626 (familial acute myelogenous or myeloid leukemia); 151380 (familial acute monocyte leukemia); 133180 (familial erythroleukemia [FEL]).

Inheritance pattern: Varied: autosomal dominant—FPD/AML, FEL; uncertain mode—acute myelogenous/myeloid leukemia, FEL, familial acute monocytic leukemia (1).

Gene and chromosomal location: Genetic heterogeneity predominates, with risk of acute myeloid leukemias (AMLs) linked to at least three different loci. Only in FPD/AML has the etiologic gene been identified: *CBFA2/RUNX1*, on 21q22.3. One acute myelogenous leukemia family is linked to 16q22. Neither chromosomal loci nor gene(s) have been determined for familial acute monocytic leukemia or FEL [(2–5); reviewed by Owen et al. (6)].

Mutations: *CBFA2/RUNX1* mutations appear to result in haploinsufficiency (7).

Incidence: Very rare.

Diagnosis: Affected proband plus one or more first- or second-degree relatives with the same acute leukemia subtype. Germline *RUN*XI mutation in an individual with acute leukemia is also diagnostic.

Laboratory features: Thrombocytopenia in FDP/AML, with a functional platelet disorder similar to that seen as a consequence of aspirin use. A myelodysplastic syndrome precedes development of leukemia in most cases.

Associated malignant neoplasms: Population studies suggest an increased risk of hematologic malignancies in families of children with acute myeloid leukemias (odds ratio = 13.3, 95% confidence interval = 2.5 to 69) and a trend toward increased risks of solid tumors that did not reach statistical significance (8).

Associated benign neoplasms: None described.

Cancer risk management: None recommended.

Comments: Multiple genetic syndromes include a predisposition to acute leukemia (See Table 4). These should be considered in the differential diagnosis. Note also that juvenile myelomonocytic leukemia may be caused by *somatic* mutations in *PTPN11*. Germline mutations in this gene cause Noonan syndrome and LEOPARD syndrome. Individuals with Noonan syndrome due to a germline mutation in *PTPN11* have a predisposition to this childhood acute leukemia (9).

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21. Leukemia, Chronic Lymphocytic, Familial

OMIM number: 151400.

Inheritance pattern: Variable. Multigenerational pedigrees with male-to-male transmission have been described, suggesting autosomal dominant inheritance in some families. Other pedigrees consist of affected siblings or affected cousins only, a pattern compatible with autosomal recessive inheritance.

Gene and chromosomal location: Linkage studies identified several regions having suggestive associations with chronic lymphocytic leukemia (CLL), with the strongest evidence supporting linkage to chromosomes 2q21.2, 6p22.1, and 18q21.1 (1) and suggestive findings also at 11p11 and 13q21.33–q22.2 (2–4). Recent reports of birth order effects (5) and allelic silencing at chromosome 13q14.3 (6) suggest a possible role for epigenetic factors in disease susceptibility.

Mutations: No gene has been cloned.

Incidence: Uncommon.

Diagnosis: Two or more first- or second-degree relatives with CLL, based on family and medical history. Mean age at diagnosis was reported to be 10 years younger among familial B-CLL cases than sporadic controls (57.9 ± 12.1 vs 70.1 ± 11.9 years) (7). Of all the major hematologic malignancies, CLL has the highest familial incidence. Most clinical and biological characteristics of familial CLL resemble those of sporadic disease. However, age at diagnosis of offspring is approximately 20 years younger than that of their affected parents; it is unclear whether this observation represents true anticipation. A study of CCG- and CAG-trinucleotide repeats (the basis for anticipation in several neurodegenerative disorders) in 18 CLL families and 140 sporadic CLL patients did not detect evidence of repeat instability (8). There may also be different

patterns of second primary cancer development following CLL in familial disease.

Laboratory features: No specific findings. A precursor condition (designated "monoclonal B-cell lymphocytosis") has been described, defined as clonal B-cell expansions in the absence of an absolute lymphocytosis in the peripheral blood in first-degree relatives of CLL patients (9). The risk of progression to frank CLL in such patients is unknown, although two such patients shared their family's at-risk genotype in a fine-mapping study of the 13q21.33–q22.2 candidate susceptibility locus (4).

Associated malignant neoplasms: First-degree relatives of CLL cases are at sevenfold increased risk of CLL. In a large population-based study (10), first-degree relatives of CLL probands appeared to be at increased risk of other B-cell malignancies as well (relative risk [RR] = 2.1; 95% confidence interval [CI] = 1.6 to 2.9), most notably Hodgkin (RR = 2.4; 95% CI = 1.1 to 5.1) and non-Hodgkin (RR = 1.4; 95% CI = 1.0 to 2.2) lymphoma. Ishibe et al. (7) reported a higher percentage of second primary tumors (eg, bladder cancers) among familial CLL cases compared with sporadic CLL cases, but the number of cases was too small to demonstrate statistical significance and further studies are needed to explore this topic.

Associated benign neoplasms: None known.

Cancer risk management: None has been defined. Although clonal B-cell expansions can be detected in peripheral blood of at-risk family members by flow cytometry, the natural history of such clones remains unknown. There is currently no indication for early treatment of asymptomatic patients with low-risk CLL in standard clinical practice. Thus, routine screening of asymptomatic relatives of familial CLL patients is not advised.

Comment: A recent modification of the diagnostic criteria for CLL reflects the World Health Organization (WHO) classification of CLL as a disease of neoplastic B-cells distinct from the entity now called T-cell prolymphocytic leukemia. Diagnosis of CLL now requires the presence of at least 5000 B-lymphocytes per microliter in the peripheral blood for a duration of at least 3 months (12). This change has the effect (among others) of increasing prevalence estimates for the precursor condition, monoclonal B-cell lymphocytosis.

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22. Li–Fraumeni Syndrome, including Li-Fraumeni-Like Syndrome

OMIM number: 151623, 191170, 609265, 604373, 609266, 202300.

Inheritance pattern: Autosomal dominant.

Gene and chromosomal location: Germline mutation in *TP53* (17p13.1), commonly called *p53*, is the molecular basis of Li–Fraumeni syndrome (LFS). *p53* regulates the cell-cycle arrest that is required to permit repair of DNA damage. In *p53* mutation-negative LFS families (most of which meet Li-Fraumeni-Like [LFL] criteria), germline *CHEK2* mutations have been reported (1). *CHEK2* (located at 22q12.1) is in the *p53* pathway, and germline mutations were originally found in a few LFL families. Currently, there is disagreement as to whether *CHEK2* truly causes LFS or LFL, or whether it is etiologically related only to the early-onset breast cancers which occur in this disorder (2,3). The *CHEK2**1100delC mutation, the frequency of which varies across populations, appears to increase risk of breast cancer by about twofold and may predispose to earlier age at diagnosis [reviewed by Narod and Lynch (4)]. A third LFS locus has been mapped recently to chromosome 1q23, but no specific gene has yet been implicated (5).

Mutations: When clinical mutation testing targets only exons 5–8, as is often done, approximately 70% of Li–Fraumeni families meeting the stringent diagnostic criteria (see below) have *p53* mutations. Mutations in exons 4–9 are found in 95% of such families. LFL kindreds have detectable mutations in 8%–22% of probands, depending upon the stringency of the syndrome definition (6,7). Overall, about 75% of *p53* mutations involve exons 5 through 8 (8). Missense mutations represent the majority (approximately 75%) of genetic lesions, and most generate a truncated p53 protein. Brain tumors and adrenocortical carcinomas each have been associated with a location-specific set of mutations within the *p53* gene (9). Partial deficiency alleles are associated with milder family history, lower numbers of tumors, and delayed disease onset (10). A web-based repository of *p53* mutation information has been created (http://www-p53.iarc.fr/index.html); it contains information on nearly 300 deleterious germline mutations.

Incidence: LFS appears to be rare, with approximately 400 reported families in the cumulative literature, but its actual population incidence is unknown. Variations in selection criteria introduce

selection biases that cannot be accurately estimated. Children with adrenocortical carcinoma were found to have the highest frequency of detected *p53* mutations (approximately 80%). Mutations were detected in approximately 2%–10% of childhood brain tumors, 2%–3% of patients with osteosarcomas, and in 9% of patients with rhabdomyosarcoma. Patients with multiple primary tumors had an estimated *p53* mutation frequency of 7%–20%.

Diagnosis: The classical definition requires 1) one patient with sarcoma diagnosed before age 45, 2) a first-degree relative diagnosed with cancer (of any kind) before age 45, and 3) a third affected family member (first- or second-degree relative) with either sarcoma at any age or cancer (type not specified) before age 45 years (11). Although these criteria are highly specific for LFS, they exclude some clinically atypical, mutation-positive families; consequently, relaxed criteria have been proposed.

Studies based on so-called LFL criteria detected 8%–22% of mutation-positive individuals from these clinically atypical families. The Birch LFL criteria require 1) a proband with any childhood cancer or sarcoma, brain tumor or adrenal cortical carcinoma diagnosed before age 45, 2) a first- or second-degree relative with a typical LFS malignancy (sarcoma, leukemia, or cancers of the breast, brain or adrenal cortex) regardless of age at diagnosis, and 3) a first- or second-degree relative with any cancer diagnosed before age 60 (6). The Eeles definition simply requires two first- or second-degree relatives with LFS-related malignancies at any age (7). Evans et al. (12) studied 21 families with a single proven sarcoma (any age) and a first-degree relative with early-onset breast cancer (<60 years) and found only one family (5%) with a *p53* mutation.

A striking predilection for young age at cancer diagnosis and development of multiple primary cancers are LFS features (9,13). The probability of developing a second primary cancer in 200 LFS patients reached 57% by 30 years follow-up (14). Risk of second cancer was higher in younger patients and in those whose first primary was a sarcoma. The estimated probability of developing a third cancer was 38% at 10 years. Given the nature of the genetic defect in a gene that is central to DNA repair, there is a theoretical basis for concern regarding sensitivity to radiation carcinogenesis in *p53* germline mutation-positive patients, a concern that has substantial anecdotal clinical support (14).

Laboratory features: None that are syndrome specific.

Associated malignant neoplasms: Risk of developing any invasive cancer (excluding skin cancer) was approximately 50% by age 30 (compared with 1% in the general population), and approximately 90% by age 70 (15). The tumor spectrum includes osteogenic and chondrosarcoma, rhabdomyosarcoma, breast cancer, brain cancer (especially glioblastomas), leukemia, lymphoma, and adrenocortical carcinoma (9,16). Early-onset breast cancer accounts for 25% of all LFS-related cancers, followed by soft-tissue sarcoma (20%), bone sarcoma (15%), and brain tumors (13%). The risks of sarcoma, female breast cancer, and hematopoietic malignancies in mutation carriers are more than 100 times greater than those seen in the general population (17). One specific TP53 mutation was reported to result in adrenocortical tumors in 9.9% of carriers (18). Malignancies reported (but not proven) to be associated include melanoma, Wilms and other kidney tumors, gonadal germ cell, pancreatic, gastric, and choroid plexus, colorectal (19), and prostate cancers.

The "classical" LFS malignancies (sarcoma and cancers of the breast, brain, and adrenal glands) comprise about 80% of all cancers that occur in LFS families. The incidence of these cancers varies by age, with soft-tissue sarcomas, adrenal and brain tumors predominating before age 10, bone sarcoma the most frequent in the teen years, and breast and brain tumors comprising the majority after age 20 (9). Relative to LFL families, kindreds meeting stringent LFS criteria have more brain tumors, earlier onset of breast cancer, and exclusive occurrence of adrenocortical carcinoma.

A strong interaction between gender and cancer risk has been described in LFS families, with mutation-positive women reported to be seven times more likely to develop cancer than mutation-positive men (20).

In a search for genetic modifiers of p53 penetrance in LFS families, a SNP in the promoter region of *MDM2* (a direct negative regulator or inactivator of *p53*) was found to attenuate the p53 pathway and accelerate the formation of both hereditary and sporadic tumors, as measured by significantly reduced age at cancer diagnosis (21). Multiple subsequent reports have confirmed this observation (22). Acclerated telomere attrition has been suggested to play a role in progressively earlier age-at-cancer onset in this context as well (23). Several common SNPs in the p53 gene have been suggested to increase the risk of sporadic osteogenic sarcoma, with significant odds ratios ranging from 6.7 to 7.5 (24).

Associated benign neoplasms: None known.

Cancer risk management: Breast cancer is the only LFS-related malignancy for which effective screening exists. The National Comprehensive Cancer Network Practice Guidelines (25) recommend training and education in breast self-examination by age 18, with monthly BSE thereafter. Breast imaging was advised beginning at ages 20–25 or 5–10 years before the earliest known breast cancer in the family (whichever is earlier). Based on expert consensus opinion, the American Cancer Society recommends annual breast magnetic resonance imaging screening as an adjunct to mammography in women with LFS and their first-degree relatives (26). Options for risk-reducing mastectomy should be discussed on a case-by-case basis. We would add a clinical examination of the breasts every 6 months to these published guidelines.

The risks and benefits of screening for other malignancies in this syndrome are not established; the pros and cons of embarking on cancer screening with strategies of unproven value should be frankly discussed with each family before proceeding. The costs of such an approach, both economically, medically, and emotionally (due to the consequences of false-positive test results), may be quite high. Additional surveillance activities might be tailored to the phenotype of individual families, although there is no evidence that this is beneficial. Pediatricians should be alerted to the risk of specific childhood malignancies in affected families. An annual comprehensive health examination is suggested, in which a high index of suspicion for symptoms related to syndromic malignancies (and second cancers in previously treated patients) is warranted. Patients should be advised regarding the potential genetic risk to bloodline relatives and the possibility of their undergoing genetic risk assessment and, possibly, genetic testing (25). Preimplantation genetic diagnosis has been reported in a number of LFS families (27).

Comments: The diversity of malignancies that are known or suspected to be part of LFS poses a particular challenge

relative to the validity of these patients' family histories. In a study comparing the accuracy of reported cancer history among LFS and hereditary breast/ovarian cancer families, breast cancer was accurately reported in both groups, but nonbreast LFS-related cancer diagnoses were accurate only 55% of the time vs 74% in breast/ovarian cancer families (28). Fewer than half of LFS historians provided information that would have led to *p53* mutation testing. Confirmation of reported family history is particularly important if LFS is in the differential diagnosis. A small but encouraging experience is accruing relative to the use of a molecularly targeted therapy, Advexin (a replication-defective adenoviral vector containing the wild-type p53 gene under the control of the cytomegalovirus promoter). While still in the earliest stages of new drug development, this may evolve into another example of novel therapeutic approaches based on an understanding of the molecular basis of the cancer being treated (29).

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23. Lymphoma, Hodgkin, Familial

OMIM number: 236000.

Inheritance pattern: Uncertain. Most published pedigrees contain only affected siblings or first cousins; however, some multigenerational families exist. Both Chakravarti et al. (1) and Goldin et al. (2) provided evidence favoring an autosomal recessive mode of inheritance. Shugart et al. (3) estimated a heritability of approximately 28% and described anticipation in familial Hodgkin lymphoma (HL), using a population-based database in Sweden. A study of HL in monozygotic and dizygotic twin pairs revealed concordance in 10 of 179 pairs vs none of 187 pairs, respectively (4). Population-based epidemiological studies have documented a significant familial component to the etiology of HL (5–9). Risk is highest among siblings of affected patients (relative risk [RR] = 5.6), compared with parents or offspring (RR = 3.0) (10). Gender concordance was observed as well, with the highest risks in this study being observed in brother pairs (RR = 8.0) and sister pairs (RR = 11.8).

Gene and chromosomal location: Undefined. Genome-wide linkage analysis has provided preliminary evidence suggesting susceptibility genes on chromosome 4p (2), with additional regions on chromosomes 2 and 11 also showing evidence for linkage.

Mutations: No gene has been cloned.

Incidence: Rare.

Diagnosis: Two or more first- or second-degree relatives with HL.

Laboratory features: None specific.

Associated malignant neoplasms: First-degree relatives of HL cases are at threefold increased risk of HL. Note that based on rates from 2002 to 2004, 0.22% of men and women (one in 453) in the general population will be diagnosed with HL some time during their lifetime, at a median age at diagnosis of 38 years of age; 12% diagnosed younger than age 20; 32% between ages 20–34; 30% between ages 35–54; and 25% at older ages) (11). According to Goldin et al. (12), first-degree relatives of patients affected with HL also appear to be at statistically significant increased risk of other lymphoproliferative diseases, particularly chronic lymphocytic leukemia (RR = 2.1), and male relatives have an elevated risk of non-HodgKin lymphoma (RR = 1.5). Based on Scandinavian population data, cancers of the breast, ovary, kidney, cervix, and brain were more frequent among relatives of unselected HL subjects in the general population, compared with population controls. It is not clear whether these latter risks are characteristic for multiple-case HL families.

Associated benign neoplasms: None known.

Cancer risk management: No consensus. The risks and benefits of cancer screening in this syndrome have not been established.

Comments: Susceptibility may be modulated by exposure to infectious agents or immunodeficiency (13,14). Numerous familial aggregations of HL have been reported in which a variety of nonspecific abnormalities in cellular and humoral immunity were noted, but no reproducible abnormality of clear etiologic significance has been found. Despite a strong association between sporadic HL and evidence of exposure to or infection with Epstein–Barr virus (EBV), including identification of viral genome in at least half of HL tumor biopsies, the relationship between EBV and HL remains unclear. Studies have suggested an association between specific human leukocyte antigen (HLA; ie, histocompatibility) phenotypes and HL; in such families, there is a higher than expected concordance of HLA haplotypes (1).

Genetic anticipation (the occurrence of an inherited disease at progressively younger ages in successive generations) has been noted, although the mechanism for this, if confirmed, is unknown (15).

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24. Lymphoma, Non-Hodgkin, Familial

OMIM number: 605027.

Inheritance pattern: In case–control studies, risk appears to be highest for siblings; however, multigenerational pedigrees do occur.

Gene and chromosomal location: Unknown.

Mutations: No gene has been cloned.

Incidence: Rare. Familial clustering is estimated to account for less than 5% of non-Hodgkin lymphoma (NHL) cases (1).

Diagnosis: Two or more first-degree relatives with NHL, based on family and medical history.

Laboratory features: No specific findings. In the few families that have been studied systematically, a variety of immune-related abnormalities, particularly alterations in immunoglobulin levels, have been observed, but these findings are inconsistent.

Associated malignant neoplasms: First-degree relatives are at about threefold increased risk of NHL (2). Note that based on rates from 2002–2004, 2% of men and women in the general population (one in 50) will be diagnosed with NHL during their lifetime, at a median age of 67 years (of these, about 1.7% are diagnosed younger than age 20; 4% between 20 and 34; 22% between 35 and 54; 41% between 55 and 74; and 32% older than age 75) (3). Risk of other hematolymphoid cancers, especially Hodgkin lymphoma (among relatives of early-onset NHL cases, relative risk = 3.2) and chronic lymphocytic leukemia, also appears to be increased. A pooled analysis of 10 211 NHL cases and 11 905 controls from the InterLymph Consortium documented increased NHL risk in persons who reported first-degree relatives with NHL (odds ratio [OR] = 1.5; 95% confidence interval [CI] = 1.2 to 1.9), Hodgkin disease (OR = 1.6; 95% CI = 1.1 to 2.3), and leukemia (OR = 1.4; 95% CI = 1.2 to 2.7) (4). Risk patterns differed by specific hematopoietic malignancy and gender of the relative. Some studies have found modestly increased risk of solid tumors; the evidence is most consistent for cancers of the stomach, pancreas, and prostate, although melanoma and tumors of the breast,

colon, ovary, and kidney have also been less convincingly reported (2,5,6). Whether these patterns of risk also characterize familial NHL is unclear.

Associated benign neoplasms: None known.

Cancer risk management: No consensus.

Comments: A growing body of epidemiological evidence supports a familial component to NHL risk, especially B-cell NHL. Overall, a family history of NHL confers about a threefold risk, which is a stronger association than that related to most other suspected risk factors. Given the continuing evolution and complexity of NHL histological classification schemes, studies cannot be easily pooled to assess the familial or genetic patterns related to specific NHL subtypes (7–9). Histological concordance within families is variable, and families with cases limited to specific subtypes (eg, mantle cell lymphoma or mycosis fungoides) are *very* rare. Some familial clustering of certain lymphoma subtypes may represent transmission of an infectious agent (eg, human T-cell lymphotrophic virus type 1 in adult T-cell leukemia–lymphoma and Epstein–Barr virus in Burkitt's lymphoma in Africa) or other shared environmental exposure(s). Several recent studies have suggested that some familial clustering may be due to gene-environment interactions; for example, the risk of NHL associated with certain exposures is greater among individuals with a family history of hematolymphoid cancer (10,11).

A small subset of familial clustering of NHL can be explained on the basis of rare inherited syndromes, in which NHL may appear alone or as part of a constellation of malignancies. Many of these syndromes have distinctive clinical manifestations, and the underlying genetic defect has been identified in several, so the clinician must be especially alert to unusual patterns of nonneoplastic illness within multiplex NHL families. For example, NHL occurs as a manifestation of inherited syndromes featuring immunodeficiency (eg, Wiskott–Aldrich syndrome, X-linked immunoproliferative disease, common variable immunodeficiency, severe combined immunodeficiency), genomic instability (eg, ataxia telangiectasia, Bloom syndrome, Nijmegen breakage syndrome), and autoimmunity (eg, autoimmune lymphoproliferative syndrome).

A growing body of evidence has suggested that a variety of biologically plausible candidate genes of lesser effect may modify the risk of developing NHL [reviewed by Skibola et al. (12)], including genetic variants in *TNF*, *IL10*, DNA repair genes, n-acetyltransferase, cyclin D1, oxidative stress, metabolic genes, one-carbon metabolism, and proinflammatory and immunoregulatory genes (13).

Genetic anticipation (the occurrence of an inherited disease at progressively younger age in successive generations) has been suggested, although true anticipation is difficult to prove (14).

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25. Melanoma, Hereditary Multiple (includes Dysplastic Nevus Syndrome, Familial Atypical Mole–Malignant Melanoma Syndrome, Melanoma–Pancreatic Carcinoma Syndrome, Melanoma–Astrocytoma Syndrome, Familial Uveal Melanoma)

OMIM numbers: 123829, 155600, 155601, 155755, 600160, 606660, 606661, 606719, 608035, 609048.

Inheritance pattern: Autosomal dominant.

Gene and chromosomal location: At least four melanoma susceptibility loci have been identified. CMM1 (at 1p36) is characterized by multiple melanomas and dysplastic nevi. This linkage finding is controversial, and no candidate gene has yet been identified. CMM2 (at 9p21) is caused by germline mutations in *CDKN2A*, a tumor-suppressor gene that produces two alternative transcripts: $p16^{INK4A}$ and $p14^{ARF}$. The former protein, which is affected by most *CDKN2A* mutations, participates in the retinoblastoma (*RB*) gene pathway, whereas dysfunction in the latter protein acts through the *p53* pathway. It has been suggested that functional impairment of *CDKN2A* is associated with reduced cellular capacity to repair UV-related DNA damage (1). Approximately 20%–40% of melanoma-prone kindreds are linked to *CDKN2A*. CMM3 is caused by germline mutations in *CDK4* (at 12q14), which functions downstream to *CDKN2A* in the *RB* pathway, as a dominant oncogene. *CDK4* mutations are quite rare, with only a few affected families identified thus far (2). A fourth melanoma susceptibility locus (CMM4 at 1p22) has been mapped, but the gene has not yet been identified (3).

Common, low-penetrance variants in the melanocortin-1 receptor (*MC1R*) are associated with a twofold to fourfold increase in risk of both sporadic and familial melanoma compared with carrying wild-type *MC1R*, particularly in individuals with multiple variant alleles (OR = 3.9; 95% CI = 3.3 to 4.6) (4). *MC1R* is regarded as a low-risk melanoma susceptibility gene, even in patients with *CDKN2A* mutations (5).

Similar, but weaker and less consistent associations have been reported for variants in the *ARLTS1* tumor suppressor gene (6), in the Nijmegen breakage syndrome gene *NBS1* (7), a common variant in *CDKN2A* (A148T), which confers a 2.5-fold increase in melanoma risk in the general population (8), and a common *BRCA2* variant (associated with a 1.8-fold increase in sporadic melanoma risk: $P = 0.002$) (9). These low-penetrance genetic variants would not be expected to cause familial clustering of melanoma, but (if confirmed) may be important modifiers of melanoma risk.

Mutations: Two online *CDKN2A* mutation databases: http://emelanobase.wmi.usyd.edu.au:/melanoma.html and https://biodesktop.uvm.edu/perl/p16 document many nonsense, missense, and insertion mutations in this gene that disrupt the $p16^{INK4A}$ transcript (this disorder is often referred to as being caused by mutations in p16). Occasionally, unusual deleterious genetic lesions in *CDKN2A* (such as intronic variants leading to aberrant splicing and large deletions or rearrangements) are identified in patients without detectable mutations in sequencing assays When this affects the $p14^{ARF}$ transcript, different clinical manifestations may be seen (described below). Only two germline *CDK4* mutations have been identified to date: Arg24Cys and Arg24His (2). A logistic regression model that permits estimating *CDKN2A* carrier probability has been developed (10).

Incidence: It is estimated that 5%–7% of melanoma patients are from genetically high-risk families and that 0.2%–2.0% of unselected melanoma patients have germline *CDKN2A* mutations (11). Approximately 8% of families containing two affected first-degree relatives with melanoma have germline *CDKN2A* mutations vs 20%–54% of families with more than two cases (12,13). Individuals with multiple primary melanomas, regardless of family history, have a 10%–15% probability of germline *CDKN2A* mutation. An individual with melanoma who has a family member with multiple melanomas has a 45% probability of germline *CDKNA2* mutation. An individual with melanoma who has a family history of both melanoma and pancreatic cancer has a 45% probability of carrying a *CDKN2A* mutation (14,15). In greater than 50% of multiple-case families, no mutations in *CDKN2A* or *CDK4* can be found.

Diagnosis: A "melanoma family" is defined by the presence of three or more affected blood relatives in families located in regions of intense sun exposure and two or more affected blood relatives in less heavily insolated locales. Early age at melanoma diagnosis (mean = 34 years) and a tendency to develop multiple primary melanomas characterize these families (16). The presence of 10 to more than 100 moles on the upper trunk and limbs, with variability in mole size (5–15 mm), outline, and color, suggests the presence of dysplastic nevi, the most important melanoma precursor (17,18). These clinical features, together with the presence of other cancers linked with familial melanoma (see below), suggest the presence of a genetic susceptibility to melanoma.

The presence of dysplastic nevi in the general population is not uncommon, and their genetic basis is uncertain. They may be found in some melanoma kindreds with *CDKN2A* or *CDK4* mutations, but mutation carriers do not invariably develop dysplastic nevi. There are data suggesting that *CDKN2A* mutations confer a "nevogenic" predisposition, as there are strong correlations between mutation status and total nevus number and nevus density (19). A genome-wide search for genes controlling nevus density showed linkage several loci, including 9p21 (where *CDKN2A* resides), 9q21 (the Dutch cutaneous and/or ocular melanoma locus—see below), and 5q31 (20).

Laboratory features: There is no evidence to suggest that the microscopic appearance of hereditary melanoma or dysplastic nevi differs significantly from that of their sporadic counterparts.

Associated malignant neoplasms: The presence of melanoma in one first-degree relative confers a 2.5- to 3.0-fold risk of melanoma, whereas an affected sibling and parent together confer a ninefold increase in risk (21).

In contrast, the relative risk (RR) of melanoma in *CDKN2A* mutation carriers is 75–100 times greater than that observed in the general population. Families with *CDKN2A* mutations have an average melanoma penetrance of 30% by age 50 years, and 67% by age 80 years (22), a figure that varies considerably between populations. Lifetime risks have been estimated as 53% in Europe, 76% in the United States, and 91% in Australia. Limited data suggest that the penetrance related to *CDK4* mutations is similar (23). Familial melanoma risk is also influenced significantly by year of birth, levels of sun exposure, age, geographic location, and modifier genes (11).

A prospective study of cancers other than melanoma in a cohort of *CDKN2A* mutation carriers demonstrated a significantly elevated overall risk of cancer, with a 38-fold increase in the risk of pancreatic cancer accounting for most of the excess (24). The cumulative lifetime risk of pancreatic cancer in mutation carriers ranges from 11% to 17% (11). A review of the "familial melanoma with pancreatic cancer syndrome" (OMIM 606719) identified 42 *CDKN2A*-positive families with both malignancies and suggested that these kindred were more likely to display mutations affecting splice-sites or Ankyrin repeats 3 and 4 than were mutations in families lacking pancreatic cancer. No other clinical differences were observed between these two familial melanoma subsets (25). The age at diagnosis for pancreatic cancer occurring in the context of a melanoma family history is, on average, 5.8 years younger than that observed for sporadic pancreatic cancer (26).

Astrocytoma and other neural-derived tumors occur with melanoma in rare families, a constellation designated the melanoma with astrocytoma syndrome (OMIM 155755) (27,28). Analysis of affected families demonstrated the potential role of $p14^{ARF}$, the protein created by alternative splicing of the first exon (exon 1β) to exons 2 and 3 of *CDKN2A*. Loss of $p14^{ARF}$ function may be the critical genetic lesion in the melanoma–astrocytoma syndrome (29) as well as predisposing to a small subset of site-specific cutaneous melanoma families (30,31).

One Swedish study suggested that a subset of *CDKN2A* mutation-positive families presents an excess risk of breast cancer, documenting a fourfold increase in breast cancer risk within mutation-positive families, in which women also seemed particularly prone to

multiple primary melanomas (32). The plausibility of a link between familial melanoma and breast cancer is supported by evidence that a common, less highly penetrant *CDKN2A* variant is associated with a significant increase in the risk of sporadic breast cancer (8).

Ocular melanoma (primarily of the uveal tract) has been reported occasionally in multiple-case familial cutaneous melanoma kindred both with and without *CDKN2A* mutations, but only one of 385 (33) and none of 155 (34) uveal melanoma patients have been found to carry *CDKN2A* mutations. The current consensus is that *CDKN2A*-positive cutaneous melanoma patients should *not* be considered at increased risk of ocular melanoma. A novel genetic locus linked to families with both ocular and cutaneous melanoma was mapped to chromosome band 9q12.32; no specific gene has yet been implicated (35).

A pooled analysis by the Melanoma Genetics Consortium of 2137 patients from 466 families with three or more melanomas confirmed a strong association between pancreatic cancer and *CDKN2A* mutations ($P < 0.0001$) but revealed little evidence to support hypothesized associations with neural ($P = 0.52$) or ocular ($P = 0.25$) tumors (16). An analysis of cancer occurrence among the relatives of 4079 melanoma patients from the Utah Population Database found significantly increased risks (ranging from 32% to 72%) for a number of cancer sites that have not been previously implicated in the hereditary melanoma disease spectrum, including cancers of the prostate, breast, and colon, as well as non-Hodgkin lymphoma and multiple myeloma (36).

Associated benign neoplasms: Dysplastic nevi.

Cancer risk management: A prospective, 14-year follow-up of 2080 members of 280 Swedish melanoma families confirmed prior reports suggesting that close skin surveillance identifies melanomas with a very favorable prognostic profile, including a high proportion (37%) of in situ melanomas, very thin median tumor thickness (0.5 mm) for the invasive melanomas, near absence of ulceration (8%), and a low prevalence of vertical growth phase (54%) (37). In this series, there were no melanoma recurrences or deaths among 32 family members whose melanomas were diagnosed during prospective follow-up. An online computer tool is now available to permit efficient identification of persons at increased melanoma risk, to guide prevention and management efforts (http://www.cancer.gov/melanomarisktool/) (38). An Italian study has demonstrated significantly increased likelihood of finding *CDKN2A* mutations with increasing numbers of affected family members (RR = 6.3, $P = 0.0009$), multiple primary melanomas (RR = 3.4, $P = 0.001$), and early-onset melanoma (RR = 4.6; $P = 0.003$) (39). Clinical mutation testing for *CDKN2A* mutations is available, but its utility is subject to debate (40,41). The Melanoma Genetics Consortium (GenoMEL) has summarized the issues as follows: the majority of multiple-case families (≥60%) will not have a detectable mutation; up to 10% of melanomas developing in mutation-positive families occur in *mutation-negative* family members (therefore, melanoma screening and risk-reduction activities must still be applied to such individuals); counseling mutation carriers regarding melanoma risk is difficult due to wide variations in confidence intervals and point estimates of lifetime gene penetrance; functional consequences of many *CDKN2A* variants are uncertain; there is considerable uncertainty regarding the risk of cancers other than melanoma in these families; and the efficacy of specific management strategies for mutation carriers remains unproven. The Consortium concluded that genetic testing for germline mutations in *CDKN2A* should be offered clinically only in "rare, exceptional" circumstances because "clinical evaluation of risk remains the gold standard for prevention of melanoma" (40). Some investigators advocate judicious utilization of *CDKN2A* mutation testing, citing the successful introduction of predisposition testing for hereditary breast and colon cancers notwithstanding many of the same issues (41), particularly when attention is paid to selection of patients at sufficiently high risk, education and counseling needs of the patient and their family, valid test interpretation, and alteration of medical management in appropriate individuals. Hansen et al. (41) also noted that skin self-examination was strongly associated with one's understanding of personal risk and that increased surveillance results in earlier detection of thinner melanomas (42). Hansen et al. (41) also pointed out that there may be some value (both psychological and financial) in being able to offer less aggressive surveillance for those family members who can be proven to not carry a *CDKN2A* mutation that has been previously been demonstrated in another family member.

Although hereditary melanoma is characterized by a younger-than-usual age at diagnosis and a predilection for multiple independent primaries, the prognosis and survival of these patients are equivalent to that of sporadic melanoma patients (43). Hereditary melanoma should therefore be managed according to standard clinical guidelines. A key point relative to the surgical management of dysplastic nevi: complete excision with negative margins represents adequate treatment. Wide excisions should not be employed in the removal of dysplastic nevi which lack histological evidence of melanoma.

The Melanoma Genetics Consortium has published guidelines for the management of high-risk patients (44):

- Educate family members regarding the need for cutaneous photoprotection and the need to avoid sunburn, particularly in children;
- Educate family members regarding pigmented lesion characteristics that suggest the presence of melanoma; Perform a baseline, head-to-toe skin examination (including the scalp and genitals) at age 10, and repeat every 6–12 months;
- Perform monthly self-examination of the skin, seeking to identify new or changing pigmented lesions;
- Supplement skin cancer surveillance with clinical photographs to facilitate recognizing clinically important pigmented lesion changes, especially in patients with numerous clinically atypical nevi;
- Increase the frequency of skin examination during puberty and pregnancy, periods during which nevi may change rapidly;
- Consider the use of epiluminescence microscopy as an adjunct to evaluating pigmented lesions (45);
- Excise all pigmented lesions that are clinically suggestive of melanoma as well as those that are changing in a clinically worrisome manner. Avoid wholesale, prophylactic removal of all nevi;

- Remain alert to the possibility that melanomas may arise de novo on clinically normal skin. They do not invariably evolve from preexisting nevi; and
- Follow standard breast cancer screening guidelines, as determined by each woman's breast cancer risk profile.

There are no data to suggest clinical value for routine cancer screening that targets the pancreas or the brain. However, pancreatic screening has been advocated by some (46) and is included in the American Gastroenterological Association Medical Position Statement (47), which states that screening for pancreatic cancer "should be initiated 10 years before the age at which pancreatic cancer has been first diagnosed in families with syndromes and after age 35 in hereditary pancreatitis." See Pancreatic Cancer chapter for a discussion of screening, which remains controversial and of unproven benefit. The management of familial melanoma has been recently reviewed (48).

Epiluminescence microscopy (ELM) is an office-based technique that allows noninvasive in vivo evaluation of colors and microstructures of the epidermis, the dermoepidermal junction, and the papillary dermis that are not visible to the naked eye. It offers improved sensitivity and specificity in distinguishing between atypical melanocytic lesions and melanoma (49). Digital ELM has been reported to further improve the performance characteristics of this screening tool, identifying a significant number of lesions as melanoma that were not so classified by other approaches (45). Although proof of screening efficacy using the metric of reduced melanoma mortality is still lacking, this strategy is being used (particularly in Europe) in the management of persons at increased melanoma risk.

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26. Mosaic Variegated Aneuploidy

OMIM number: 257300, 602860.

Inheritance pattern: Autosomal recessive.

Gene and chromosomal location: *BUB1B* at 15q15, encoding a protein involved in mitotic spindle checkpoint regulation.

Mutations: May be either missense or truncating.

Incidence: Rare. Biallelic mutations found in five of eight families with this disorder (1). Matsuura et al. (2) found only monoallelic *BUB1B* mutations in seven cases of mosaic variegated aneuploidy (MVA) with premature chromatid separation (PCS) but identified a haplotype associated with reduced *BUB1B* transcript and concluded that a more than 50% decrease in *BUB1B* activity was required to cause abnormal spindle checkpoint function and MVA syndrome.

Diagnosis: Affected individuals most often have severe intrauterine growth retardation, microcephaly, and anomalies of the eyes. Also reported are dysmorphism, variable developmental delays, seizures, congenital heart anomalies, genitourinary anomalies, Dandy–Walker complex, and quadriplegia.

Laboratory features: Chromosomal analysis of blood and other tissues manifests mosaic aneuploidies, predominantly trisomies and monosomies, involving multiple different chromosomes and manifests PCS. PCS involves separated chromatids with visible centromeres and may involve most chromosomes of a metaphase. PCS is reported in approximately 2% of metaphases in cultured lymphocytes from approximately 40% of normal individuals. When present in 5% or more of cells, this has been called "heterozygous PCS trait" and is not associated with any specific phenotype except possible reduced fertility (3). Inheritance is autosomal codominant (4), and any association with *BUB1B* mutations is undefined.

Associated malignant neoplasms: Embryonal rhabdomyosarcoma seemed most strongly associated, with Wilms tumor and leukemias also reported (1). However, in the series of Matsuura et al. (2), all seven patients had Wilms tumor, whereas two also had embryonal rhabdomyosarcomas.

Associated benign neoplasms: None known.

Cancer risk management: The risks and benefits of screening in this disorder are entirely undefined. Of the tumors to which affected individuals may be predisposed, screening for Wilms tumor should be offered despite acknowledging that the absolute risk of this tumor in MVA is unknown. Abdominal palpation and ultrasound every 3–4 months from infancy through age 6 has been suggested. A high clinical index of suspicion for sarcomas and hematologic abnormalities is warranted.

Comments: Mosaic variegated aneuploidy and translocation mosaicism as a laboratory finding have been reported in Rothmund–Thomson syndrome and Werner syndrome and so is not unique to MVA. These disorders do not manifest PCS.

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27. Multiple Endocrine Neoplasia Type 1 (MEN1; Wermer Syndrome; includes Zollinger–Ellison [Z–E] Syndrome; also Multiple Endocrine Neoplasia Type 1B [MEN 1B] noted)

OMIM number: 131100, 600778.

Inheritance pattern: Autosomal dominant.

Gene and chromosomal location: *MEN1* is a 10-exon gene at 11q13. Its function is unknown, although recent data suggest that it is a regulator of gene transcription, cell proliferation, apoptosis, and genome stability (1).

Mutations: More than 400 different frameshift, nonsense, missense, insertion, and deletion mutations have been reported; the gene is suspected to function as a tumor suppressor gene. Ten percent of germline mutations are de novo. Clinical recommendations cannot currently be based upon genotype, although Kouvaraki et al. (2) reported increased risks of pancreatic endocrine tumors in those with truncating mutations vs mutations of other types (100% vs 79%, $P = 0.03$); all four glucagonomas in their series had truncating mutations ($P = 0.004$), and frameshift mutations in exon 2 were associated with pituitary tumors ($P < .001$). A trend toward overrepresentation of truncating mutations was observed among those developing thymic carcinoid tumors (3).

Incidence: One in 5000–50 000 estimated in white populations.

Diagnosis: This disorder is generally diagnosed when there are two major lesions (metachronous or synchronous) involving the parathyroid, endocrine pancreas, and/or anterior pituitary or one major MEN 1–related lesion is present in an individual who has a first-degree relative previously diagnosed with MEN 1. Others make the diagnosis of MEN 1 based on having three or more of the following: tumors of the parathyroid, endocrine pancreas, pituitary, adrenal, or neuroendocrine carcinoid. MEN 1 is characterized by a high frequency of disorders of the pituitary (30%–55%), parathyroid (95%), pancreas (50%–75%), and adrenal (16%) glands. Hyperparathyroidism (HPT) is the presenting symptom (65%) and/or is diagnosed simultaneously with the presenting symptom in 94% of cases. Penetrance of MEN 1 is high: 45%, 82%, and 96% by ages 30, 50, and 70 years, respectively (4). Because of the relatively common nature of these endocrine disorders, it has been estimated that 10% of patients diagnosed with sporadic MEN 1 might be phenocopies (5). The prevalence of *MEN1* mutations was studied in 124 subjects who exhibited 1–4 MEN 1-related features in the absence of a positive family history. Mutations were found in 26% of persons with two or more manifestations and 100% of those with four (6).

Laboratory features: One may find elevated adrenocorticotropic hormone (ACTH), hypoglycemia, high gastrin and/or insulin levels, HPT, and/or glucose intolerance. Other abnormalities may include elevated pancreatic polypeptide, glucagon, proinsulin, somatostatin, vasoactive intestinal peptide (VIP), or neurotensin.

Associated malignant neoplasms: Pancreatic or duodenal neuroendocrine tumors occur in 30%–80% of patients with MEN 1; pancreatic endocrine tumors are the most common cause of death. Nearly half of tumors have metastasized to regional nodes at diagnosis. The MEN 1 pancreas may show islet hypertrophy, hyperplasia, dysplasia, micro- or macroadenomas, and islet carcinomas. Even the smallest or earliest of these lesions, so-called monohormonal endocrine cell clusters, demonstrate loss of heterozygosity of the *MEN1* locus, which was not observed in islet cell hypertrophy (7). A prospective endoscopic ultrasound imaging study of 82 mutation carriers documented that small (<15 mm) tumors grow very slowly and seldom metastasize. Approximately 0.6 new tumors develop per patient year (8).

Gastrinomas, often multicentric, occur in 54% of mutation carriers and are most often in the duodenum (90% of gastrinomas) or head of pancreas. These may present as peptic ulcer disease. Zollinger–Ellison (Z–E) syndrome is diagnosed when serum gastrin is more than 1000 pg/mL and the gastric pH is 3 or less while fasting. Approximately 25% of Z–E patients have MEN 1. However, two-thirds of gastrinoma patients have gastrin levels that require provocative testing to make the diagnosis of Z–E. Recent data suggest that the secretin stimulation test (positive = increase ≥120 pg/mL) has the highest diagnostic sensitivity and specificity. A negative secretin test in a patient highly suspect of having Z–E should be followed by the calcium test, and 38%–50% will be positive (9).

Malignant islet cell tumors (glucagonomas, VIPomas, PTHrPomas, insulinomas) are treated with resection. Insulinomas (benign or malignant) occur in less than 10% of MEN 1 cases but are the most common functioning pancreatic endocrine tumor in MEN 1 patients younger than age 25 years. Less than 10% of individuals with insulinomas have MEN 1. Glucagonomas occur in approximately 3% of MEN 1 patients.

Carcinoids are the second most common cause of death in MEN 1 and are more likely to arise in the thymus, bronchus, or stomach than are sporadic carcinoids. Up to 25% of thymic carcinoids are due to MEN 1. These are aggressive tumors, so much so that prophylactic thymectomy may be offered at the time of parathyroid gland surgery. Gastroduodenal carcinoids may be either nonfunctioning or secrete gastrin or serotonin products. Malignant schwannoma, ovarian tumors, pancreatic islet cell carcinomas, adrenocortical carcinomas, non-medullary thyroid neoplasms, and gastrointestinal stromal tumor have also been reported in mutation carriers.

Associated benign neoplasms: HPT is present in more than 95% of MEN 1 patients and occurs at younger ages (mean = 19 years) than sporadic HPT (mean = 50s), with hypercalcemia reported in 66%, 85%, and 87% of MEN 1 patients by ages 25, 55, or older, respectively.

Anterior pituitary adenomas are found in 10%–60% of patients with MEN 1 (of which two-thirds are prolactinomas); note that about 10% of the general population have microadenomas. In a

series of 324 MEN 1 patients, the mean age at diagnosis of pituitary neoplasm was 38 years (range 12–83), and most were macroadenomas (10). Pituitary adenomas may secrete ACTH (about 5%), growth hormone (about 25%), or be nonsecretory (about 10%) and tend to be larger, more aggressive tumors than their sporadic counterparts. About 14% of prolactinomas and 1%–3% of all pituitary adenomas are due to MEN 1.

Adrenal cortical adenomas are said to occur in 35% of individuals with MEN 1. Most are nonfunctioning but they may produce aldosterone or cortisol (Cushing syndrome). Pheochromocytomas are uncommon in MEN 1. A prospective study of adrenal tumors in 38 mutation-positive MEN 1 patients revealed that 55% had adrenal disease, which was detected a mean of 7 years after MEN 1 diagnosis, with a median tumor size of 12 mm (5–40 mm). Twelve were unilateral vs nine bilateral. All were detected by endoscopic ultrasound. Three were functioning tumors, vs 18 nonfunctioning. Only one was malignant. The authors concluded that MEN 1-associated adrenal tumors are mostly small, benign, nonfunctioning and more common than previously recognized (11).

Multiple lipomas (30%), collagenomas (5%), tumors secreting vasointestinal peptide, thyroid neoplasms (non-medullary thyroid cancer), facial angiofibromas (75%, usually on the lip or other area not generally seen in tuberous sclerosis), meningiomas (5%), ependymomas (1%), and leiomyomas (10%) have also been reported.

Cancer risk management: In years past, experts have generally suggested starting MEN 1 screening in adolescence, but the optimal screening initiation age, tests, and frequencies are still undefined. Best clinical judgment guidelines proposed by the International Workshop on MEN 1 (12) and Dreijerink and Lips (13) recommend starting annual biochemical checks at age 5 years for known or suspected carriers of MEN 1 mutations. Serum glucose, insulin, proinsulin, prolactin, and IGF-1 and offering brain imaging every 3 years are recommended. Starting at age 8, serum parathyroid hormone and ionized calcium are suggested annually. Starting around age 20, consider annual fasting serum gastrin and, if gastrin is elevated, conduct a secretin-stimulated gastrin test. At the same age, monitoring of fasting and meal-stimulated pancreatic polypeptide is suggested, as well as fasting VIP and glucagon; somatostatin receptor scintigraphy with computerized tomography (SRS/CT) of thorax and abdomen every 2–3 years; endoscopic ultrasound if there is biochemical evidence of disease but normal SRS/CT imaging. Other markers that may be checked include 24-hour urinary 5-HIAA, calcitonin, and parathyroid hormone. Others recommend some variation of this scheme, and all note that the efficacy, risks, and benefits of these recommendations are unproven. The age at which testing can be discontinued among at-risk individuals is unknown; it probably should be continued for life.

Comments: Familial isolated pituitary adenoma in the absence of MEN 1 or Carney complex has been recognized as a neoplasia syndrome distinct from MEN 1 and Carney complex (14). Viermaa et al. (15) studied three families from northern Finland with low-penetrance predisposition to pituitary somatotropinomas (growth hormone–producing) or prolactinomas and discovered germline founder mutations in a gene called *AIP* on 11q12–11q13. In a population-based series, 16% of Finnish patients with somatotropinomas had *AIP* mutations and 40% of these were diagnosed younger than age 35 years. A nonsense mutation in *AIP* was also detected in Italian siblings with somatotrophinoma.

A mutation in *CDKN1B* (p27) at 12p13 was found in a woman with primary HPT and a pituitary adenoma and her sister who had a renal angiomyolipoma, but not among 380 controls. This was called MEN 1B (16).

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28. Multiple Endocrine Neoplasia Type 2A, 2B (Sipple Syndrome), and Familial Medullary Thyroid Cancer

OMIM number: 171400, 155240, 162300.

Inheritance pattern: Autosomal dominant.

Gene and chromosomal location: The *RET* proto-oncogene, at 10q11.2.

Mutations: *RET* mutations are identifiable in more than 98% of cases of multiple endocrine neoplasia type 2A (MEN 2A) and 85% of familial medullary thyroid cancer (FMTC), in which they involve exons 10 and 11, targeting one of five cysteines in the extracellular binding domain of the encoded protein. MEN 2B is characterized by a M918T mutation in codon 918 of exon 16 in 95% of cases and an A883F mutation in exon 15 in most of the others. Nearly all germline *RET* mutations causing MEN 2A and FMTC are inherited; 40% of mutations causing MEN 2B occur de novo. Among human cancer susceptibility syndromes, this set of disorders comprises one of the best examples of the relationship between genotype–phenotype correlation (1,2). Mutations associated with MEN 2A are reported to accelerate cell proliferation, whereas those associated with MEN 2B enhance suppression of apoptosis. These differential effects are hypothesized to account for some of the clinical differences between these groups of patients (3).

Incidence: The incidence of MEN 2 is one in 30,000 births. About 3–10% of all thyroid cancers in clinical practice are medullary thyroid cancer (MTC). Among these, 25% are due to germline *RET* mutations; of these, 5% have MEN 2B. Between 3% and 4% of apparently sporadic MTC will carry occult or de novo germline *RET* mutations. Those resulting from germline *RET* mutations differ from sporadic tumors by being multifocal.

Diagnosis: Based on DNA results, biochemical results, family history, and physical diagnosis. There are three clinical subtypes: 1) MEN 2A is the most common and manifests MTC in nearly all cases, pheochromocytoma (PC) in about 50% of cases, and hyperparathyroidism (HPT) in 15%–30%; 2) MEN 2B, in which the onset of MTC is younger (often younger than age 10 years), HPT seldom occurs, and which is associated with a marfanoid phenotype with mucosal ganglioneuromas; and 3) FMTC, in which MTC is the only finding, and its age at diagnosis is generally older than MTC in MEN 2A or MEN 2B.

Laboratory features: Elevated calcitonin after pentagastrin stimulation; elevated metanephrines or catecholamines if pheochromocytoma is present; possible elevation in serum parathyroid hormone and calcium levels.

Associated malignant neoplasms: MTC with metastatic disease reported as early as ages 3 and 5 in MEN 2B and MEN 2A, respectively. Pheochromocytomas are malignant in 10% and are bilateral (either synchronous or metachronous) in one-third of patients. MTC is almost always diagnosed before the age of 40 in MEN 2A and 2B. MTC in FMTC is a more indolent disease, with onset often after the age of 50 years. Papillary thyroid cancer has also been associated with MEN 2 and FMTC (4).

Associated benign neoplasms: HPT is found in 10%–20% of individuals with MEN 2A; however, this condition is rare in MEN 2B and is never found in FMTC (by definition). Pheochromocytomas are most often benign. Ganglioneuromas of the gastrointestinal tract and mucosal neuromas are present in nearly all patients with MEN 2B.

Cancer risk management: Genetic testing for at-risk individuals is an accepted clinical procedure; evidence suggests that early diagnosis favorably alters outcome, although no prospective trials have been or will be conducted. For those who test positive, prophylactic thyroidectomy should be strongly considered before age 6 months for MEN 2B, before age 6 years for MEN 2A, and between 6 and 10 years in FMTC. Alternatively, age at thyroidectomy may be based on genotype: thyroidectomy before age 5 was advised for patients with "level 2" mutations in codons 611, 618, 620, or 634, as per Brandi et al. (5). Mutations were categorized as level 1 if they carried the least risk of MTC, level 2 for intermediate risk, and level 3 for the most aggressive MTC (generally mutations associated with MEN 2B). There was no consensus on the approach to children with mutations in unclassified codons, but Machens et al. (6) reported no need for thyroidectomy before age 10 in asymptomatic carriers of mutations in codons 609, 630, 768, 790, 804, or 891. The assigned risk levels of some codons have been changed as data have accumulated (2). Skinner et al. (7) presented outcomes of prophylactic thyroidectomy in 50 MEN 2A patients that supported performing thyroidectomy before age 8 years. Although MTC can secrete a diverse array of neuroendocrine markers, calcitonin level and CEA appear to be the most useful in the clinical follow-up of postthyroidectomy patients (8).

Annual screening for pheochromocytomas (urine or plasma fractionated metanephrine) is recommended at the same ages as thyroidectomy, and *must* be done before the patient undergoes any surgery. Screening for HPT (serum calcium and parathyroid hormone) is indicated annually from age 6 onward for MEN 2A carriers. Some have advocated removal of 3.5 parathyroid glands at the time of thyroidectomy in MEN 2A patients (2).

An unsuspected hereditary basis for apparently sporadic pheochromcytoma is found in 17%–24% of such patients. Screening for a genetic etiology in this setting has been recommended for patients with 1) age at diagnosis younger than 20 years and 2) family history or features suggestive of hereditary pheochromocytoma (9). Others advocate genetic screening in all pheochromocytoms patients because hereditary disease has been detected in individuals who did not meet these criteria (10). Some patients with familial pheochromocytoma have no detectable mutations in any of the associated genes, suggesting that additional susceptibility genes remain to be identified (11).

Biochemical screening with pentagastrin-stimulated calcitonin evaluation can be diagnostic in 80% of cases of MEN 2A and 85% of cases of MEN 2B, but up to 82% of the individuals diagnosed in this manner had invasive carcinoma and 10% already had metastatic disease (12). Therefore, aggressive pursuit of genetic testing offers the best chance for evidence-based, proactive management. Families not informative for genetic markers need to decide between aggressive biochemical screening for MTC vs prophylactic thyroidectomy in the at-risk person whose genetic status cannot be determined.

Comments: Studies have shown that mutations of codon 634, which are present in 85% of MEN 2A families, are associated with development of pheochromocytoma and HPT. However, the association is not sufficiently strong to recommend prophylactic surgery to those with the high-risk mutations or to omit pheochromocytoma screening for those without the mutation.

Cutaneous lichen amyloidosis and Hirschsprung disease are associated with specific codons in MEN 2A.

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29. Multiple Myeloma, Familial

OMIM number: 254500.

Inheritance pattern: Uncertain. The most commonly reported pedigree structure involves affected siblings or first cousins; however, a number of multigenerational parent–offspring and proband–aunt and/or uncle relationships have also been observed (1).

Gene and chromosomal location: Undetermined. A *BRCA2* mutation of uncertain significance has been described in one affected member of a myeloma family that also had multiple cases of breast cancer (2). Some investigators have postulated a relationship to major histocompatibility complex genes based on occasional findings of HLA haplotype identity among cases within single families (3,4). No common interfamilial haplotype has been identified.

Mutations: No gene has been cloned.

Incidence: Rare. Based on retrospective reviews of hospital records, familial cases are estimated to account for approximately 2%–2.5% of all myeloma diagnoses.

Diagnosis: Two or more first- or second-degree relatives diagnosed with multiple myeloma (MM).

Laboratory features: None known. When sought, evidence of nonspecific immunoregulatory dysfunction has occasionally been found in relatives of affected cases. Data from systematic screening of first-degree relatives of MM cases are sparse. A proportion of first-degree relatives has been found to have monoclonal gammopathy of undetermined significance (MGUS) in some families. Although infrequent, the prevalence of asymptomatic paraproteinemia in relatives appears to be higher than population estimates predict. Quantitative polyclonal abnormalities in immunoglobulin levels have been seen even more commonly than monoclonal components among relatives.

Associated malignant neoplasms: Population-based case–control studies have indicated an approximate fourfold familial risk of MM in first-degree relatives of cases (5,6). In the Swedish Family-Cancer Database, the standardized incidence ratio (SIR) for myeloma in first-degree relatives of myeloma probands was 2.4. Corresponding SIRs for non-Hodgkin lymphoma and chronic lymphocytic leukemia were 1.3 and 2.4, respectively. All three SIRs were statistically significant (7). The risk to relatives from multiple-case families for cancers other than MM remains undefined. Note that based on rates from 2002 to 2004 in the general population, 0.61% of men and women (one in 165) will be diagnosed with MM during their lifetime, at a median age at diagnosis of 70 years (approximately 0.0% were diagnosed younger than age 20; 4% between 20 and 44; 31% between 45 and 64; 65% age 65 or older) (8).

Associated benign neoplasms: None known. In the general population, patients with MGUS are at increased risk of developing MM. Logic suggests that this applies to familial MM as well, but this issue has not been well studied.

Cancer risk management: No consensus.

Comments: The high proportion of siblings with MM in early reports and reports among married couples, community clusters, and descriptions of virus-like particles in MM cells led to hypothesizing horizontal transmission of an unidentified infectious agent as the basis for these clusters. Because more multigenerational pedigrees have been ascertained over time, it seems that susceptibility may arise through multiple mechanisms. Familial myeloma appears to resemble sporadic MM in most biological respects except that the age at diagnosis appears to be younger in the second generation (9–11).

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30. Neuroblastoma, Hereditary

OMIM number: 256700, 603851.

Inheritance pattern: Autosomal dominant.

Gene and chromosomal location: Etiology appears to be heterogeneous. Mutations found in *PHOX2B* on 4p12. Linkage analyses have identified potential susceptibility loci at 16p12–p31 (1), 4p16 (2), and 2p21–p25.1 and 12p12.1–p13.33, suggesting a possible oligogenic model in which two loci have a synergistic effect on neuroblastoma (NB) risk (3).

Mutations: Heterozygous mutations in the *PHOX2B* found only in one of eight families cosegregating for NB (4,5).

Incidence: The prevalence of NBs in the general population is thought to be about one in 7500–10 000. Inherited cases represent approximately 2%–3.5% of new cases. The penetrance of hereditary cases is estimated at 11.4%, and overall risk to sibs in an unselected series of NB was 0.2% (6). Among 86 individuals with nonsyndromic NB, *PHOX2B* mutations were found in only two (7).

Diagnosis: NB is a neural crest–derived tumor that usually presents in childhood. Most cases of familial NB are diagnosed before the age of 1 year (60%). The age at diagnosis in the other 40% is extremely variable. Familial NB patients are thought to have an earlier median age at diagnosis than those with sporadic NB. *PHOX2B* was considered a candidate gene because of reported increased risk of NB in individuals with congenital central hypoventilation syndrome (CCHS), which is most often due to de novo *PHOX2B* mutations. Individuals with CCHS have a 5%–10% risk of NB, ganglioneuroblastoma, or ganglioneuroma.

Laboratory features: May have increased urinary catecholamines.

Associated malignant neoplasms: NB. Patients with familial NB have a 20% risk of developing bilateral adrenal or multifocal primary tumors.

Associated benign neoplasms: Ganglioneuroma.

Cancer risk management: Investigators demonstrated that NB could be detected by screening for urinary catecholamines at 6 months of age and offered evidence of improvement in the survival of children with screen-detected NB (8). Woods et al. (9) detected NB in 43 of 476 654 children born in Quebec between 1989 and 1994; however 18 cases of NB were missed. The original samples were reanalyzed, but only one case tested positive for catecholamines. Almost all of the tumors that were detected by screening had favorable biologic features—for example, none of the 43 had an amplified *MYCN* oncogene and all 43 children were alive upon follow-up, whereas the tumors that were missed by screening had unfavorable prognoses. However, the risk of mortality due to NB for children in Quebec up to 8 years of age was not significantly lower compared with the risk in the control groups, raising questions regarding whether or not the detected lesions were truly biologically significant.

The efficacy of screening in familial NB is unknown, and the issues are the same as for screening in the general population: uncertainties regarding the performance characteristics of the screening test and the risk of detecting lesions that might never become clinically significant. Urinary homovanillic acid and vanillimandelic acid in urine are increased in 95% of cases of NB. One could screen annually from birth onward after careful discussion with the family of the issues of screening in this disorder. Because of the clinical heterogeneity of hereditary NB, and the possibility of a later age at presentation, it may be necessary to perform screening on individuals at risk of familial NB for a prolonged period of time.

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31. Neurofibromatosis Type 1 (NF1; includes von Recklinghausen Disease)

OMIM number: 162200, 162210, 193520, 609291, 611431.

Inheritance pattern: Autosomal dominant.

Gene and chromosomal location: *NF1* at 17q11.2; encodes a Ras guanosine triphosphate–activating protein known as neurofibromin. Recent studies suggest that neurofibromin plays a role in the adenylate cyclase and AKT-mTOR signaling pathways and modulates cell motility by binding with actin in the cytoskeleton (1)

Mutations: Unique from family to family; all types of mutations have been reported. No genotype–phenotype correlations have been established except for those with deletions of the whole gene, which is associated with facial dysmorphism, early onset of neurofibromas, a higher frequency of learning disabilities, and malignant peripheral nerve sheath tumors (MPNSTs), and a 3 basepair deletion in exon 17 associated with only cutaneous pigmentary features.

Incidence: One in 3000; one-third to one-half of cases represent a new germline mutation.

Diagnosis: National Institutes of Health consensus criteria are shown in Table 12. Because features of NF1 develop with age, the

Table 12. National Institutes of Health Consensus Conference Criteria for the diagnosis of neurofibromatosis type 1 (2)

Diagnosis requires two or more of the following:
1. Café-au-lait macules:
• In children, five or more that are 0.5 cm in diameter or more and
• In adults, six or more that are 1.5 cm in diameter or more
2. Two or more neurofibromas of any type or one plexiform neurofibroma
3. Multiple axillary or inguinal freckles
4. Sphenoid wing dysplasia or congenital bowing or thinning of the long bone cortex (+/-pseudoarthrosis)
5. Bilateral optic nerve gliomas
6. Two or more iris Lisch nodules (iris hamartomas)
7. A first-degree relative with neurofibromatosis type 1 by these criteria

criteria do not reach a level of high sensitivity until about age 8 years.

Genetic testing can also establish a diagnosis. NF1 can present at any age (although it is typically detected by age 6) and in any organ system. Café-au-lait macules (CALs) are sometimes present at birth, but more often appear in late infancy and early childhood, increase in number and size over time, and may decrease in adulthood. Freckling of the axilla and the groin develop during the first 5 years of life up through puberty.

Peripheral neurofibromas can be dermal or epidermal, are soft in texture, do not undergo malignant degeneration, but cause substantial cosmetic problems. Nodular neurofibromas arise on peripheral nerve trunks and may cause neurological symptoms. Their removal, if feasible, requires the expertise of a skilled neurosurgeon to spare the involved nerve. Plexiform neurofibromas are soft, ill-defined peripheral nerve sheath tumors, which extend along the length of a nerve and nerve fascicles. They are a common source of morbidity, including malignant transformation, and may be associated with tissue hypertrophy, CAL pigmentation, or hypertrichosis. They develop in approximately 25% of individuals with NF1, and most are diagnosed in early childhood.

Seizures are reported in 2%–5% of affected individuals; learning disabilities are reported in 25%–40%, with frank mental retardation in 5%–10%. An unknown percent have visceral arterial aneurysms and pulmonary fibrosis. Lisch nodules, which are harmless hamartomas of the iris, are present in only 10% of affected individuals younger than age 10, 50% by age 29, and nearly 100% of affected individuals by age 60 (3,4).

NF1 can manifest as skeletal abnormalities, including short stature (15%–20%), a distinctive dysplasia of the sphenoid wing, cortical bone thinning, or vertebral dysplasia associated with scoliosis (10%). Of all patients with congenital pseudoarthroses, 40%–50% likely have NF1. Up to 10% of NF1 patients may have a congenital pseudoarthrosis.

Laboratory features: The histopathology of any given lesion is not specific for NF1. Skin biopsy examination of CALs reveals giant melanosomes or melanin macroglobules, which are nonspecific. Histologically, evidence suggests that neurofibromas form from Schwann cells, with proliferation of neurons, fibroblasts, and perineurial cells being stimulated by mast cells drawn to nullizygous Schwann cells, creating a cytokine-rich environment.

Associated malignant neoplasms: MPNSTs, formerly called neurofibrosarcomas or malignant schwannomas, occur in 3%–15% of affected individuals, with mean age at diagnosis of 29 years, and typically develop in preexisting plexiform neurofibromas. Conversely, it has been estimated that 50% of individuals with MPNSTs have NF1. Complete surgical removal of MPNST is the only curative treatment; the latter requires early diagnosis. Outcome appears to be worse for NF1-associated MPNSTs compared with sporadic MPNSTs (5,6). Also, there is increased risk (no greater than 1%) for astrocytomas, carcinoids (usually duodenal), pheochromocytomas, neuroblastomas, ependymomas, primitive neuroectodermal tumors, rhabdomyosarcomas (especially of the pelvis), and undifferentiated sarcomas as well as for Wilms tumor and leukemia (juvenile myelomonocytic leukemia). About 15% of children with NF1 have signs of optic pathway tumors by imaging studies, due to pilocytic astrocytoma. Only a subset of these will become symptomatic and require treatment (7). Malignant optic nerve gliomas also occur, causing vision loss and other neurological symptoms due to direct extension into the brain (8). A prospective follow-up study of 304 women with NF1 20 years or older documented the occurrence of 14 breast cancers (standardized incidence ratio [SIR] = 3.5; 95% confidence interval [CI] = 1.9 to 5.9); six cases occurred in women aged 50 or younger (SIR = 4.9; 95% CI = 2.4 to 8.8) (9).

Associated benign neoplasms: Peripheral, nodular, or plexiform neurofibromas; benign pheochromocytomas (risk = 0.1%–1.0%); meningiomas; Lisch nodules of the iris; and hamartomatous intestinal polyps (10). Gastrointestinal stromal tumors (preferentially of the small intestine) can arise via hyperplasia of the interstitial cells of Cajal, located within the intestinal wall (11). Although some optic nerve gliomas are histologically benign, they are still a source of marked clinical morbidity.

Cancer risk management: Guidelines for management of the nonneoplastic complications of NF1 have been published (11–13); the details are beyond the scope of this handbook. In screening for neoplasia, an annual physical examination with twice-a-year blood pressure monitoring is advised (hypertension can be caused by renal vascular dysplasia or pheochromocytoma). Patients should be educated to report any lesion that shows rapid enlargement, pain, or new itching. 2-[^{18}F] fluoro-2-deoxy-D-glucose (FDG) and positron emission tomography (PET) may facilitate the identification of malignant transformation in deep-seated neural tumors (14). New onset of headaches, hearing loss, visual change, or other neurological deficits should be carefully sought and fully evaluated. Serial ophthalmologic examinations, particularly in young children, are recommended to monitor for the presence of optic pathway tumors. Mammographic screening is recommended to begin at age 40. The risks and benefits of cancer screening in this syndrome are not established. Oral pirfenidone has been evaluated to slow the progression of NF1-related neural tumors (15). Vitamin D deficiency is inversely correlated with the number of dermal neurofibromas; the potential therapeutic value of vitamin D supplementation has not yet been determined (16).

Comments: There are several recent reports that germline homozygosity for mutations in one of four DNA mismatch repair genes (*MLH1*, *MSH2*, *MSH6*, or *PMS2)*, heterozygous mutations of which cause Lynch syndrome, can result in CALs or neural tumors sufficiently numerous to suggest NF1; these individuals are

at high risk of brain tumors, hematologic malignancies, and very early onset of colorectal tumors (17). Note that 10%–25% of the general population has one to three CALs.

Germline loss of function mutation in *SPRED1* on 15q, another member of the *RAS-MAPK* pathway, has recently been reported to cause a NF1-like phenotype (18). The phenotype includes multiple CALs, axillary freckling, macrocephaly, and Noonan-like dysmorphism. Thus, affected individuals could fulfill the NF1 diagnostic criteria. Radiation therapy has been associated with development of MPNST in the field of radiation (19,20).

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32. Neurofibromatosis Type 2 (sometimes called Central Neurofibromatosis or Bilateral Acoustic Neurofibromatosis)

OMIM number: 101000, 607379.

Inheritance pattern: Autosomal dominant.

Gene and chromosomal location: Neurofibromatosis type 2 (*NF2*) at 22q12.2.

Mutations: More than 150 mutations (none are common) have been reported in *NF2*, which encodes a protein designated neurofibromin-2 (also called merlin). It functions as a tumor suppressor and a regulator of Schwann cell and leptomeningeal cell proliferation (1). Genetic testing by direct mutation analysis or by linkage analysis is available clinically. Nonsense or frameshift mutations are associated with younger age at onset of symptoms and a greater number of tumors (2). Approximately 25% of individuals with de novo gene mutations are mosaic for the mutation, increasing the difficulty of making a molecular diagnosis. Chromosomal changes detectable on karyotyping are infrequent. Large submicroscopic deletions encompassing the *NF2* gene affect 10% of families and are not associated with cognitive impairment even if quite large. Cytogenetically visible deletions do cause cognitive impairment and/or congenital anomalies. Ring chromosome 22 has been reported in patients with multiple meningiomas and vestibular schwannomas fulfilling NF2 criteria. Apparently the ring contains the *NF2* locus, but the ring may be lost somatically.

Incidence: One in 35 000, of which 50% have de novo mutations. About 7% of vestibular schwannomas are due to NF2.

Diagnosis: Tables 13a and 13b show two different sets of suggested clinical diagnostic criteria. The Manchester Criteria (5) have been reported to increase diagnostic sensitivity without a decrease in specificity (6).

Genetic testing can also establish a diagnosis. If a person with documented NF2 has no family history of NF2 and no detectable gene mutation in peripheral blood, DNA analysis of cultured skin fibroblasts or frozen tumor may permit the recognition of somatic mosaicism.

The clinical features vary widely between families and have recently been reviewed (1). In a report of 150 affected individuals, the mean age at onset was 21.6 years, with no patient presenting with a new diagnosis after the age 55. Forty-four percent presented with hearing loss, which was unilateral in 35%. Tinnitus was present in 10%. "Acoustic neuromas" are now designated "vestibular schwannomas," and similar lesions occur in other cranial and peripheral nerves, affecting sensory nerves more often than motor nerves. Slattery et al. (7) reported that approximately 10% of untreated vestibular schwannomas had increased by at least 5 mm during 4 years of follow-up. Muscle weakness and wasting was the presenting symptom in 12% (due to spinal cord tumors or peripheral neuropathy). Café-au-lait spots were found in 43%, and they tended to be few, large, and pale. Only 1% had six or more café-au-lait macules (ie, unlikely to fulfill NF1 criteria). Cataracts were present in 34 of 90 individuals in this group. Bouzas et al. (8) described 54 patients; 80% had posterior subcapsular cataracts, which often remained minor. Retinal hamartomas are present in 22% of individuals with NF2. Twenty percent of affected individuals have intradermal neurofibromata, with 33% showing a

Table 13a. National Institutes of Health Consensus Conference Criteria for the diagnosis of neurofibromatosis type 2 (3)[a]

Diagnosis of NF2 requires one of the following two major criteria to be met:
1. Bilateral eighth nerve masses seen by MRI with gadolinium or
2. First-degree relative with NF2 plus one of the following:
• CT or MRI evidence of an unilateral eighth nerve mass
• A plexiform neurofibroma
• Neurofibromas (two or more)
• Gliomas (two or more)
• Posterior subcapsular cataract at a young age
• Meningioma (two or more)
• Imaging evidence of an intracranial or a spinal cord tumor

[a]MRI = magnetic resonance imaging; NF2 = neurofibromatosis type 2; CT = computed tomography.

Table 13b. Neurofibromatosis Type 2: Manchester Criteria (4)[a]

Diagnosis of NF2 requires the following:
1. Bilateral vestibular schwannomas or
2. A first-degree relative with NF2 and
• A unilateral vestibular schwannoma or
• Two of meningioma, schwannoma, glioma, neurofibroma, posterior subcapsular lenticular opacities or
3. Unilateral vestibular schwannoma and any two of meningioma, schwannoma, glioma, neurofibroma, posterior subcapsular lenticular opacities or
4. Multiple meningiomas and
• unilateral vestibular schwannoma or
• any two of schwannoma, glioma, neurofibroma, cataract

[a]NF2 = neurofibromatosis type 2.

palpable spherical tumor involving a peripheral nerve and 47% having a raised rough pigmented area with excess hair. NF2 is most likely associated with a mononeuropathy in childhood and a polyneuropathy in adulthood (9).

Laboratory features: No specific findings. Subtle but nondiagnostic differences in histopathological findings have been noted between tumors from NF2 patients and sporadic tumors of the same type. Predictive genetic testing based either on linkage or mutation analysis is available.

Associated malignant neoplasms: Gliomas (4%), ependymomas (3%) (10). Astrocytomas and ependymomas may present as intramedullary tumors in approximately one-third of NF2 patients with spinal cord tumor.

Associated benign neoplasms: Vestibular schwannomas (acoustic neuromas), meningiomas, and spinal cord schwannomas (in about two-thirds subjects). Individuals who develop a unilateral vestibular schwannoma younger than age 30 are at high risk of having NF2, whereas those who develop unilateral disease older than age 55 seldom have NF2. Two-thirds of patients with NF2 develop intramedullary spinal cord tumors, usually multiple, although not always symptomatic. Most often these are schwannomas, which present a "dumbbell shape" on imaging studies, as the tumor extends medially and laterally through the foramina. Approximately 50% of patients with NF2 develop intracranial or spinal meningiomas.

Cancer risk management: The UK Neurofibromatosis Association has published the only consensus guidelines for management (11). On the basis of expert opinion, they have recommended management of patients in specialty centers, and, allowing for some variation according to severity of family history, ophthalmology examinations are recommended to begin at birth. Audiological examinations are suggested to start in early childhood. An annual full neurological examination is advised. Gadolinium-enhanced magnetic resonance imaging (MRI) monitoring of the head and full spine, starting around age 10–12 years, is recommended for all patients, as tumor growth may occur without symptoms. It may be sufficient to perform MRIs every other year up to age 20 and every 3 years thereafter for asymptomatic at-risk individuals without tumors. The guidelines are unclear as to how to proceed if tumors are not found on spine scans after several scans. If tumors are present, MRIs should be conducted at least annually until the rates of tumor growth are established. The risks and benefits of screening in NF2 have not been established.

Vestibular schwannomas can be safely and effectively managed with endoscopic tumor resection (12) or stereotactic radiosurgery (13). The serviceable hearing rate appears higher in the latter than the former, but no direct comparisons have been made; thus, it is unclear which is the preferred treatment modality.

Comments: Schwannomatosis (also called neurolemmomatosis), defined as multiple schwannomas without vestibular lesions, includes some individuals who have mosaic or segmental NF2 but can also be a genetically distinct disorder that maps in close proximity to the *NF2* gene on chromosome 22q (14). Germline mutations in the tumor suppressor gene *INI1/SMARCB1* have recently been identified as the predisposing gene (15). This gene maps to chromosome 22q11.2, and its protein is a subunit of the SWI/SNF (SWItch/Sucrose NonFermentable) ATP-dependent chromatin-remodeling complex.

A disorder comprised of multiple meningiomas, usually diagnosed in adulthood, without vestibular schwannomas, has also been reported. Most evidence suggests that this is *not* due to *NF2* mutations. Meningiomas in NF2 may precede development of vestibular schwannomas, so NF2 should be considered when meningioma is diagnosed in childhood.

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33. Nijmegen Breakage Syndrome (formerly called Ataxia Telangiectasia Variant or AT-V1; includes Berlin Breakage Syndrome, formerly called AT-V2)

OMIM number: 251260; 602667.

Inheritance pattern: Autosomal recessive.

Gene and chromosomal location: *NBS1* at 8q21 encodes a protein designated nibrin. Like the *ATM* gene product, nibrin is involved in DNA double-strand break repair.

Mutations: Truncating mutations. In the United States, 70% of Nijmegen breakage syndrome (NBS) patients are homozygous for one common founder mutation (657del5) and 15% are compound heterozygotes (having two different mutant alleles). Clinical testing is available for the common mutation, but full sequencing is not generally available.

Incidence: In Germany, the carrier rate is one in 866 and one in 3 million are affected with NBS. In Slav populations, the carrier rate is closer to one in 100.

Diagnosis: Diagnosis is established based on clinical, laboratory, and molecular data. Affected patients show growth deficiency, microcephaly, characteristic facies (sloping forehead, prominent midface, retrognathia), and recurrent sinopulmonary infections. Developmental milestones usually are normal in the first year of life, but there may be a subsequent decline in cognition, with most children having mild-to-moderate cognitive impairment by age 7. Premature ovarian failure is frequent; it is unclear if males have a gonadal phenotype. Hyper- and hypopigmented irregular spots on the skin are observed in most patients. A variety of congenital anomalies has also been reported, each of which is individually uncommon.

Laboratory Features: Immunodeficiency includes agammaglobulinemia (in 35%), IgA deficiency (in 20%), other immunoglobulin deficiencies, and T-cell defects as well. As in ataxia telangiectasia, there are chromosomal inversions and translocations involving the immunoglobulin loci (5%–50% of metaphases), especially those on chromosomes 7 and 14. The frequency of chromosome breaks and multiradials formed among nonhomologous chromosomes is increased, and exposure to ionizing radiation or radiomimetic agents further increases this instability.

Associated malignant neoplasms: About 35% of patients (70 reported cases) develop a malignancy, typically before age 15 years, most often a B-cell lymphoma or other hematopoietic malignancy. Patients with lower levels of intracellular nibrin appear to be at greater risk of lymphoma (1). Glioma, rhabdomyosarcoma, and medulloblastoma have been reported (2). Heterozygotes are phenotypically normal, but a report in 2004 suggests an increased risk of prostate cancer in carriers. Nine percent of men with familial prostate had the common mutation, compared with 2.2% of men with nonfamilial prostate cancer and 0.6% of the general population in Poland (3). One subsequent report could not confirm this association (4). *NBS1* mutation carriers may also be at increased risk of breast cancer (5), gastrointestinal lymphoma (6), and gastric and colorectal cancers (7). An overall odds ratio of 10.7 (95% CI = 1.4 to 81.5) for any type of cancer was reported in heterozygote grandparents of index cases with NBS (8). Larger studies are needed to clarify the magnitude and site specificity of neoplastic phenotypes in heterozygous carriers of *NBS1* mutations.

Associated benign neoplasms: None reported.

Cancer risk management: No disease-specific treatment is available. A high index of suspicion for hematologic malignancies is warranted, but specific screening is not advised. Avoidance of unnecessary exposure to ionizing radiation is suggested on the basis of the biological similarities between NBS and ataxia telangiectasia (AT).

Comments: As in AT, health-care providers need to be aware of increased sensitivity to ionizing radiation; conventional therapeutic doses could be fatal. Recently, germline mutations in *LIG4* (OMIM 601837) were reported in five individuals with an NBS-like phenotype with even more pronounced radiosensitivity in cell lines (9,10). Unlike NBS, there was normal cell-cycle checkpoint response, but impaired DNA double-strand break rejoining in the "LIG4 syndrome" (OMIM 606593).

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34. Pancreatic Cancer, Hereditary

OMIM number: 260350, 606856.

Inheritance pattern: Autosomal dominant suggested by segregation analysis and reports of rare families.

Gene and chromosomal location: One large family with multiple affected family members was found to have a germline palladin (*PALLD*) mutation, at 4q32–q34, which tracked with all affected family members and was absent in the nonaffected members. This appears to be a proto-oncogene (1).

Mutations: *PALLD* mutation (P239S) in one family. Linkage analysis was performed in 42 US and 77 European familial pancreatic cancer kindreds, and no statistically significant evidence of linkage was noted for the 4q32–34 region (2,3). Mutations in *PALLD* may account for only a small proportion of all familial pancreatic cancer.

Incidence: Unknown. Between 3.5% and 10% of pancreatic cancer patients have a first-degree relative with pancreatic cancer and thus are classified as "familial," but this represents a heterogeneous group because pancreatic cancer is a constituent of multiple hereditary cancer syndromes, including hereditary breast cancer (*BRCA1*, *BRCA2)*, hereditary melanoma (*CDKN2A)*, Peutz–Jegher syndrome (*STK11/LKB1*), HNPCC–Lynch syndrome (*MLH1*, *MSH2*, *MSH6*, *PMS2*), hereditary pancreatitis (*PRSS1*, *SPINK*), familial adenomatous polyposis (*APC*), cystic fibrosis and/or pancreatitis (*CFTR*), ataxia telangiectasia (*ATM*), and von Hippel–Lindau (*VHL*) syndrome (4). A family history of cancers associated with these various syndromes (eg, breast, ovary, colorectal, melanoma) is associated with a younger-than-usual age at pancreatic cancer development (5). Reduced ages at pancreatic cancer diagnosis included 3.2 years, 5.6 years, 3.2 years, and 5.8 years younger for probands with family histories of breast, ovarian, colorectal cancer, and melanoma, respectively.

In the family with the *PALLD* mutation, all grades of precancerous lesions were prominent throughout the pancreatic tissue of affected family members before cancer development, and all developed diabetes and exocrine insufficiency before their cancer diagnosis. This clinical picture is not common among families with apparent hereditary site-specific predisposition to pancreatic cancer.

Mutations in *BRCA2* are most commonly identified in familial pancreatic cancer families. Murphy et al. (6) showed that 17% of patients with pancreatic cancer and two or more family members with pancreatic cancer (at least two being first-degree relatives) carried germline *BRCA2* mutations; 12% of families with at least two first-degree relatives with pancreatic cancer carry deleterious germline *BRCA2* mutations (7). *BRCA2* mutations have also been reported in 5%–10% of pancreatic cancer patients with no family history of pancreatic disease. A pooled analysis of moderate- to high-risk pancreatic cancer families from the Mayo Clinic and Johns Hopkins (total series = 180) documented 10 *BRCA2* mutation carriers, suggesting that germline mutations in this gene may account for 6% of familial pancreatic cancer (8).

Diagnosis: There is no universally accepted definition, but hereditary pancreatic cancer might be suspected in families with two first-degree relatives with pancreatic adenocarcinoma or three or more first- or second-degree relatives. For selecting families that might be suitable for pancreatic cancer surveillance, some experts include kindreds with two or more affected family members regardless of age at diagnosis, although more stringent criteria have also been proposed (9).

Laboratory Features: Some pancreatic cancer families appear to have multifocal intraductal papillary mucinous neoplasms (IPMNs) as a pancreatic cancer precursor, but it is unclear if all hereditary pancreatic cancer evolves from this entity. IPMNs can follow a progression from IPMN adenoma to borderline IPMN with dysplasia, to IPMN with carcinoma in situ, and eventually to invasive carcinoma (10).

Associated malignant neoplasms: Adenocarcinoma of the pancreas. In two series of pancreatic cancer probands, lifetime risk of pancreatic cancer among first-degree relatives was 4.1%–4.7%, compared with 1.4% in controls. The risks were 7.2% and 3.8% among relatives of probands diagnosed younger than age 60 vs 60 or older, respectively (11,12). In some extensively affected families with an autosomal dominant pattern, risk to first-degree relatives may approach 50%.

Associated benign neoplasms: Some families may have diffuse intraductal papillary pancreatic neoplasia. A report describing the histological findings in a small series of patients who underwent prophylactic pancreatectomy in the context of a strong family history documents more frequent pancreatic intraepithelial neoplasia and IPMNs than in age-matched controls (13). These lesions appeared to cause obstructive lobular atrophy, which may be the source of the chronic pancreatitis-like changes frequently seen in these patients. The multifocal nature of these lesions suggests that partial pancreatectomy in this context is likely to be a suboptimal cancer risk reduction strategy.

Cancer risk management: There are no consensus guidelines regarding strategies for either evaluating or screening members of hereditary pancreatic cancer kindreds. Most symptomatic pancreatic cancers are incurable at diagnosis. Only 7% pancreatic cancers are diagnosed at a localized stage (14). As prognosis may correlate with tumor size, attempting to identify early lesions in high-risk families has been proposed (15–17). At present, there is no known screening strategy that has been demonstrated to alter the natural history of pancreatic cancer. Research is underway to determine if there is value in prospective screening in familial pancreatic cancer families (18). The hazards of applying screening algorithms with unknown performance characteristics to high-risk populations are well known. Thus, any approach to screening in this setting must be regarded as unproven and undertaken with caution. No consensus on the best approach to assess tumor stage or resectability has been achieved [reviewed by Vitone et al. (18)].

Based on limited data, endoscopic ultrasound (EUS) of the pancreas and CA 19-9 tumor marker serology have been offered to at-risk individuals, starting at age 50 years or 10 years younger than the youngest case of pancreatic cancer in that family. If normal, a repeat EUS/CA 19-9 every 1–2 years has been suggested. If the pancreas is abnormal in appearance, fine needle aspiration of the pancreas can be performed under EUS guidance. Due to the possibility of diffuse IPMN, multiple random biopsies could be considered. Some experts perform endoscopic retrograde pancreatogram and/or spiral computed tomography (CT) of pancreas after abnormal EUS despite the potential morbidity of the former and the unproven efficacy of either. If severe dysplasia (or cancer) is found, discussion of

partial or total pancreatectomy is inevitable. For those declining surgery for dysplasia, a follow-up EUS in 3–6 months is suggested. Magnetic resonance cholangiopancreatography is more sensitive for small tumors than CT and does not expose the patient to radiation. Use of CA19-9 is sometimes advocated in this setting, but its performance characteristics as a screening tool are suboptimal: with a cutoff of 37 U/ml, sensitivity is reported at 81%–85% and specificity at 81%–90% for detecting pancreatic cancer. Only 50% of cancers smaller than 2 cm have a rise in CA19-9. Note that patients who are Lewis blood group antigen negative (4%–15% of the population) are unable to synthesize Ca19-9, so the test is of no value in this group. Brand et al. (2007) have proposed screening only in those with a 10-fold increased risk of pancreatic cancer. Very careful multidisciplinary consultations are advised prior to embarking on a screening program, with emphasis on the facts that a high percentage of "control" subjects have an abnormal appearing pancreas by EUS (19), that IPMNs, like colonic polyps, are very common in the general population, and that prophylactic pancreatectomy is an option that carrries with it 100% morbidity (e.g., Type I diabetes) and potential mortality. Windsor (2007) has also cautiously endorsed screening for pancreatic cancer in high-risk individuals at age 50, or 10 years younger than the youngest affected family member, on an annual basis, but only after careful genetic counseling and risk assessment and only if a pancreatectomy would be considered (20). Because the optimal screening regimen for pancreatic cancer is unknown, and selection of an appropriate population for screening is undefined, enrollment of subjects in prospective clinical screening research studies is strongly encouraged.

There is abundant evidence that smoking greatly increases risk of pancreatic cancer both in sporadic and familial disease; at-risk family members must be strongly encouraged to stop smoking and offered every assistance in implementing an effective smoking cessation program.

Comments: Because pancreatic cancer is a component of multiple hereditary cancer syndromes, these need to be excluded before classifying a family as having site-specific hereditary pancreatic cancer. Identifying an underlying syndrome, if one is present, is essential to proper management of both the patient and his or her relatives. Because of the relatively high rate of mutations in pancreatic cancer families, *BRCA2* testing warrants serious consideration in multiple-case families even in families without breast cancer reported.

A risk prediction model, PancPRO, and free software for estimation of absolute risk of pancreatic cancer have recently been made available (21).

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35. Paraganglioma, Hereditary

OMIM number: 168000 and 602690 (PGL1), 601650 (PGL2), 605373 and 602413 (PGL3), 115310, and 185470 (PGL4).

Inheritance pattern: Autosomal dominant. However, a unique parent-of-origin effect is consistently reported for hereditary paraganglioma (PGL) type 1: *offspring of female gene carriers do not develop disease, whereas 50% of offspring of male gene carriers do.* This observation is consistent with genomic imprinting of the associated gene, but no evidence of parentally determined methylation has been demonstrated for *SDHD*. Hensen et al. (1) attributed the second "hit" in paragangliomas in *SDHD* kindreds to loss of the entire maternally derived chromosome and hypothesized a somatic genetic mechanisms involving both *SDHD* on11q23 and a paternally imprinted gene on 11p15.5 rather than imprinting of

SDHD. No parent-of-origin effect is found for familial paraganglioma linked to the other susceptibility loci.

Gene and chromosomal location: Hereditary PGL1 is caused by mutations in *SDHD*, at 11q23. PGL2 maps to 11q13.1; the causative gene has yet to be identified. PGL3 is caused by mutations in *SDHC* on 1q21. PGL4 is caused by mutations in *SDHB* at 1p36.

Mutations: In 32 Dutch paraganglioma families, Taschner et al. (2) identified two founder mutations, Asp92Tyr and Leu139Pro, in the *SDHD* gene in 24 and six families, respectively, or 94% of all families. *SDHD* mutations were also discovered in a total of 20 of 55 simplex cases in the Dutch population.

In an American population, *SDHD* mutations were found in five of 10 familial and two of 37 nonfamilial cases, whereas *SDHB* mutations were found in two of 10 familial and one of 33 nonfamilial cases (3). Mutations were mostly unique to each family.

Incidence: Unknown in the US population. Grufferman et al. (4) reviewed case reports for 916 carotid body tumors; approximately 10% were familial. In the Dutch population, familial cases cause about 50% of all paraganglioma cases, corresponding to an incidence of approximately one in 1 million.

Diagnosis: There are no formal criteria. Should be considered in any individual with a sympathetic paraganglioma, or pheochromocytoma at a young age (5), but most strongly suspected in those with 1) multiple paragangliomas or 2) in an individual with a single paraganglioma *and* a relative reported to have paraganglioma, in whom no other disorder is evident. Some patients with familial pheochromocytoma have no detectable mutations in any of the associated genes, suggesting that additional susceptibility genes remain to be identified (6).

Laboratory features: For patients who are suspected to harbor a catecholamine-secreting tumor because of paroxysmal symptoms, biochemical documentation of catecholamine or metanephrine hypersecretion in blood and/or urine should precede any imaging study or surgery.

There are no histological or immunologic features that indicate malignant potential of a given tumor; only the presence of metastasis can confirm malignant potential.

Associated malignant neoplasms: Approximately 10% of hereditary paragangliomas undergo malignant degeneration, including 16%–19% of vagal paragangliomas, approximately 6% of carotid body paragangliomas, and 2%–4% of jugulotympanic paragangliomas (7,8). Brouwers et al. (9) found *SDHB* mutations in 30% of 48 malignant paragangliomas and in 48% among extradrenal paragangliomas. The International Succinate Dehydrogenase (SDH) Consortium studied 116 individuals from 62 families and confirmed that patients with the *SDHB* mutation are more likely to develop malignant disease and intra-abdominal tumors, though at a slightly older median age compared with *SDHD* carriers (34 vs 28 years). On the other hand, penetrance for any tumor was greater in *SDHD* cases compared with *SDHB* cases: 48% vs 29% by age 30 and 73% vs 45% by age 40 (10). The prevalence of malignancy in carriers of *SDHD* D92Y, a founder mutation in the Netherlands, was estimated as at least 2.5% (11). In a focused study of 29 *SDHB* carriers with paragangliomas, mean age of malignancy was reported as 33.7 ± 15.7, 76% had hypertension, 90% had a negative family history, hypersecretion of both norepinephrine and dopamine was found in 46%, norepinephrine only was secreted in 41%, dopamine only reported in 3%, and 10% were nonsecretory (12). Patients with all *SDH* mutations may also be at risk of other tumor types, including renal cell cancer (in *SDHB*), astrocytomas, papillary thyroid carcinoma, and parathyroid adenoma (risks not well defined or proven) (13–17).

Carney–Stratakis syndrome consists of paraganglioma and gastric stromal sarcoma and/or gastrointestinal stromal tumor (GIST; OMIM 606864), inherited in an autosomal dominant manner. Paragangliomas were observed in 92% of patients in this series, and GISTs in 42% (18). Recently, germline mutations have now been found in *SDHB*, *SDHC*, and *SDHD* [(19); see chapter on Carney Complex].

Associated benign neoplasms: Van Baars et al. (20) found that carotid body paragangliomas accounted for 78% of all head and neck paragangliomas discovered; 16% were jugular, 4.5% were vagal, and 1.5% were tympanicum. Adrenal paragangliomas (pheochromocytomas) occur in an unknown proportion. In most series, familial cases manifest bilateral tumors about one-third of the time. C-cell hyperplasia now reported in a family with SDHD mutation.

Cancer risk management: No internationally accepted guidelines on cancer screening have been issued. The most appropriate age to begin and interval between screenings as well as the risks and benefits of tumor screening in these syndromes have not been validated. Based upon published suggestions and recommendations from the authors and reviewers, the following guidelines are suggested. For patients at risk of head and neck paraganglioma, ultrasound imaging or magnetic resonance imaging (MRI) of the carotid body region every 1–3 years beginning at age 15 is advised. Because paragangliomas can be hormonally active (5% of head and neck tumors vs 50% of abdominal lesions), annual screening with 24-hour urinary and/or plasma fractionated metanephrines (ie, metanephrine and normetanephrine each measured separately) beginning at age 15 is also advised. This approach has been proven to be superior in diagnostic sensitivity to the historical strategy of measuring parent catecholamines. There is no current consensus regarding whether performing these assays in urine or plasma is preferable (21). Imaging with ^{123}I-metaiodobenzylguanidine and computed imaging (CT or MRI) of the thorax, abdomen, and pelvis is indicated in patients with catecholamine or catecholamine metabolite hypersecretion. Annual neck, abdominal, and thoracic imaging by MRI has also been advised by some experts for all individuals found to carry any deleterious SDH mutation; patients with *SDHB* mutations are of particular concern (15,22). For this subgroup, Boedeker et al. (8) have suggested that a three-body region imaging and scintography or DOPA-PET (18F-DOPA-positron emission tomography) may be required to exclude metastasis.

Comments: *SDHB*, *SDHC*, and *SDHD* encode three of the four subunits of the mitochondrial aerobic respiratory chain, complex II, that may regulate the response of the carotid body to hypoxia. Loss of function of these genes results in chronic hypoxic stimulation and cellular proliferation and/or neoplasia. Baysal et al. (23) reviewed studies showing increased incidence of paragangliomas among residents at higher altitudes and in other environments of chronic hypoxia.

Sympathetic ganglia, including the adrenal medulla, may secrete catecholamines and are symmetrically distributed along the paravertebral axis from high in the neck near the superior cervical ganglion to the abdomen and pelvis and also near the urinary bladder and prostate gland. The parasympathetic ganglia are located at the skull base and neck. Paragangliomas can arise at any of these locations, although the carotid body, anatomically the largest, is the most common site of origin.

Paragangliomas are part of other well-known multitumor syndromes (Tables 4 and 5) as well as the Carney triad (OMIM #604287 gastric stromal tumor, paraganglioma, pulmonary chondroma) and the syndrome of paraganglioma and gastric stromal cell tumor (OMIM #606864). In a series of apparently nonsyndromic pheochromocytomas or paragangliomas, germline mutations were found in *VHL*, *RET*, *SDHD*, and *SDHB* in 5%–11%, 2%–5%, 4%, and 4%–6%, respectively (5,24). It has been recommended that all patients with functional paragangliomas should be screened for an underlying genetic disorder, regardless of family history (25).

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36. Peutz–Jeghers Syndrome

OMIM number: 175200, 602216.

Inheritance pattern: Autosomal dominant.

Gene and chromosomal location: *STK11/LKB1*at 19p13.3. Some studies suggest locus heterogeneity.

Mutations: *STK11* mutations have been found in 70% of individuals with a positive family history of Peutz–Jeghers Syndrome (PJS) and in 20%–70% of individuals with clinical PJS, without affected relatives. Mutations are presumed deleterious due to loss of function. Sixteen to forty percent of mutations involve large gene deletions (1–3)

Incidence: The estimated frequency is from 1 : 8300 to 1 : 280 000 live births.

Diagnosis: Genetic testing can establish the diagnosis. Clinical suspicion is often based on the presence of numerous pigmented spots on the lips and the buccal mucosa and multiple gastrointestinal hamartomatous polyps (most commonly in the jejunum). Pigmentation abnormalities appear in infancy or childhood as 1- to 5-mm melanotic macules, most often on the lips and buccal mucosa but also on the face, forearms, palms, soles, digits, perianal area, and, rarely, on the intestinal mucosa. The pigmentation may fade with age. Pigmentation of this type occurs in more than 95% of individuals with PJS. The most common clinical signs associated with PJS intestinal polyps are obstruction, abdominal pain, rectal bleeding, and rectal extrusion of the polyp. Although the typical PJS polyp has a characteristic histology, individuals with PJS also develop adenomatous polyps, especially in the colon, which can mimic familial adenomatous polyposis.

Clinical diagnostic criteria were proposed in l987 (4). Definitive diagnosis of PJS requires histopathologic confirmation of

Table 14. Cumulative cancer risks in Peutz–Jegher syndrome estimated from 419 individuals with Peutz–Jegher syndrome (297 with known *STK11* mutations) (5) and from 149 individuals with Peutz–Jegher syndrome (all with *STK11* mutations) (6)

	To age 30 (%)	To age 40 (%)	To age 50 (%)	To age 60 (%)	To age 70 (%)
Overall cancer risks	5–6	17–18	31	41–60	67–85
Overall gastrointestinal cancer risks	1	9–12	15–24	33–34	63
Colorectal	–	3	5	15	39
Pancreas	–	3	5	7	11
Uterine, ovary or cervix	1	3	8–13	18	18
Breast cancer	–	5–8	13	31	45
Lung	–	1	4	13	17

hamartomatous gastrointestinal polyps with the distinctive PJS morphology *and* two of the following three features: 1) small-bowel polyposis; 2) family history of PJS demonstrating autosomal dominant inheritance; and 3) pigmented macules of the buccal mucosa, the lips, fingers, toes, and external genitalia. A probable diagnosis can be made based upon two of the three criteria above, without histopathologic demonstration of PJS-type polyps. Among individuals with a first-degree relative with PJS, a presumptive diagnosis of PJS can be made if the characteristic mucocutaneous hyperpigmentation is present.

Laboratory features: PJS hamartomatous polyps have a morphology that is distinguishable from juvenile polyps, including mucosa with interdigitating smooth muscle bundles that produce a branched-tree pattern, sometimes displacing the underlying epithelium and showing pseudocarcinomatous "invasion" of the muscularis mucosa.

Associated malignant neoplasms: Table 14 summarizes data from two current studies regarding cumulative risks of cancer in PJS.

It has been reported that cancer risk was greatest in those with exon 6 mutations in *STK11/LKB1* (6). Giardiello et al. (7) reported cumulative risks from age 15 to 64 as 93% for all cancers combined and 0.5% esophagus, 29% stomach, 13% small intestine, 39% colon, 36% pancreas, 15% lung, 9% testes, 54% breast, 9% uterus, 21% ovary, and 10% cervix. Note: nearly 80% of the cervical cancers were of the rare and highly malignant cervical adenoma malignum subtype. Ovarian tumors were primarily of granulosa cells subtype. Cancers of the kidney, thyroid, male breast cancer, and prostate have been reported in PJS; their relationship to the genetic syndrome is uncertain.

Gastrointestinal cancers as a group were the most common malignancies (see Table 14). In the general population, the risk of any gastrointestinal cancer by age 70 is 18%. Cancer risks were not appreciably different in PJS kindreds carrying an *STK11* mutation vs those with no mutation.

Associated benign neoplasms: Multiple PJS polyps occur throughout the gastrointestinal tract, most commonly the jejunum, ileum, and duodenum. One-third of patients have PJS polyps in the colon and rectum as well. Polyps range in size from 1 mm to 4 cm and occasionally occur in the nose, bronchi, renal pelvis, ureters, and bladder. Age at onset of symptoms is variable, sometimes developing in the first years of life. In one study, the mean age at gastrointestinal symptom onset was 10 years and the mean age at first polypectomy was 13 years; another study reported an average age at diagnosis of 22.5 years.

Ovarian tumors in affected individuals are "sex cord tumors with annular tubules," which are considered characteristic of PJS, and are present in almost all affected females. These tumors may present with hyperestrogenism, leading to menorrhagia or precocious puberty. Males may develop Sertoli cell tumors of the testis, some of which also secrete estrogen.

Cancer risk management: Experts have suggested surveillance guidelines, but the optimal screening strategy for PJS has not been determined (8). Substantial morbidity arises from short-gut syndrome, as a consequence of multiple small-bowel resections for intussusception; therefore prophylactic removal of polyps, if feasible, is advised. In a review of 225 PJS probands, approximately half experienced an intussusception at median age of 15 years (range = 3.7–45 years) (9). Thus, most recommendations emphasize screening affected individuals with upper gastrointestinal endoscopy and small-bowel follow-through (barium study) starting at age 10 years (sooner if symptoms develop), every 2 years. Video capsule endoscopy or double-balloon endoscopy may supplant barium visualization of the small bowel in PJS (10–12). For polyps not endoscopically accessible, surgery has been recommended for removal of small-bowel polyps that are symptomatic or larger than 1.5 cm. Some experts advise intraoperative small-bowel endoscopy, when laparotomy is necessary, to remove all identifiable polyps; data suggest that this strategy and endoscopic surveillance decrease the frequency of laparotomy (13,14). A baseline colonoscopy is also advised at age 25 years and every 2–3 years thereafter. Breast screening with annual mammography in women with PJS is advised beginning between ages 25 and 35 years. Annual testicular examination is recommended, starting at age 10, whereas annual pelvic examination, ultrasound, and papanicolaou (PAP) test are suggested to begin at age 20 in women. Pancreatic cancer screening is being evaluated in research trials but has not generally been recommended routinely in PJS.

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37. Polyposis, Familial Adenomatous (includes Gardner Syndrome, Familial Multicentric Fibromatosis and/or Hereditary Desmoid Disease, and a subset of Turcot Syndrome)

OMIM number: 175100, 611731, 135290.

Inheritance pattern: Autosomal dominant.

Gene and chromosomal location: *APC* at 5q21–q22.

Mutations: Protein truncation mutations comprise 70%–80% of mutations, and approximately 25% of cases represent new germline mutations. Attenuated polyposis (<100 polyps) is correlated with mutations before codon 157, after codon 1595, and in the alternatively spliced region of exon 9. Mutations between codons 1250 and 1464 correlate with severe polyposis (>1000 polyps). Mutations in other areas have an intermediate polyp phenotype. Desmoid tumors are associated with mutations after codon 1444. No consistent correlations were found for upper gastrointestinal tumors (1).

One specific missense mutation (I1307K) has been reported in 6% of Ashkenazi Jews and in about 28% of Ashkenazim with a family history of colorectal cancer (CRC) (2). This is a low-penetrance mutation, with a twofold increased risk of CRC; carriers do not manifest the polyposis coli phenotype that is characteristic of familial adenomatous polyposis (FAP).

Incidence: One in 6000 to one in 13 000 live births. The frequency of gene mutations in the general population is unknown.

Diagnosis: Direct DNA mutational analysis (85%–90% sensitivity) is available for clinical testing. Linkage-based predictive clinical testing is also available for kindreds with unidentified mutations. Clinical diagnosis is based on characteristic polyposis (usually the presence of greater than 100 adenomatous colorectal polyps).

Laboratory features: No specific findings.

Associated malignant neoplasms: In untreated individuals, colon adenocarcinoma occurs at a mean age of 39 years (7% by age 21 and 87% by age 45) (3). Duodenal carcinomas, especially around the ampulla of Vater, occur on average 20 years later than colon cancers, with a lifetime risk of 4%–12% (4). Follicular or papillary thyroid cancer occurs in about 2% of affected individuals, at a mean age of 28 years (5). The risk of childhood hepatoblastoma is estimated 0.6%; it is rare after age 6 years. Germline mutations in *APC* were found in 10% of 50 cases of apparently sporadic hepatoblastomas (6). Gastric carcinomas arise in only 0.5% of individuals in Western cultures (higher in Asian cultures) (7). The lifetime risk of pancreatic cancer is 2%, and this may include islet cell tumors. Some FAP families have brain tumors (odds ratio = 3.7); 60% are medulloblastomas (gliomas and ependymomas also reported). They are more frequent in females younger than age 20 (mean = 14.7 years, SD = 9.2). In this series, those with mutations in codons 679–1224 were more likely to have brain tumors (8). The combination of multiple adenomatous colon polyps and a brain tumor has been called "Turcot syndrome"; this dyad occurs in both FAP and Lynch syndrome/ hereditary non polyposis colon cancer (HNPCC), with brain tumors in the latter more likely to be gliomas. The term "Gardner syndrome" refers to FAP plus extracolonic features. Essentially all families with FAP have Gardner features, if carefully sought.

Associated benign neoplasms: FAP includes numerous nonmalignant neoplasms (9). Adenomatous polyps of the colon appear at a mean age of 16 years but may occur before age of 10 in gene carriers (<10%); they are detectable in more than 90% of gene carriers by age 20, and more than 95% by age 35. Duodenal polyps (especially periampullary) occur in 50%–90% of patients (4). Hamartomatous gastric polyps (also called cystic fundic gland polyps) occur in up to half of FAP patients. Ten percent of individuals with FAP may also have adenomatous gastric polyps. Dental abnormalities including supernumerary or congenitally absent teeth, dentigerous cysts, and osteomas of the jaw occur in 17% of individuals with FAP. Other benign lesions include sebaceous or epidermoid cysts, lipomas, and congenital hypertrophy of the retinal pigment epithelium. Osteomas may arise in any bone.

Desmoid tumors—histologically benign clonal neoplasms comprised of fibrous tissue—cause substantial morbidity and mortality in approximately 5% of FAP patients. Abdominal surgery, APC mutations distal to codon 1444, female gender, and the presence of osteomas are independent predictors of desmoid tumor risk. Desmoid tumors are reported in 30% of FAP kindreds, with overall lifetime risks of 8% for males and 15% for females; the risk of desmoid tumors is 25% if a first-degree relative with FAP has a desmoid and declines to 8% if a third-degree relative has desmoid tumors. Smith et al. (10) found that 13% of patients with FAP had adrenal masses greater than 1 cm in diameter. These are nonfunctioning adenomas; screening to detect these lesions is not currently advised. Juvenile nasopharyngeal angiofibroma is a rare, locally invasive neoplasm associated with FAP, seen more commonly in affected males.

Cancer risk management: The National Comprehensive Cancer Network (NCCN) has regularly updated expert guidelines on FAP management (11). Morton et al. (12) described 47 families with FAP, in which only 6% of those undergoing periodic endoscopic screening (with routine polypectomy) developed a colon cancer compared with 64% in unscreened patients, supporting the value of CRC screening in FAP.

A genetic consultation is recommended for newly diagnosed FAP families to determine whether genetic testing might be informative for at-risk relatives. For relatives from molecularly informative families who test negative for the family's *APC* mutation, CRC screening can be deferred to age 50, as for individuals at general population risk; some centers recommend baseline sigmoidoscopy in the young adult years as a precaution, to verify molecular genetic test results, if affection status is based on linkage studies rather than direct DNA results.

For those at risk of FAP or known to have the FAP phenotype or the causative gene mutation, the following screening regimen has been advised:

- Annual screening for hepatoblastoma from birth to 6 years of age, by physical examination and/or abdominal ultrasound examination and measurement of serum concentration of alpha-fetoprotein (13).
- Sigmoidoscopy or colonoscopy every 1–2 years beginning at age 10–12 years. As the polyps in classical FAP are concentrated in the left colon, some experts advise that full colonoscopy may not be warranted until rectosigmoid adenomas are identified. If dealing with an attenuated FAP family, begin colonoscopy screening in the late teens, repeating every 2–3 years (NCCN Practice Guidelines in Oncology, v.1.2007).
- Colonoscopy is done annually once polyps are detected. If individuals are younger than age 20 years and adenomas are less than 6 mm and without villous component or advanced dysplasia, delay in colectomy may be considered.
- Esophagogastroduodenoscopy with a side-viewing endoscope is recommended beginning when colonic polyposis is detected, or by age 25 years at the latest, repeated every 1–3 years, depending on the severity (number, size, degree of dysplasia) of duodenal adenomas. Biopsy of an enlarged ampullary papilla may be justified even if no polyps are visualized but is not indicated if the papilla appears normal. In some cases, endoscopic retrograde cholangiopancreatography may be necessary to identify adenomas of the common bile duct.
- Some experts suggest small-bowel X-ray or abdominal and pelvic computerized tomography with orally administered contrast when duodenal adenomas are detected or before colectomy, repeated every 1–3 years depending on findings and presence of symptoms.
- Annual palpation of the thyroid gland.
- The need for gastric cancer screening is uncertain in Western populations, regardless of gastric polyp status, because the risk of malignant transformation is clinically significant only in specific Asian populations.

Colectomy after adenomas develop is a standard treatment for classic FAP. The timing of the colectomy will depend on size, number, and degree of dysplasia of the polyps. Colectomy may be necessary for individuals with attenuated FAP but is often deferred until polyps become difficult to control. Surgical management of the large bowel is complex; decisions regarding the best approach and timing require careful discussions between the individual patient and their doctor [see Rodriguez-Bigas et al. (14)]. Endoscopic or surgical removal of duodenal adenomas is indicated if polyps 1) exhibit villous or severe dysplastic changes, 2) exceed 1 cm in diameter, or 3) cause symptoms. Pancreaticoduodenectomy (Whipple procedure) may occasionally be necessary to treat duodenal adenomas. There is no standard approach to the management of desmoid tumors [reviewed by Knudsen and Bulow (15)], although, anecdotally, surgery is thought to trigger accelerated growth; therefore, a conservative approach to surgical intervention in FAP patients is prudent (16) and new data support this (17).

Several studies have shown that nonsteroidal anti-inflammatory drug (NSAID) use (sulindac, celecoxib, and rofecoxib) can induce regression of adenomas in FAP and decrease the number of recurrent polyps in the remaining rectum for those who have had a subtotal colectomy. However, NSAID use currently does not obviate need for the colectomy nor the cancer risk management plan outlined above. NSAIDs, as a strategy to safely postpone colectomy, remain experimental.

Comments: Attenuated FAP can be very difficult to distinguish from *MYH*-associated polyposis and HNPCC–Lynch syndrome; the latter occasionally presents with increased numbers of adenomatous polyps (despite its name). Some cases of attenuated FAP manifest a rightsided predominance of polyps. Analysis of tumor microsatellite instability (MSI) may help clinicians distinguish between FAP and HNPCC–Lynch syndrome because tumors related to *APC* or *MYH* mutations nearly always lack tumor MSI. Evidence of FAP should be aggressively sought among individuals with more than one desmoid tumor or in families with desmoids.

Hyperplastic polyposis or serrated pathway syndrome, which has not yet garnered an OMIM number, is another clinical entity that can be confused with FAP. The causative genes are unknown. The polyps in these disorders may be hyperplastic, adenomatous, or serrated adenomas (18). Hereditary mixed polyposis syndrome (OMIM 601228) is a dominant disorder with linkage to 15q15.3-q22.1, characterized by atypical juvenile polyps, colonic adenomas, and colorectal carcinomas (19). Tooth agenesis-colorectal cancer syndrome (OMIM 608615) was discovered in one family being studied for oligodontia. Little data were reported regarding the precancerous lesions noted. Mutations in *AXIN2*, a component of the Wnt signaling pathway, were discovered in this Finnish family (20).

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38. Polyposis, Familial Juvenile (includes Hereditary Mixed Polyposis Types 1 and 2)

OMIM number: 174900, 175050, 600993, 601299.

Inheritance pattern: Autosomal dominant.

Gene and chromosomal location: Mutations in *BMPR1A* at 10q and *SMAD4* (also called *MADH4*) on 18q21.1 account for approximately 25% and 15%–20% of familial juvenile polyposis (JPS), respectively. Some cases of JPS were ascribed to *PTEN* mutations at 10q22.3; it is currently thought that other features of *PTEN* hamartoma tumor syndrome and/or Cowden syndrome distinguish these cases from true JPS. A contiguous gene deletion syndrome—juvenile polyposis of infancy—was reported in which both *PTEN* and *BMPR1A* were deleted (1). Mutations in *ENG*, 9q34.1, have also been rarely reported in early-onset cases with juvenile polyposis [Sweet et al. (2); Howe et al. (3) was not able to confirm]. This gene, like *SMAD4*, has been associated with hereditary hemorrhagic telangiectasia (HHT; OMIM 175050), though a history of HHT may be lacking in the juvenile polyposis cases attributed to these genes. Table 15 shows the current relationship between JP and HHT. About 20% of SMAD4 mutation carriers will have some features of HHT (14).

Mutations: Most mutations in the causative genes result in truncated proteins, predicting a tumor suppressor gene function. Friedl et al. (4) reported increased prevalence of massive gastric polyposis in patients with *SMAD4* mutations compared with *BMPR1A* mutation patients.

Incidence: Estimated between one in 16 000 and one in 100 000 live births. In all, 20%–50% of all JPS cases are inherited.

Diagnosis: The term "juvenile" refers to a histopathologically characteristic hamartomatous polyp and has nothing to do with the age at onset in this genetic disorder. Sporadic juvenile polyps do occur in children, with an incidence of 1% younger than age 21 years. JPS is a diagnosis of exclusion (ruling out Cowden and/or *PTEN* hamartoma syndrome or simple juvenile polyps). JPS can be diagnosed if one or more of the following criteria are met: 1) more than five juvenile polyps in the colorectum, 2) multiple juvenile polyps throughout the gastrointestinal tract, or 3) one or more juvenile polyps plus a family history of juvenile polyps (5). Giardiello (6) modified the first criterion to require only three juvenile polyps. Histological verification of the polyp type is essential, and care must be taken to distinguish juvenile polyps from Peutz–Jeghers polyps.

JPS is characterized by juvenile polyps of the stomach, small intestine, colon, and rectum. Polyps may be few (<5) or many (>100) over a lifetime. JPS may be diagnosed at any age, from infancy through the adult years. Most affected individuals have some polyps by their 20s. Polyps vary greatly in size and shape. They may cause bleeding, abdominal pain, intussusception, and protein-losing enteropathy. Digital clubbing has also been noted. JPS can occur in combination with HHT in some families due to mutations in *SMAD4* and *ENG*. Digital clubbing may be related to arteriovenous shunting in these patients (7).

Laboratory features: Features may include anemia, hypoalbuminemia, and hypokalemia. Woodford-Richens et al. (8) reported that the histopathology of polyps from *SMAD4*-associated JPS includes a more prominent epithelial component than JPS patients without *SMAD4* mutations.

Associated malignant neoplasms: Risk estimates for developing gastrointestinal malignancy range from 9% to 68% and vary with the gene involved (9). Colorectal cancer accounts for most of the excess cancer risk in JPS. In one kindred with a *SMAD4* mutation, the lifetime risks of colorectal and other gastrointestinal cancer (stomach, duodenal, pancreatic) were 40% and 20%, respectively (10). Cancer incidence in JPS families is declining as a

Table 15. Juvenile polyposis and hereditary hemorrhagic telangiectasia: related clinical and molecular entities

Gene (OMIM number)	Juvenile polyposis	HHT[a]
BMPR1A/ALK3 (601299)	Approximately 20%–25%	Not yet reported
SMAD4/MADH4 (600993)	Approximately 20%	Reported
ENG (131195)	Reported	30%–40%
ACVR1/ALK1 (601284)	Not yet reported	30%–40%
PTEN (601728)	Phenocopy—see text	Not reported
Unknown	>50%	>20%

[a]OMIM = online Mendelian inheritance in man; HHT = hereditary hemorrhagic telangiectasia (also known as Osler–Weber–Rendu syndrome [OMIM # 187300, 175050, 600376).

consequence of endoscopic screening and polypectomy in young at-risk relatives.

Associated benign neoplasms: Gastrointestinal polyps involving the stomach (which can be very extensive), small bowel, and colorectum. Colorectal adenoma has also been reported.

Cancer risk management: There have been no consensus statements or randomized trials addressing cancer screening guidelines in JPS. Expert opinion suggests that for those diagnosed with, or at-risk of, JPS, a complete blood cell count, upper gastrointestinal endoscopy, and colonoscopy is advised at age 15 (sooner if symptoms develop). If no polyps are found, repeat screening is recommended in 3 years. If polyps are found, they should be removed and annual screening implemented until no polyps are found. Thereafter, screening reverts to an every 3-year schedule (11). For patients with extremely numerous polyps, colectomy and/or gastrectomy may be indicated.

Comments: Two clinically similar but etiologically distinct disorders—hereditary mixed polyposis types 1 and 2 (OMIM 601228, 610069)—are in the JPS differential diagnosis. Affected individuals have multiple atypical juvenile polyps that contain some adenomatous components and have a high risk of colorectal cancer. HMP1 has been mapped to 15q13–q14 and has been reported only in the Ashkenazi Jewish population (12). HMP2 was reported in two Chinese families, one of which carried a deleterious mutation in *BMPR1A* (13). Hamartomatous gastrointestinal polyps can also occur in basal cell nevus syndrome, Cowden syndrome, Peutz–Jeghers syndrome, and neurofibromatosis type 1.

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39. Polyposis, MYH-Associated (MAP)

OMIM number: 608456, 604933.

Inheritance pattern: Autosomal recessive.

Gene and chromosomal location: *MYH* (*MUTYH*) on 1p32.1–p34.3, a base-excision repair gene, the product of which participates in repair of mutations caused by reactive oxygen species (1).

Mutations: North American studies suggest that two mutations (Y165C and G382D) account for 80%–85% of mutations occurring in individuals of Caucasian ancestry; early evidence suggests that the Y165C mutation may be more deleterious (2, 3a and 3b, 4). If only these mutations are tested, true biallelic carriers would have both mutations identified in approximately 72% of cases, only one mutation identified in approximately 26% of cases, and no mutation detected in approximately 2%. Full gene sequencing can be offered to those who are suspected of having undetected *MYH* mutations. It is notable that in a recent German series, up to 20% of biallelic carriers did not have either of these two mutations (5).

Incidence: In the general population, approximately 1% are heterozygous (monoallelic) *MYH* mutation carriers. In large population-based series of colorectal cancer cases, biallelic *MYH* mutations were found in 0.54%–1% (2,4,6). Of note, polyps were absent in 36% of biallelic carriers in one study, so the term "polyposis" may be a suboptimal name for this disorder. However, the presence of more than 15 synchronous colorectal adenomas or colorectal cancer (CRC) diagnosed before age 50 was said to be the most effective criteria for identification of biallelic *MYH* mutation carriers (4). Concordant with this observation, biallelic mutations were found in 20%–24% of individuals in whom *APC* germline testing (done for suspected familial adenomatous polyposis [FAP] or attenuated FAP) was negative (3,7). Biallelic mutations were also reported in 2% of individuals diagnosed with microsatellite-stable colorectal cancer younger than age 50 in whom no polyposis was present (7).

Diagnosis: Biallelic mutations in the *MYH* base-excision repair gene can result in somatic mutations in *APC* (which causes classical familial adenomatous polyposis); this creates a phenotype reminiscent of FAP or, more commonly, attenuated FAP. Individuals with biallelic mutations in *MYH* may have multiple colorectal adenomas (range = a few to >500). Duodenal adenomas, carcinomas, congenital hypertrophy of the retinal pigment epithelium, osteomas, and dental cysts (frequency unknown) have also been reported [reviewed in Nielsen et al., (3)]. In a recent case series, 22% of colorectal cancer patients with biallelic *MYH* mutations were missed if testing was confined to those with 15 or more polyps. In addition, a number of subjects in this series reported family histories that were suggestive of Lynch syndrome.

Laboratory features: The molecular signature of base-excision repair deficiency is somatic G:C→T:A transversion (8), but clinical

testing for this genetic lesion is not available. Tumors show stable microsatellites (22 of 23 tumors in one series), a finding that helps distinguish this group of patients from those with Lynch syndrome (hereditary DNA mismatch repair deficiency).

Associated malignant neoplasms: Excess risks of colon cancer and duodenal cancer occur in biallelic *MYH* mutation carriers (3,5,9–12). A recent meta-analysis suggested that the odds ratio for colon cancer in biallelic mutation carriers ranged from 6.1 to 7.4, depending on the analytic method used (13). In a population-based study, Jenkins et al. (14) reported a threefold increased risk of CRC in monoallelic carriers (8% cumulative risk to age 70) and a 50-fold increased risk (80% cumulative risk to age 70) in biallelic carriers. In the Netherlands, mean age at colorectal cancer diagnosis in biallelic *MYH* carriers was 45 years. In a single study, female breast cancer occurred in 18% of *MYH*-associated polyposis (MAP) patients (age range = 49–76 years; standardized morbidity ratio = 3.75; 95% CI = 1.02 to 9.57) (3). This finding has not been reproduced. The meta-analysis of Webb et al (13), combining data from seven case–control studies that included 5256 subjects, yielded a colorectal cancer odds ratio of 1.2 for monoallelic (heterozygous) carriers; however this did not reach statistical significance despite the appearance of a trend.

Associated benign neoplasms: Colonic and duodenal adenomas; gastric fundic gland polyps. Osteomas, sebaceous gland adenomas, pilomatricomas (suggestive of Muir–Torre syndrome variant of Lynch syndrome) (15).

Cancer risk management: The National Comprehensive Cancer Network issued practice guidelines for MAP in 2008 (16), including colonoscopy starting at age 25–30 years, repeated every 3–5 years if negative. Consider upper gastrointestinal endoscopy with side-viewing duodenoscope at age 30–35 years and every 3–5 years thereafter. If adenomas are discovered, then patients should be managed thereafter as per FAP. Although carriers of monoallelic *MYH* mutations were not addressed in these guidelines, it may be reasonable to consider some increase in screening; we suggest colonoscopy beginning about age 40 years and repeated every 5 years.

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40. Prostate Cancer, Hereditary

OMIM number: 176807, 601518, 602759, 300147, 603688, 608656, 153622.

Inheritance pattern: Heterogeneous. Multiple-case families manifesting patterns consistent with autosomal dominant, recessive, or X-linked inheritance modes have been reported. A segregation analysis of 4288 radical prostatectomy patients did not identify any single-gene model of inheritance that clearly explained familial clustering of disease. The best-fitting model was a rare autosomal dominant susceptibility gene, particularly when probands were diagnosed at younger than 60 years. The model predicted that the susceptibility gene frequency in the population was 0.006 and that prostate cancer risk by age 85 years was 89% and 3% among gene carriers and noncarriers, respectively (1). Twin data support a genetic etiologic component, with concordance rates of 19%–26% vs 4%–9% for identical and nonidentical twins, respectively.

Gene and chromosomal location: Based upon linkage studies, sites of proposed prostate cancer susceptibility loci include hereditary prostate cancer (HPC) 1 (1q24–q25; candidate gene *RNASEL*), HPC2 (17p; candidate gene *ELAC2*), PCAP (1q42.2–q43), HPCX (Xq27–q28), CAPB (1p36), HPC20 (20q13), and candidate gene *MSR1* (8p21–q23). Recently, linkage to 8q24 was confirmed by multiple independent groups [reviewed by Platz (2)]. This finding is one of the most unexpected and provocative observations to emerge from applying the technology of genome-wide association studies to the study of prostate cancer. This is a gene-poor genomic region, suggesting that novel insights into genetic susceptibility to prostate (and other) cancer may well emerge from research into this finding (3).

Male *BRCA1* and *BRCA2* mutation carriers are also at increased risk of prostate cancer (4). Mutations in *BRCA2* were found in 2.3%

of men in the United Kingdom with prostate cancer diagnosed younger than the age of 56 years, underscoring the importance of including information on all cancers when performing family cancer risk assessment (5). One multigenerational Finnish prostate cancer family was found to segregate a *PALB2* truncating mutation (6).

Heterozygous mutations in *NBS1* (8q21), which causes Nijmegen Breakage syndrome in the homozygous state, were reported in 9% of men with familial prostate cancer, compared with 2.2% of men with nonfamilial prostate cancer and 0.6% of the general population in Poland (7), an observation that was not confirmed in a subsequent study (8). Similar data have implicated *CHEK2* and *KLF6* as low-penetrance prostate cancer susceptibility genes (9,10).

Mutations: Genetic testing for HPC is not available unless the family history suggests hereditary breast/ovarian cancer.

Incidence: Unknown. Five to ten percent of prostate cancer patients report a positive family history.

Diagnosis: The "Hopkins Criteria" for HPC include 1) prostate cancer in three or more first-degree relatives or 2) prostate cancer in three successive generations of either the maternal or the paternal lineages or 3) at least two relatives affected younger than age 55 years. Families need to fulfill only one criterion to be classified as having HPC.

Laboratory features: HPC is commonly multifocal.

Associated malignant neoplasms: Prostate cancer, with cumulative risks of prostate cancer to age 80 in men with a first-degree relative with prostate cancer of 35%, 30%, and 23% when the proband was diagnosed younger than age 60 years, ages 60–70, and older than age 70, respectively. Corresponding general population cumulative prostate cancer risks are 0.06% by age 55, 1.5% by age 65, and approximately 8% lifetime, per recent studies in England, Wales, and Sweden. Other studies have calculated absolute risks to men as follows: 12% if a father is affected at age 60 or older; 15% if one brother is affected at age 60 or older; 20% if a father is affected younger than age 60; 25% if one brother is affected younger than age 60; 30% if there are two affected male relatives in the same lineage; and 35%–45% with three or more affected relatives (11,12). An increased risk of central nervous system tumors has been observed in families with linkage to the putative 1p36 prostate cancer susceptibility locus.

Some patients with HPC are diagnosed at an average age 6–7 years younger than those with sporadic prostate cancer. A study of prostate cancer risk in carriers of Ashkenazi Jewish founder mutations in *BRCA1/2* did not demonstrate a younger age at diagnosis for mutation-associated cases (13).

Associated benign neoplasms: Prostatic intraepithelial neoplasia is likely a precursor lesion to invasive prostate cancer.

Cancer risk management: Routine screening with digital rectal examinations, measurements of serum prostate-specific antigen, and consideration of transrectal ultrasound is commonly advised in members of high-risk families. The possibility of false-positive prostate-specific antigens (PSAs) must be carefully discussed before testing, although the positive predictive value of these tests is increased in high-risk populations; a recent study reported twice as many prostate cancers on the baseline screen among family history–positive vs family history–negative men (14). The clinical presentation and prognosis was similar in these two groups. Men from multiple-case families who have a PSA of 3 ng/ml or more warrant consideration of prostate biopsy. Annual screening may begin at age 45 or 5 years younger than the youngest diagnosis of prostate cancer or 10 years younger than the youngest metastatic cancer diagnosis in that family. The role of prophylactic prostatectomy in management of these families is unknown and is not widely practiced at present. The efficacy of the screening approach outlined above and the optimal age to start screening are not validated. The lack of a prospective randomized clinical trial of prostate cancer screening makes it likely that multiple forms of bias (including lead-time bias) influence current data on the efficacy of this intervention.

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41. Renal Cell Carcinoma, Hereditary, with Multiple Cutaneous and Uterine Leiomyomas (HLRCC; Reed Syndrome)

OMIM number: 605839, 136850, 150800.

Inheritance pattern: Autosomal dominant.

Gene and chromosomal location: Fumarate hydratase, *FH*, on 1q42.1.

Mutations: Mutations in *FH* have been found in 76 of 89 probands with multiple cutaneous leiomyomas (MCULs; 85%). Mutations include missense (58%), frameshift (27%), nonsense (9%), and large deletions (7%). Alam et al. (1) demonstrated loss of enzymatic activity associated with many of these mutations. Nine percent of 93 *FH* gene mutation carriers were reported as nonpenetrant (2). No confirmed genotype–phenotype correlations are established. Homozygous or compound heterozygous mutations cause fumaric aciduria (OMIM 606812), a severe inborn error of metabolism.

Incidence: Unknown. Fifty-six families have now been studied at the U.S. National Institutes of Health (3).

Diagnosis: No formal diagnostic criteria established. Fumarate hydratase activity in Fibroblasts or lymphoblasts is reduced and DNA testing is available. Clinical dermatologic diagnosis requires MCULs with at least one histologically confirmed leiomyoma or a single leiomyoma in the presence of a family history of HLRCC. Leiomyoma penetrance varied from 40% to 100% between affected families. Seventy-six percent of those with HLRCC present with single or multiple leiomyomas, at mean age of 25 years (range = 10–47). Forty percent have 5 or less cutaneous lesions (3), which usually appear as firm nodules on the back and extensor surface of the extremities (occasionally the face) and may be pruritic or painful to the touch or sensitive to cold temperatures. Segmental cutaneous leiomyomatosis has been reported and is likely a manifestation of somatic mosaicism (4).

FH mutations result in a predisposition to uterine leiomyomata with early onset, approximately age 20–35. Nearly all women with HLRCC do have uterine leiomyomas (fibroids), which are more likely to be numerous and large, requiring hysterectomy, than their sporadic counterpart (5).

Laboratory features: Distinctive, mainly type II papillary RCC, were originally reported in HLRCC, but now a variety of histologies have been noted including tumors with mixed cystic, tubular-papillary, and clear cell elements and collecting duct tumors. Of 20 HLRCC individuals with RCC, 17 had solitary, unilateral tumors and three had bilateral or multifocal tumors (3,6).

Associated malignant neoplasms: RCC is the primary type of cancer reported in this disorder with a median age at diagnosis of 44 years. HLRCC-associated RCC is clinically aggressive and may prove to constitute a new clinical entity (5). Penetrance for RCC was 23% in three Finnish families, whereas RCC occurred in only one of 39 families from United Kingdom and in 13 of 21 families in the United States, likely reflecting ascertainment differences (3,7,8). Six cases of "uterine leiomyosarcoma" have been reported in HLRCC families, but the risk in HLRCC is unclear. Two adult Leydig cell tumors of the testis were reported in FH mutation carriers (9). Lehtonen et al. (10) also reported evidence suggesting possible association with cancer of the breast and bladder, though not reaching statistical significance.

Associated benign neoplasms: MCULs. The cutaneous lesions have not been reported to undergo malignant degeneration. Thirty-three women with a papillary RCC, a single-skin leiomyoma, and either ovarian cystadenoma or carcinoma were evaluated for germline FH mutations: two women with cystadenoma of the ovary were found to have mutations (6%) (11).

Matyakhina et al. (12) reported an HLRCC patient with bilateral macronodular adrenocortical hyperplasia and atypical Cushing syndrome, speculating that this could be an unrecognized association with HLRCC. Lehtonen et al. (10) recorded several cases with bilateral adrenal adenomas, adding support to this impression.

Cancer risk management: Although precise cancer risks are unclear, and there is no consensus on optimal cancer screening, annual urinalysis and cytology and renal imaging by computed tomography (alternating with magnetic resonance imaging) beginning at age 18–20 years may be reasonable. (Papillary RCC is not consistently visible by ultrasound.) If studies are normal, examinations may be repeated every 2 years. Recently, children as young as age 11 have been diagnosed with RCC, suggesting that screening for kidney cancer may be beneficial. The tumors in HLRCC appear to have a very aggressive clinical course [(13); Genetests.org]. Transvaginal ultrasound screening for rapid growth of uterine leiomyomas (which might raise the possibility of malignant transformation) is also suggested, starting at age 18–20. A hysterectomy may be an option after childbearing for at-risk women. It is difficult to be enthusiastic about these latter two recommendations in the absence of data on magnitude of risk in uterine fibroids in this setting. Myomectomy to remove symptomatic fibroids while preserving the uterus may be an option.

Comments: Uterine leiomyomas (fibroids) are very common in the general population (minimum prevalence >20%), and estimate of familial risk in first-degree relatives with nonsyndromic fibroids is approximately 25%. Fumarate hydratase catalyzes the conversion of fumarate to 1-malate in the mitochondrial tricarboxylic acid cycle, and thus, like *SDH* genes in hereditary paraganglioma, *FH* is important in cellular energy metabolism.

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42. Renal Cell Carcinoma, Hereditary (used here to apply only to Familial Nonpapillary, Clear Cell or Conventional Cell, or Clear Cell Adenocarcinoma of the Kidney)

OMIM number: 144700, 601153.

Inheritance pattern: Autosomal dominant and recessive.

Gene and chromosomal location: Chromosome 3p14.2 was implicated as a genomic region containing a kidney cancer susceptibility gene by finding chromosomal translocations involving this genomic region in a small proportion of families with hereditary renal cell carcinoma (HRCC) and a high prevalence of somatic loss of 3p heterozygosity in tumor studies, suggesting the presence of a tumor suppressor gene at this locus. Causative gene(s) have not been identified.

Mutations: The gene for the nonpapillary clear cell type is thought to be distinct from the von Hippel–Lindau gene. Most affected families have normal chromosomes, but as of 2004, eight families with HRCC had been reported with chromosome 3 translocations (all different) (1).

Incidence: RCC accounts for approximately 3% of all adult cancers, of which 2% are estimated to be inherited. Nonpapillary RCC accounts for approximately 80% of all RCCs. Hemminki and Li (2) provided epidemiological evidence for a recessive genetic component to RCC, with a relative risk of 2.4 for offspring vs 10.2 for siblings of affected case; risks were higher if the RCC had been diagnosed younger than age 50. This was a population-based study in Sweden, with no attempt to exclude RCC occurring in known hereditary syndromes.

Diagnosis: The diagnosis of HRCC is based on personal and family history and the exclusion of other hereditary syndromes. Early cancer onset (<50 years) or bilateral disease suggests genetic predisposition. Rarely, a constitutional chromosome anomaly can be found in HRCC families.

Laboratory features: Tumors consist predominantly of cells with clear cytoplasm, although foci of cells with eosinophilic cytoplasm are not uncommon. The histology is not distinctive from sporadic clear cell cancers.

Associated malignant neoplasms: RCCs only. The mean age at cancer diagnosis in HRCC is approximately 45 vs 60 years for sporadic cases. Teh et al. (3) reported that eight of nine patients from two families developed clear cell RCC at ages older than 50, whereas Woodward et al. (4) reported that 12 of 23 cases were diagnosed younger than age 50. These differences suggest heterogeneity in age at onset in familial cases, as illustrated by the two largest families in the Woodward series, one of which displayed early onset (mean = 28 years) whereas the other had late-onset disease (mean = 56 years).

Associated benign neoplasms: None known.

Cancer risk management: von Hippel–Lindau, tuberous sclerosis, and Birt–Hogg–Dubé syndromes must be ruled out in cases of familial clear cell RCC before the diagnosis of HRCC can be made. A peripheral blood cytogenetic analysis of an affected family member is suggested because detecting a constitutional rearrangement facilitates identifying other at-risk family members. There is no evidence to suggest an increased risk of nonrenal cell cancers in this syndrome; cancer surveillance can be limited to the kidneys. It is suggested that renal imaging be done every 1–2 years, beginning at age 35 or 10 years younger than the earliest diagnosis of renal cancer in that family. The late onset of RCC in some families suggests that at-risk relatives need to be monitored until at least age 65. Risks and benefits of cancer screening in this syndrome are not established.

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43. Renal Cell Carcinoma, Hereditary Papillary

OMIM number: 605074, 164860.

Inheritance pattern: Autosomal dominant.

Gene and chromosomal location: The *MET* proto-oncogene at 7q31.1–34.

Mutations: Mutations were originally found in four of seven families with hereditary papillary renal cell carcinoma (HPRCC) (1); more than 30 families have now been reported worldwide. Schmidt et al. (2) found *MET* mutations in 17 of 129 tumors from patients with apparently sporadic PRCC; eight (6%) proved to be germline. Lindor et al. (3) found no germline mutations in a clinically based study of 59 patients unselected for family history.

Incidence: Papillary renal cell cancer accounts for 15%–20% of all RCCs and occurs in both sporadic and familial forms. Among all RCC combined, approximately 2% represent familial cases. In a population-based study of 1733 unselected PRCC cases, Czene et al. (4) found only five families with an affected parent–child pair. A striking male predominance has been consistently noted in sporadic but not HPRCC.

Diagnosis: Patients with either bilateral and multifocal tumors without a family history or patients with a single tumor or multifocal tumors and a first- or second-degree relative with type 1 papillary renal cell cancer warrant consideration of genetic assessment for possible HPRCC.

Laboratory features: Patients with HPRCC and germline *MET* mutations develop tumors that are histologically distinct from most other types of hereditary renal cancers. Features include multiple, bilateral renal lesions with type 1 PRCC histology: microscopic papillary lesions (<0.5 cm in size), papillary adenomas

(<0.5 cm in size), and papillary renal carcinomas (>0.5 cm in size) (5–7).

Associated malignant neoplasms: PRCC. Schmidt et al. (7) reported three new families in which PRCC was diagnosed at ages ranging from 19 to 70 years. Schmidt et al. (8) estimated age-dependent penetrance of the specific H1112R *MET* mutation as 100% by age 80.

MET mutation carriers have been reported to develop gastric, rectal, lung, pancreatic, and bile duct cancers (9), but data are insufficient at present to determine whether gene carriers are at increased risk of specific non-RCC malignancies.

Associated benign neoplasms: Papillary renal adenomas may precede carcinoma development.

Cancer risk management: Renal imaging, urinalysis, and urine cytology are suggested every 1–2 years, beginning at age 25 or 10 years younger than the youngest person diagnosed with renal cancer in that family. Ultrasound may not be sufficiently sensitive to detect PRCCs, so magnetic resonance imaging is often recommended. Risks and benefits of cancer screening in this syndrome are not established.

Comments: Walther et al. (10) proposed a 3-cm renal tumor diameter as a threshold above which renal parenchymal–sparing surgery should be considered in both HPRCC and von Hippel–Lindau syndrome patients. In the HPRCC group, no patient with tumors smaller than 3 cm (0/10) developed metastatic disease during a mean follow-up time of 44 months, whereas 13% (2/13) patients with tumors larger than 3 cm developed metastases.

Acquired cystic disease (ACD) of the kidney develops in approximately 40% of patients with end-stage renal disease, and ACD is associated with a 40-fold increased risk of RCC, evenly distributed between papillary or clear cell subtypes. A high incidence of bilateral and/or multifocal PRCC has been reported in ACD patients, a pattern which represents a potential source for misdiagnosis of HPRCC.

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44. Retinoblastoma, Hereditary

OMIM number: 180200.

Inheritance pattern: Autosomal dominant with incomplete penetrance (estimated at 90%).

Gene and chromosomal location: *RB1* on 13q14.

Mutations: Many distinct deletions (large and small) and point mutations distributed widely across the gene have been reported. The majority of classical families show nonsense and frameshift mutations. Lower penetrance retinoblastoma (RB) families have in-frame deletions, missense mutations, and mutations in the promoter region (1). In bilateral RB patients, splice-site mutations are associated with late age at RB onset (2).

The sensitivity of current mutation analysis is about 90%. The probability of a germline *RB1* mutation is 100% for those with a family history of RB and unifocal, multifocal, or bilateral RB. For those with no family history of RB, the probability of a germline mutation is about 15% for unifocal RB, 15%–90% for multifocal unilateral RB, and greater than 90% for bilateral RB.

Chromosomal deletions of 13q14 have been reported in a minority of individuals with RB: 5% in unilateral RB and 7.5% with bilateral RB. Deletions are also found as a somatic mosaic abnormality in some affected individuals.

Incidence: RB has an incidence of one in 13 500 to one in 25 000 live births. Approximately 60% are unilateral and nonhereditary, 15% are unilateral and hereditary, and 25% are bilateral and hereditary. Males and females are equally affected. Approximately 20%–30% of mutation-positive individuals have de novo mutations. The frequency of gene mutation carriers in the general population is unknown.

Diagnosis: Usually discovered upon evaluation of strabismus and/or leukocoria. Approximately 90% of all RBs are diagnosed before the age of 3 years; the average age at diagnosis is 12–15 months in bilateral disease, and 18–24 months in unilateral disease (the latter usually nonhereditary).

Laboratory features: None are specific to hereditary RB.

Associated malignant neoplasms: Hereditary RB has greater than 90% penetrance. Family members with an affected parent and sibling have a 900-fold increase in RB risk (3). Age at onset has some predictive value with respect to the development of bilateral disease: bilateral disease develops in 85%, 82%, 44%, and 6% of patients who present younger than age of 6, 6–11, 12–23, and 24 or older months, respectively.

Second malignant tumors in RB patients were originally attributed exclusively to the carcinogenic effects of therapeutic irradiation; radiation treatment increases the risk of second cancers by threefold (4). However, it is now clear that some second cancers occur without prior radiation exposure. The incidence of second tumors in hereditary bilateral RB has been reported as 4.4%, 18.3%, and 26.1% at 10, 20, and 30 years after RB diagnosis, respectively (5). The cohort with the longest follow-up was found to have cumulative risks of a new cancer of 36% and 6%

for hereditary and nonhereditary patients, respectively, at 50 years after RB diagnosis (4). Abramson et al. (6) found that approximately 1% of patients with bilateral (hereditary) RB develop a nonocular second primary tumor (SPT) each year; at least 50% die of these second malignant neoplasms. For those who survive an SPT, there is approximately 2% per year risk of developing a third tumor. Moll et al. (7) confirmed a greater risk of SPT in children diagnosed and irradiated before the age of 1 year; however, the equal number of SPT inside and outside the radiation field suggested that irradiation was not the direct cause; rather, receiving radiation at a younger age may be a marker of SPT risk. The risk of any soft tissue sarcoma 50 years after irradiation for RB was reported as 13.1 %, and leiomyosarcoma was the most frequent type (8).

Osteosarcoma is the most common second tumor (500-fold risk increase) in RB patients. Melanoma, brain tumors, and nasal cavity cancers also occur excessively (4). Fibrosarcomas, chondrosarcomas, rhabdomyosarcomas, Ewing's sarcomas, leukemias, lymphomas, pinealoblastomas, and malignant phyllodes tumors have also been reported. The combination of bilateral RB and pinealoblastoma has been referred to as "trilateral retinoblastoma" (9).

Kleinerman et al. (10) reported a statistically elevated 15-fold risk of death from lung cancer among patients with hereditary RB. They noted, "our reported excess of early-onset lung cancer suggests that carriers of *RB1* mutations may be highly-susceptible to smoking-induced lung cancers. If so, patients with hereditary RB should be especially targeted for smoking cessation." Fletcher et al. (11) confirmed this association and also noted increased risk of urinary bladder cancer (another smoking-related malignancy) in hereditary RB survivors. In both studies, small cell lung cancers outnumbered non–small cell lung cancers.

Sebaceous carcinomas of the eyelid have been reported in RB survivors, both in patients treated with and without radiation therapy.

Associated benign neoplasms: Retinomas, benign retinal tumors, and lipomas (12). Li et al. (12) showed a statistically significant association between hereditary RB and multiple lipomata (3%–6%) vs an incidence of 0%–6% in sporadic RB cases.

Cancer risk management: No consensus guidelines exist regarding screening for retinoblastoma in those at risk for hereditary disease. Conventional screening in some centers has involved ophthalmologic examination (under anesthesia as needed) as soon as possible after birth, then every 4–6 weeks til age three months, then at 5,7,9,12 and 16 months, then every 6 months until age 3 years. Annual or semiannual examination is continued thereafter (13). In the UK, children have two examinations without anesthesia at birth and at age 6 weeks, followed by examination under anesthesia (EUA) every three months until age 2 years, then six more times to age 4 years (14). Currently, the GeneReviews experts suggest an examination every 3–4 weeks for the first year of life, then "less frequently until age three years" (15). Since 1992, all newborns in the Netherlands have been screened for RB within 2 weeks of birth. Children with familial RB screened from birth are generally diagnosed with minimal intraocular disease, although advanced cancers occur occasionally (6% of affected eyes were enucleated). Nearly 90% of patients retained long-term visual acuity of 20/20–20/40 (16).

A high index of suspicion for sarcoma development is warranted in mutation carriers. Baseline ophthalmologic examination is recommended for the parents and siblings of patients with a negative family history; the presence of a spontaneously regressed RB would confirm hereditary RB and dictate different prognosis and screening guidelines. Although the risk of various SPTs is substantial, specific screening strategies aimed at their detection is not advised because there are no data to suggest a survival advantage for persons with screen-detected second cancers. Aggressive smoking cessation interventions are recommended for *RB1* mutation carriers. The value of lung cancer screening in this population is unproven but may be considered. The risks and benefits of cancer screening in hereditary RB have not been established.

Comments: The following empiric risks of recurrence have been used for genetic counseling (15):

- For *offspring* of an individual with *unilateral* RB in which the family history is clearly negative and before any affected children have been born, the risk is 2–6%.
- For the *siblings* of an individual with *unilateral* disease in which the family history is clearly negative, the risk is about 3%.
- For the *offspring* of an individual with *bilateral* disease regardless of family history, the risk is up to 50% (40% historically cited).
- For the *siblings* of an individual with *bilateral* disease in which the family history is clearly negative, the risk is 2–10%.
- For the additional siblings of an individual with bilateral or unilateral disease in which a second sibling is also affected (either unilaterally or bilaterally) but no other relatives are affected, the risk is 50% (40% historically cited).

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45. Rhabdoid Predisposition Syndrome (includes Brain Tumors in Infancy, Familial Posterior Fossa Tumors, and Renal Rhabdoid Tumors)

OMIM number: 601607, 609322.

Inheritance pattern: Autosomal dominant inheritance, with incomplete penetrance.

Gene and chromosomal location: *SNF5/IN11* (*SMARCB1*) at 22q11.2.

Mutations: *SNF5* is thought to be a tumor suppressor gene; the presence of a variety of biallelic somatic mutations and deletions in tumors supports this role. In a series of children with atypical teratoid and rhabdoid tumors (AT/RTs; a subset of primitive neuroectodermal tumors [PNETs]), germline *SNF5* mutations were found in one of eight children with teratoid brain tumors and three of seven with renal RTs (1). Sevenet et al. (2) identified germline *SNF5* mutations in four families with malignant RTs and various central nervous system neoplasms; parental gonadal mosaicism occurred in two instances. In four other single cases or in families with germline *SNF5* mutations, two had a nonpenetrant parent, one demonstrated a de novo mutation, and the mutation origin was unclear in the third (3–6). A family with two nonpenetrant males is notable (7). The existence of a second susceptibility gene is indicated by an extensively characterized family not linked to *SNF5* (8).

Incidence: Extremely rare.

Diagnosis: Tumors generally appear in children younger than 2 years of age and can develop prenatally. Multiple primary RTs in an affected individual have been reported (eg, brain and kidney).

Laboratory features: No specific findings.

Associated malignant neoplasms: Renal and extrarenal malignant AT/RTs, choroid plexus carcinoma, medulloblastoma, and central PNET have been reported.

Associated benign neoplasms: Meningioma, myoepithelioma and familial schwannomatosis have been reported (9). In 1 of 21 unrelated patients with schwannomatosis, a de novo germline mutation in the SNF5 gene was found. Based on tumor analyses, Sestini et al. (10) postulated that a 4-hit mechanism involving at least 2 distinct but linked tumor suppressor genes, SNF5 and NF2, may underlie the development of tumors in a subset of patients with schwannomatosis.

Cancer risk management: Increased index of suspicion for the development of brain and renal tumors in families with known *SNF5* mutations. Monitoring for renal tumors by ultrasound every 4 months up to age 3 has been suggested, but objective data regarding efficacy are very limited. The value of screening with central nervous system imaging is unknown but has been considered in these rare families.

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46. Rothmund–Thomson Syndrome

OMIM number: 268400; allelic with RAPADILINO (OMIM 266280) and Baller–Gerold (OMIM 218600) syndromes.

Inheritance pattern: Autosomal recessive.

Gene and chromosomal location: The *RECQL4* gene on chromosome 8q24.3. Rothmund–Thomson syndrome (RTS) is a member of the RecQ helicase chromosomal instability disorders, which include Bloom and Werner syndromes [reviewed by Hickson (1) and Kellermayer (2)].

Mutations: A variety of mutations have been reported to date.

Incidence: Very rare (through 1990, 200 cases had been reported).

Diagnosis: Based upon clinical gestalt; can be confirmed with genetic testing. The most notable clinical feature is a characteristic sun-sensitive rash (100% of patients). The rash usually presents between 3 and 6 months (range = birth to 24 months) as erythema, swelling, and blistering on the cheeks and face (acute phase) and then spreads to the buttocks and flexural areas of the extremities,

sparing the chest, back, and abdomen. Over months to years, the rash enters a chronic phase, with poikiloderma (telangiectasias, reticulated pigmentation, punctate dermal atrophy) that lasts through adulthood.

Wang et al. (3) identified the following clinical manifestations in a cohort of 41 patients: rash (100%), small stature (66%), skeletal dysplasias (75%), radial ray defects (20%), sparse scalp hair (50%), sparse brows or lashes (73%), cataracts (6%), and osteosarcoma (32%). Skin cancer was also observed in one of the 41 (2%) patients. Compared with other reports, this series was notable for a higher prevalence of osteosarcoma and fewer cataracts.

Laboratory features: No consistent findings. Five patients were reported with clonal and nonclonal cytogenetic rearrangements, often involving chromosome 8, representing acquired mosaicism (4). There are inconsistent reports of reduced DNA repair after exposure of cells to ultraviolet C and gamma irradiation. Lindor et al. (4) reported a normal response to mitomycin C in vitro, normal sister chromatid exchange, normal bleomycin-induced breakage, no evidence of tumor microsatellite instability, and normal p53 expression.

Associated malignant neoplasms: Wang et al. (3) reported that 13 of 41 (32%) RTS patients developed osteosarcoma (median age = 11.5 years; range = 4–41). Ascertainment bias is unlikely to account for this association because the diagnosis of RTS *preceded* diagnosis of osteosarcoma in all but one case. Additionally, 22 of the 28 cancer-free patients in the cohort were younger than age 15 when studied and are thus still at risk of developing osteosarcoma. Somatic mutations in *RECQL4* are rare in sporadic osteogenic sarcoma (5).

Vennos et al. (6) reviewed the world literature on RTS, which consisted of 200 individual cases. They reported eight skin malignancies: four squamous cell carcinomas, two Bowen's diseases, and one each basal cell carcinoma and spindle cell carcinoma. Cancer of the tongue, acute myeloblastic leukemia, progressive leukopenia, and aplastic anemia have been reported several times (7,8), as has myelodysplasia (9–12). Because of the very small number of RTS patients, it is unclear which, if any, of these associations are significant; risks of specific sites or types of cancers have not yet been defined, except for osteogenic sarcoma.

Associated benign neoplasms: Warty dyskeratosis, actinic keratoses.

Cancer risk management: No formal guidelines exist. It is prudent to maintain an increased index of suspicion for cancer (especially skin, bones). Protection from excess sun exposure may be indicated; periodic dermatologic examination beginning in childhood is suggested. The risks and benefits of cancer screening in this syndrome are not established.

Comments: Reduction of standard chemotherapy doses was required in siblings because of excessive marrow suppression (4). Others have since reported similar experiences.

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47. Simpson–Golabi–Behmel Syndrome (SGBS)

OMIM number: 312870, 300037, 300209, 300171.

Inheritance pattern: X-linked recessive (mild manifestations in carrier females).

Gene and chromosomal location: Simpson–Golabi–Behmel syndrome type 1 (SGBS1) is caused by mutations in *GPC3* (Xq26), the glypican-3 gene, an extracellular glycoprotein thought to have a role in control of embryonic mesoderm. SGBS2 is caused by mutations in *CXORF5* (Xp22) and is allelic with orofacial digital syndrome type I (OMIM #311200).

Mutations: Inactivating mutations in *GPC3* are reported (including large and small deletions, splice sites, and point mutations) with neither mutational hotspots nor genotype–phenotype correlations appreciated to date. A *CXORF5* mutation in a single family with a very severe phenotype was reported by Budny et al. (1).

Incidence: Unknown. Approximately 100 patients had been reported by 1999 (2).

Diagnosis: SGBS1 in males is an overgrowth syndrome characterized by macrosomia, macrocephaly, coarse facies, hypertelorism, epicanthic folds, downslanting palpebral fissures, large jaw, broad nasal bridge, short upturned nasal tip, large tongue, midline groove of tongue and/or lower lip, cardiac abnormalities (cardiomyopathy, conduction problems, and congenital heart anomalies, especially pulmonic stenosis), minor skeletal anomalies, broad short hands with hypoplasia of the distal index finger, and developmental delay (not universal). Carrier females may have similar but much milder features.

In the family with SGBS2, the males were very severely affected and died at a young age, often related to impaired ciliary function. Carrier females were unaffected.

Laboratory features: No specific findings.

Associated malignant neoplasms: SGBS manifests an increased risk of embryonal malignancies, especially Wilms tumor. Neuroblastomas, hepatoblastoma, hepatocellular carcinoma, and testicular gonadoblastoma have also been reported (3).

Associated benign neoplasms: None reported.

Cancer risk management: SGBS-associated Wilms tumor and hepatoblastoma have clinical characteristics that suggest they should be amenable to successful screening (4); studies in Beckwith–Wiedemann syndrome have demonstrated a more favorable stage for screen-detected Wilms tumor (5). Based on the current understanding of SGBS, ultrasound of the kidneys every 4 months through age 7 is suggested (6). Screening for hepatoblastoma with serum alpha-fetoprotein every 6–12 weeks through late infancy has also been advised (4). There is no likely benefit from screening for the other tumors reported in SGBS.

Comment: There appears to be a predisposition to embryonal tumors in multiple overgrowth syndromes (Perlman syndrome [OMIM 267000], Weaver syndrome [OMIM 277590]), Sotos syndrome (OMIM 117550), and Beckwith–Weidemann syndrome [OMIM 130650]), all of which are in the differential diagnosis for SGBS (7,8).

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48. Testicular Germ Cell Tumor, Familial

OMIM number: 273330.

Inheritance pattern: Possible X-linked recessive, autosomal dominant, autosomal recessive.

Gene and chromosomal location: Gene(s) unknown. Linkage to Xq27 was reported in about one-third of families with more than one case of testicular cancer (1). This locus (designated "*TGCT1*," OMIM 300228) was associated with undescended testes and bilateral disease. An expanded genome-wide linkage analysis failed to strengthen this association but did provide suggestive evidence of linkage to other autosomal loci (2). The authors concluded that "no single major locus can account for the majority of the familial aggregation of TGCT" and suggested that this genetic susceptibility might be the result of multiple low-penetrance loci. The *DND1* gene, known to cause testicular tumors in mice, has been excluded as a significant contributor to human familial testicular germ cell tumor (TGCT) (3).

Mutations: Unknown. Germline deletions in the *gr/gr* locus, located on the Y chromosome and known to be related to male infertility (a known testicular cancer risk factor), are associated with twofold and threefold increases in the risks of sporadic and familial TGCT, respectively (4).

Incidence: Rare. Surveys have documented a positive family history of testicular cancer in 1%–3% of cases. Standardized incidence ratios (SIRs) are consistently greater for brothers (SIR = 8–12) than for fathers (SIR = 2–4) or sons (SIR = 4–5), perhaps explained in part by involvement of an X-linked or recessive gene. Testicular cancer rates are highest in the Scandinavian countries (5). The cumulative risk to a brother of a case is reported to be 2.2% by age 50 and 4.1% by age 60.

Diagnosis: Based on clinical history only. Unlike the pattern observed in most other hereditary cancer syndromes in adults, the most common number of affected family members with TGCT is 2. Bilateral cancers are about 3.5 times more frequent in familial (9.8%) vs sporadic (2.8%) TGCT (6). It has been suggested that the majority of bilateral TGCT cases arise as a result of a predisposing genotype (7). The median age at diagnosis is inconsistently younger in familial cases compared with nonfamilial cases (8,9). Familial TGCT cases are twice as likely to have undescended testes (11%) and inguinal hernias (8%) than the general testicular cancer population (10). The association between TGCT and undescended testicles, hypospadias, inguinal hernia, reduced fertility, and semen abnormalities (the "testicular dysgenesis syndrome") has been proposed as the etiological substrate for TGCT (11).

Laboratory features: None. Concordance of histological subtype among affected members of the same family is inconsistently observed. In a series of familial TGCT patients studied with high-resolution Giemsa-banded and SKY karyotypes, no constitutional cytogenetic abnormalities were detected (12).

Associated malignant neoplasms: Both seminomatous and nonseminomatous germ cell tumors occur in high-risk families. Several families have also included females with ovarian germ cell tumors and members with mediastinal germ cell tumors. There is no evidence at present to suggest that malignancies other than germ cell neoplasms occur excessively in these families.

Associated benign neoplasms: None known.

Cancer risk management: The risks and benefits of cancer screening in this syndrome are not established. Monthly testicular self-examination and annual clinician examination plus testicular ultrasound starting 10 years before the age at diagnosis of the youngest case in the family may be suggested, but the clinical benefits associated with this strategy are unproven. The value of incorporating tumor markers, such as AFP and beta-human chorionic gonadotropin, into screening programs is undefined.

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49. Thyroid Carcinoma, Familial Non-medullary (includes Papillary Thyroid Carcinoma with Papillary Renal Neoplasia)

OMIM number: 188550, 606240, 603386, 605642, 606240, 138800, 300273.

Inheritance pattern: Autosomal dominant.

Gene and chromosomal location: Familial non-medullary thyroid carcinoma (FNMTC) linked to 2q21 and 19p13; papillary thyroid carcinoma with papillary renal neoplasia (PTC/PRN) linked to 1q21; multinodular goiter with PTC (MNG1) linked to 14q31; MNG2 linked to Xp22.

Mutations: None known.

Incidence: From 2000 to 2004, the age-adjusted incidence rate for all thyroid cancers in the United States was 8.5 per 100 000 per year; 0.73% of men and women (one in 136) born today will be diagnosed with cancer of the thyroid during their lifetime. The median age of diagnosis is 47 years (age <20 = 2.1%; 20–34 = 18.2%; 35–44 = 23.0%; 45–54 = 23.1%; 55–64 = 15.5%; 65–74 = 10.8%; 75–84 = 6.0%; and ≥85 = 1.4%) (1). Of these cancers, 90% are well differentiated and among these, 80%–85% are papillary, 10%–15% follicular, and 3%–5% are Hurthle cell carcinomas. Approximately 5% of apparently sporadic PTC may be due to inherited predisposition (2). In population studies, the familial risks of papillary thyroid cancer were 3.2 or 6.2 when a parent or sibling was affected (3). The risk was highest among sisters (familial risk = 11.1) and in the presence of early-onset disease.

Diagnosis: Sturgeon and Clark (4) stated that FNMTC is defined by diagnosis of two or more first-degree relatives affected by differentiated thyroid cancer of follicular cell origin (includes papillary, follicular, and Hurthle cell cancers). Musholt et al. (5) developed diagnostic criteria for FNMTC when previous radiation exposure, other neoplasia syndromes, and somatic genetic alterations have been excluded. Primary criteria: 1) PTC in two or more first-degree relatives *and* 2) multinodular goiter in at least three first- or second-degree relatives of a PTC patient. Secondary criteria: 1) diagnosis in a patient younger than 33 years, 2) multifocal or bilateral PTC, 3) tumor growth beyond the thyroid, 4) metastasis, and 5) familial accumulation of adolescent-onset thyroid disease. A hereditary predisposition to PTC should be suspected if both primary criteria or one primary and three secondary criteria are met. FNMTC is comprised primarily of papillary thyroid cancer (PTC = approximately 90%), and women outnumber men by 2–3 to 1. Two subgroups of FNMTC have been suggested: 1) those in which the FNMTC is one component of a defined cancer susceptibility syndrome with a preponderance of nonthyroid cancers (eg, familial adenomatous polyposis [FAP], Cowden syndrome, Carney complex type 1, Multiple Endocrine Neoplasia Type 2A [MEN2A], and familial multinodular goiter) and 2) those in which FNMTC is the predominant neoplasm (6). Genes that predispose to familial multinodular goiter kindreds (linked to MNG1 and MNG2) can also present as FNMTC, as PTC has been reported in around 10% of those with familial goiter (7).

Laboratory features: No specific findings.

Associated malignant neoplasms: Thyroid carcinoma, often multifocal and bilateral. Familial cases of PTC are reportedly more aggressive than their sporadic counterparts. In relatives of patients with thyroid cancer, Pal et al. (8) reported a 10-fold increase in the risk of thyroid cancer. In the one PTC/PRN family studied, papillary renal cell carcinoma occurred in a single affected individual.

Associated benign neoplasms: Thyroid disease, thyroid adenoma, and multinodular goiter. In the family with PTC/PRN, multifocal renal adenomas and one oncocytoma were reported.

Cancer risk management: The family history of individuals with NMTC should be reviewed carefully to rule out other tumor predisposition disorders (eg, FAP, Cowden syndrome, Carney complex type 1, MEN2A, and familial multinodular goiter), and special attention should be paid to the risk of renal cancers. If a familial predisposition to NMTC is thought to exist, annual screening by thyroid palpation and thyroid ultrasound is recommended, beginning 10 years younger than the youngest relative diagnosed with benign or malignant thyroid tumor. Renal ultrasound is recommended for those with family history of renal cancer. Uchino et al. (9) reported that FNMTC patients were more likely to have intraglandular dissemination (41% vs 29%), multiple benign nodules (42% vs 30%), and cancer recurrence (16% vs 10%) than were patients with sporadic disease. Despite there being no difference in overall survival, they concluded that FNMTC is a distinct clinical entity that is locally aggressive and advised total or near total thyroidectomy with neck dissection. The role of prophylactic surgery in this disorder is undefined.

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50. Tuberous Sclerosis Complex

OMIM number: 191100, 605284 (*TSC1*), 191092 (*TSC2*).

Inheritance pattern: Autosomal dominant.

Gene and chromosomal location: *TSC1* on 9q34; *TSC2* on 16p13.3. Their protein products are designated hamartin and tuberin, respectively. Mutations in one or the other of these genes are detectable in about 80% of individuals with tuberous sclerosis complex (TSC), with higher detection rates for *TSC2* than *TSC1*, despite linkage studies suggesting similar prevalence of these two genes.

Mutations: *TSC1* mutations tend to be small deletions, insertions, or nonsense mutations, whereas *TSC2* mutations tend to be large deletions and rearrangements (which cannot be detected by sequencing). More than 60% of cases represent de novo mutations. Between 10% and 25% of patients show somatic mosaicism, which presents a milder phenotype. The *TSC2* and *PKD1* genes are located next to one another in opposite orientation. A large deletion of the 3' end of either gene may affect the function of both genes, leading to a contiguous gene syndrome of severe autosomal dominant polycystic kidney disease in infancy (OMIM 600273).

Incidence: TSC is estimated to be present in one of 5800 live births. Prevalence is approximately one in 30 000 individuals younger than age of 65 and approximately one in 15 000 younger than age of 5.

Diagnosis: The diagnosis relies on a careful physical examination and selected imaging studies. For a thorough review of hypomelanotic disorders in the newborn or infant, see Ruiz-Maldonado (1). Genetic testing is now clinically available. Table 16 shows the current diagnostic criteria (2).

Neuropathologic findings reflect impaired neuronal migration that results in subependymal nodules, cortical tubers, areas of focal cortical hypoplasia, and heterotopic gray matter. Among individuals with TSC, 80%–90% have seizures; approximately half have cognitive impairment of variable degrees; and autism, hyperactivity, and other behavioral disturbances are common. There is some correlation between the number of lesions in the cerebral cortex detected by magnetic resonance imaging (MRI) and the degree of cognitive impairment and difficulty with seizure control. Those with infantile seizures are more likely to develop cognitive impairment, but they also have more cortical lesions by MRI. Many TSC patients have multiple renal cysts; intracranial ("berry") aneurysms are occasionally reported, and this combination can be difficult to distinguish from autosomal dominant polycystic kidney disease (3).

Laboratory features: None specific for diagnosis.

Associated malignant neoplasms: There is a 6%–14% incidence of childhood brain tumors in patients with TSC, of which more than 90% are subependymal giant cell astrocytomas. TSC is associated with a cumulative renal cancer incidence of 2.2%–4.4% (4,5); the average age at diagnosis is 28 years, with occasional early childhood cases (6). The renal abnormalities in TSC are unusual in that patients develop epithelial lesions (cysts; oncocytomas; and clear cell, papillary, or chromophobe carcinomas) as well as mesenchymal lesions (angiomyolipomas), suggesting that the TSC genes regulate early differentiation and proliferation of renal precursor cells (7). Malignant angiomyolipoma is reported in less than 1% of individuals with TSC. Wilms tumor, Hurthle cell thyroid cancer, and chordoma have been reported in TSC families, but whether these are true associations is unknown (8).

Associated benign neoplasms: Cortical and subcortical tubers (glial harmartomas) (70%), subependymal glial nodules (90%), retinal hamartomas or achromic patches (75%), and facial

Table 16. Diagnostic criteria for tuberous sclerosis complex (2)[a]

Major features
• Facial angiofibromas or forehead plaque
• Nontraumatic ungual or periungual fibromas
• Hypomelanotic macules (three or more)
• Shagreen patch (connective tissue nevus)
• Multiple retinal nodular hamartomas
• Cortical tuber[b]
• Subependymal nodule
• Subependymal giant cell astrocytoma
• Cardiac rhabdomyoma, single or multiple lymphangiomyomatosis[c]
• Renal angiomyolipoma[c]
Minor features
• Multiple randomly distributed pits in dental enamel
• Hamartomatous rectal polyps
• Bone cysts
• Cerebral white matter radial migration lines[b,d]
• Gingival fibromas
• Nonrenal hamartoma
• Retinal achromic patch
• "Confetti" skin lesions
• Multiple renal cysts
Definite TSC: either two major features or one major plus two minor features
Probable TSC: one major plus one minor feature
Possible TSC: either one major feature or two or more minor features

[a]TSC = tuberous sclerosis complex.

[b]Cerebral cortical dysplasia and cerebral white matter migration tracts occurring together are counted as one rather than two features of TSC.

[c]When both lymphangiomyomatosis and renal angiomyolipomas are present, other features of tuberous sclerosis must be present before TSC is diagnosed.

[d]White matter migration lines and focal cortical dysplasia are often seen in individuals with TSC; however, because these lesions can be seen independently and are relatively nonspecific, they are considered minor diagnostic criteria for TSC.

angiofibromas (in 80% of postpubertal patients, known by the misnomer "adenoma sebaceum"…they are neither). Facial angiofibromas are cosmetically damaging and tend to bleed; laser ablation is the cornerstone of management. Shagreen patches (nodular cutaneous plaques that resemble pig skin) are present in 55% of affected individuals. Ungual fibromas are usually not present in children younger than age 5; they occur in 23% of affected children ages 5 to 14 and 88% of patients older than 30 years of age. Eighty percent of children with TSC have renal lesions including benign angiomyolipomas (70%), cysts (20%), and oncocytoma (<1%) (9). Renal angiomyolipomas are most often multiple (91%) and bilateral (84%); as they enlarge, they are at risk of lethal hemorrhage (managed with arterial embolization) or renal failure, from replacement of normal renal tissue with diseased tissue. Cardiac rhabdomyomas (present in >50% of TSC patients) may present prenatally or perinatally, are largest in the neonatal period, and generally regress after birth. They may cause cardiac arrhythmia. From 51% to 86% of all cardiac rhabdomyomas are associated with TSC. Jozwiak et al. (10) studied 154 TSC-related cardiac tumors and noted that whereas 68% regressed or disappeared, 4% of the tumors either grew or first appeared in later childhood, although these were generally asymptomatic. Lymphangiomyomatosis (LAM) of the lung occurs in 1%–6% of TSC patients, especially in adult women; it can be progressive and severe. Hormone therapy can be very effective in selected LAM patients. Multiple dental enamel pits in secondary teeth are seen in 71% of TSC patients, vs 0.9% of controls (11). Adrenal angiomyolipomas, adrenal adenomas and paragangliomas, pancreatic adenomas and islet cell tumors, skin acrochordons, and parathyroid adenomas may occur.

Cancer risk management: Discussion of comprehensive management of patients with TSC is far beyond the aims of this handbook [see Yates (12)]. Evidence-based cancer screening strategies have not been defined, but TSC patients are generally advised to have echocardiogram in infancy (to seek cardiac rhabdomyomas) with careful attention paid to potential symptoms of these tumors in later childhood; renal imaging every 1–3 years (to identify large angiomyolipomas or cancers); cranial imaging every 1–3 years in childhood and adolescence; and monitoring for LAM in adulthood. Additional imaging studies are indicated in individuals with new signs or symptoms suggestive of a clinically significant new lesion.

Comment: Evaluation and care of individuals with TSC is complex, requiring a multidisciplinary approach involving neurologists, ophthalmologists, dermatologists, urologists, geneticists, cardiologists, nephrologists, developmental specialists, pulmonologists, and others. Because *TSC1* and *TSC2* mutations greatly increase mTOR activity, rapamycin (an inhibitor of hamartoma growth in rodent models of TSC) was tested and shown to restore signaling downstream of mTOR to normal levels. Clinical trials are currently in progress to determine whether these drugs slow the progression of renal angiomyolipomas or pulmonary LAM (12,13).

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51. von Hippel–Lindau Syndrome

OMIM number: 193300, 608537.

Inheritance pattern: Autosomal dominant.

Gene and chromosomal location: *VHL* on 3p25–p26.

Mutations: More than 300 different pathogenic DNA variants have been reported; 72% are missense mutations, and 28% are partial or complete gene deletions. Germline *VHL* mutations can be detected in nearly 100% of clinically affected individuals. Families may be characterized by the presence (von Hippel–Lindau [VHL] type 2: 7%–20% of families) or absence (VHL type 1) of pheochromocytomas. Type 2 is subdivided into subcategories 2A and 2B, that is, VHL without and with predisposition to clear cell renal cancer, and a 2C phenotype (pheochromocytoma alone) has been described [reviewed in Lonser et al. (1)]. Approximately 95% of type 2 (see "Diagnosis") families have missense mutations, whereas approximately 96% of type 1 families have deletions or premature termination mutations. Production of an aberrant VHL protein is associated with increased risk of pheochromocytoma, consistent with the high rate of pheochromocytomas in those with the German founder missense mutation in codon 169 (tyr to his). Somatic mosaicism has been described (2) and may be more common in patients in whom there is no detectable gene mutation (3).

Incidence: Incidence is approximately one in 30 000–40 000.

Diagnosis: Traditional clinical criteria for diagnosis are shown in Table 17. VHL has nearly complete penetrance by age 65.

Laboratory features: None specific to VHL. If pheochromocytoma is present, catecholamines and their metabolic

Table 17. Diagnostic criteria for von Hippel–Lindau disease (VHL) developed before genetic testing (1,4–6)[a]

Diagnosis is established if there are
1. Two or more CNS or retinal hemangioblastomas or
2. A single CNS or retinal hemangioblastoma, plus one of the following:
• Multiple renal, pancreatic, or hepatic cysts
• Pheochromocytoma (any location)
• Renal cancer
• Endolymphatic sac tumor
• Papillary cystadenoma of the epididymis or broad ligament
• Neuroendocrine tumor of the pancreas or
3. Definite family history of VHL plus one of the following:
• CNS or retinal hemangioblastoma
• Multiple renal, pancreatic, or hepatic cysts
• Pheochromocytoma
• Renal cancer younger than age 60 years
• Epididymal cystadenoma

[a]CNS = central nervous system.

products can be detected either in plasma or in 24-hour urine collections. Measurement of fractionated metanephrines (ie, metanephrine and normetanephrine each measured separately) provides superior diagnostic sensitivity vs the historical strategy of measuring parent catecholamines. There is no current consensus regarding whether performing these assays in urine or plasma is preferable (7).

Associated malignant neoplasms: Malignant renal cell carcinoma (RCC; clear cell type) occurs in 35%–75% of affected individuals in autopsy series and in 25%–38% in clinical series; the renal cell cancers are often multiple and bilateral and may arise within complex cysts. The mean age at diagnosis is 40 years (range = 16–69). There is a lower risk of RCC in patients with complete, rather than partial, germline deletions of the VHL gene (8). Pancreatic islet cell carcinomas tend to cluster in certain families, in which the incidence ranges from 7.5% to 25%. Carcinoid tumors have been reported occasionally. Pheochromocytomas rarely undergo malignant transformation. Endolymphatic sac tumors (ELSTs) are locally aggressive papillary adenocarcinomas. They have been reported in 11%–16% of VHL patients, and in 14%–30%, they are bilateral; they cause hearing loss, tinnitus, and vertigo (9–11). A total of 10%–15% of individuals with ELSTs are thought to have VHL [reviewed by Bisceglia et al., (12)]. In one study of 35 patients with VHL-related ELSTs in 38 ears (three bilateral), tumor invasion of the otic capsule occurred in 18% causing sensorineural hearing loss (SNHL) in all. SNHL hearing loss developed in 87% of ears with no invasion, either suddenly (52%) or gradually (48%), and four ears had normal hearing. Intralabyrinthine hemorrhage was found in 11 of 14 ears with sudden SNHL (79%; $P < .001$) but occurred in none of the 17 ears with gradual SNHL or normal hearing. Tumor size was not related to SNHL ($P = .23$) or vestibulopathy ($P = .83$) (13).

Associated benign neoplasms: Hemangioblastomas, which are histologically benign tumors, occur in 50%–79% of autopsy-confirmed cases and in 18%–44% of patients in clinical series; they are the cause of the first VHL symptoms in 40% of patients and cause more than 50% of the deaths. The average age at first hemangioblastoma symptom is 30 years (range = 9–62). The majority of hemangioblastomas are cerebellar (60%–75%); the remainder are spinal. Supratentorial lesions are rare (clinical tip: rule out metastatic RCC if such a lesion is seen). Retinal angiomas (which are also hemangioblastomas) occur in approximately 70% of individuals and can result in visual loss. They have been detected in children as young as age 1 year but typically become evident between the ages of 21 and 28. Pancreatic cysts, which can be multiple and occasionally large, are detected in 9%–29% of patients by computed tomography (CT) imaging; pancreatic cystadenomas are found in 7% of patients. Pancreatic cystadenoma is a benign nonfunctional tumor that should be differentiated from a pancreatic islet cell carcinoma. A total of 20%–100% of patients have renal lesions. Cystic lesions are by far the most common, and complex cysts can contain RCC.

Pheochromocytoma occurs in 3.5%–17% of VHL patients and tends to cluster in certain kindreds; 26%–34% of these lesions are bilateral, with a typical age at diagnosis of 25–34 years. Benign adrenal adenomas and paragangliomas of the sympathetic chain are infrequently found in VHL. Epididymal cysts are found in 7%–27% of patients, ranging in size from 0.5–2.0 cm. Benign epididymal papillary cystadenomas are found in 3%–26% of males on autopsy series. The equivalent lesion reported in women is papillary cystadenoma of the broad ligament. Hepatic cysts (in 17% of patients) have been reported in autopsy series. Splenic angiomas and cysts occur in 3%–7% of autopsied patients.

Cancer risk management: Recommendations for VHL are evolving constantly and are regularly updated by the VHL Family Alliance (http://www.vhl.org/). In general, genotype–phenotype correlations are not sufficiently well defined to permit modifying screening recommendations based on genotype. The following guidelines are suggested for those at risk of VHL or known to carry a gene mutation:

- Annual ophthalmologic examination, starting by age 5 years (sooner if feasible).
- Annual physical examination, including blood pressure (seeking evidence of pheochromocytoma), and neurological evaluation for signs of cerebellar or spinal cord lesions, starting at age 5 years.
- Imaging of the central nervous system and the spinal cord by magnetic resonance imaging (MRI) with gadolinium, starting at approximately age 11. Biennial imaging is recommended by some experts, but the value of baseline and subsequent imaging in asymptomatic individuals is unproven.
- Annual complete blood count seeking evidence of polycythemia (caused by erythropoietin secretion from renal cysts and cerebellar hemangioblastoma) and annual urinalysis.
- Annual urine and/or plasma fractionated metanephrines should be measured (see "Laboratory features"), starting between ages 2 and 5 years when relatives have pheochromocytomas or at age 16 otherwise. Although lifetime risks of pheochromocytoma can be estimated based on the underlying mutations, all patients should be screened regularly and *before* any kind of surgery.
- Annual ultrasound imaging of the kidneys and pancreas, beginning no later than age 16. MRI (in children) or CT (in

adults) should be performed to evaluate any abnormalities detected by ultrasound. Ongoing surveillance of the kidney and pancreas in adults also includes CT (preferably), or MRI, every 2–3 years. Data support applying a 3-cm mass size threshold for surgery (parenchymal sparing if possible) in VHL-related RCC; among 108 patients with tumors smaller than 3 cm (mean follow-up 58 months), none developed metastatic disease (14). Observation is reasonable for lesions smaller than 3 cm.

Some argue that screening of asymptomatic pediatric *VHL* mutation carriers is justified on the basis of detecting significant numbers of tumors before symptoms first arise (15), but the optimal screening program in VHL disease and the risks and benefits of cancer screening in this syndrome have not been established (10).

Comments: All affected patients will benefit from genetic counseling, and evaluation of all family members, starting with first-degree relatives, is advised. The age at which screening of at-risk family members can be safely discontinued has not been determined. Although CT of the abdomen is important for the detection and monitoring of visceral lesions, it must be used sparingly to limit the lifetime radiation dose, which can be substantial if serial CT imaging is employed.

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52. Waldenström Macroglobulinemia, Familial

OMIM number: 153600.

Inheritance pattern: Variable. Multigenerational pedigrees with male-to-male transmission have been described, suggesting autosomal dominant inheritance in some families. Other pedigrees consist of sibships or affected cousins only (1).

Gene and chromosomal location: Unknown. A genome-wide linkage analysis in 11 high-risk families found evidence of linkage to chromosomes 1q (LOD score = 2.5, $P = 0.009$) and 4q (LOD score = 3.1, $P = 0.004$), when both Waldenström macroglobulinemia (WM) and IgM monoclonal gammopathy of undetermined significance (MGUS) were considered affected (2).

Mutations: No gene has been cloned.

Incidence: Rare.

Diagnosis: Two or more relatives with WM, based on family and medical history.

Laboratory features: None known. Cytogenetic abnormalities in the bone marrow of familial WM patients do not differ in frequency or type from those found in sporadic disease (3). First-degree relatives are reported to have an increased prevalence of subclinical immune dysfunction, including IgM MGUS, relative to general population estimates (4,5).

Associated malignant neoplasms: WM (lymphoplasmacytic lymphoma). Clinical reports and a single registry study suggest that first-degree relatives are at increased risk of other B-cell tumors, particularly chronic lymphocytic leukemia and non-Hodgkin lymphoma (1,5).

Associated benign neoplasms: None known.

Cancer risk management: None has been defined. Although IgM monoclonal gammopathy can be detected and seems to be a phenotypic marker of WM susceptibility (6), early detection of IgM MGUS has no known clinical benefit. Therefore, routine screening of asymptomatic relatives of affected patients is not advised.

Comments: Familial clustering of WM has been described since 1960. Blattner et al. (7) described one family in which members affected with either WM or clinical or subclinical autoimmune thyroid disease shared a specific human leukocyte antigen haplotype, suggesting possible association with the major histocompatibility complex. Progression from IgM MGUS to WM can occur, although the latency appears to be prolonged (8,9).

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53. Werner Syndrome (includes Adult Progeria)

OMIM number: 277700, 604611.

Inheritance pattern: Autosomal recessive.

Gene and chromosomal location: *WRN* (8p11.2–p12) encodes a DNA helicase of the RecQ family involved with DNA recombination, replication, and repair. Mutations in other members of the RecQ family are causative of Rothmund–Thomson syndrome and Bloom syndrome, providing a hypothesis for the phenotypic similarities among these disorders.

Mutations: Multiple unique mutations have been identified; nearly all lead to premature protein truncation. One founder mutation accounts for 60% of mutations in Japan.

Incidence: Estimated at one in 50 000 to one in 1 000 000 live births. Higher reported incidence rates from Japanese populations may be due to elevated rates of consanguinity. Goto et al. (1) reported consanguinity in 70% of Japanese Werner syndrome (WS) families compared with a national average of only 5%.

Diagnosis: The International Registry of Werner Syndrome used the definition shown in Table 18 (2). A report from this registry provided clinical data on 99 WS subjects, affected by 50 distinct mutations (3). Bilateral ocular cataracts were the most common feature, reported in 100% of cases with available information. Skin alterations (scleroderma-like skin, tight skin, thin skin, hyperkeratosis, etc), premature graying and/or loss of hair, and short stature were reported in 99%, 96%, and 95% of cases, respectively; 91% of the cases presented all four cardinal signs of WS. Twenty-four of 55 (44%) informative mutation carriers developed cancer; atherosclerosis and cancer were the two major causes of death.

Laboratory features: No diagnostic findings. Cells from patients with WS show premature replicative senescence in culture, abnormalities of telomere maintenance, altered apoptotic responses, excessive sensitivity to genotoxic drugs, and chromosomal variegated translocation mosaicism (4,5). Insulin resistance is also characteristic.

Associated malignant neoplasms: Goto et al. (6) summarized 34 non-Japanese cases of WS (13 from United States) with 30 cancers and 124 Japanese cases with 127 cancers. The cancers were diagnosed between the ages of 25 and 64, except for a 20 year old with osteosarcoma and a 24 year old with acute myelogenous leukemia. Among the 124 Japanese, there were 23 soft-tissue sarcomas, 21 melanomas (which occurred in unusual locations, especially intranasally and on the soles of the feet), nine osteosarcomas, and 14 hematologic malignancies. In addition, there were 63 epithelial cancers recorded, including 21 thyroid cancers (10 follicular, eight papillary, and two anaplastic), six gastric, six breast, three hepatocellular, and four biliary cancers. The risks of these specific malignancies have not been quantified.

Table 18. Diagnostic criteria for Werner syndrome (2)[a]

Cardinal signs or symptoms (onset older than 10 y of age)
• Bilateral cataracts
• Characteristic dermatologic finding (tight, atrophic skin, with pigmentary alterations ulcerations, hyperkeratosis, regional subcutaneous atrophy)
• Characteristic "bird" facies
• Short stature
• Parental consanguinity (third cousin or closer) or affected sibling
• Premature graying and/or thinning of scalp hair
• Positive 24-h urinary hyaluronic acid test, when available
Further signs and symptoms
• Type 2 diabetes mellitus
• Hypogonadism
• Osteoporosis
• Radiographic evidence of osteosclerosis of distal phalanges of fingers and/or toes
• Soft tissue calcification
• Evidence of premature atherosclerosis (eg, myocardial infarction history)
• Neoplasms: mesenchymal (ie, sarcomas); rare or multiple
• Abnormal voice (high-pitched, squeaky, or hoarse)
• Flat feet
Definite diagnosis requires all cardinal signs and two others
Probable diagnosis requires the first three cardinal signs and any two others
Possible diagnosis requires cataracts or dermatologic alteration and any four others
Diagnosis is excluded if onset of signs and symptoms occurred before adolescence (except short stature)

[a]These criteria were developed before the availability of genetic testing.

Associated benign neoplasms: Sixteen of the 124 Japanese cases had meningiomas (multiple in one case), as did seven of the 30 non-Japanese cases (multiple in one case).

Cancer risk management: A detailed summary of the management of this complex, multisystem disorder is beyond the scope of this handbook. It has been suggested that regular clinical surveillance for melanomas (including intranasal examination) and thyroid masses is warranted, beginning in adolescence. A high index of suspicion for neoplasia in general should be maintained, with new signs and symptoms being evaluated carefully (6). The risks and benefits of cancer screening in this syndrome are not established.

Comment: The high frequency of inflammatory conditions (eg, atherosclerosis, type 2 diabetes) and high levels of circulating inflammatory cytokines observed in these patients have led to the hypothesis that some of the Werner phenotype may be due to an inflammatory state superimposed upon the DNA repair disorder traditionally implicated in the manifestations of WS (7,8).

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54. Wilms Tumor, Familial (excludes Beckwith–Weidemann Syndrome and Other Overgrowth Syndromes)

OMIM number: 607102, 194070, 194071, 605982, 601363, 194090, 601583.

Inheritance pattern: Autosomal dominant.

Gene and chromosomal location: Familial Wilms tumor (FWT) is genetically heterogeneous. The *WT1* gene (11p13) is the only gene identified that causes a nonsyndromic FWT. It accounts for only a minority of FWT. *FWT1(WT4)*, *FWT2*, *WT3*, and *WT5*, located on chromosomes 17q12–q21, 19q, 16q, and 7p11.2–p15, respectively, are additional loci for which linkage to FWT has been reported, but specific genes have not yet been cloned. The 11p15 locus (associated with Beckwith–Weidemann syndrome [BWS]) is often referred to as *WT2*, although the gene at this locus has yet to be identified. Lastly, biallelic *BRCA2* mutations were reported in a sibship with FWT and brain tumor, and a particularly severe Fanconi anemia phenotype (1) (see Fanconi Anemia module).

Mutations: While fewer than 5% of apparently sporadic Wilms tumors have germline *WT1* mutations, those that do have earlier age at diagnosis (approximately age 1 vs age 4) and are more likely to be bilateral (38% vs 5%).

Mutations in *WT1* are also associated with several syndromes whose risk of Wilms tumor is estimated as greater than 20% [reviewed by Scott et al. (2)]. The Denys–Drash Syndrome (DDS; triad of Wilms tumor, nephropathy, and genitourinary tract anomalies including possible pseudohermaphrodism in males) is associated with an intragenic *WT1* mutation in 90%. Selected point mutations in the zinc-finger domains of *WT1* that affect the DNA-binding domains have a dominant-negative effect. The mesangial sclerosis of the kidney in DDS may lead to renal failure in early childhood.

WAGR syndrome (Wilms tumor–aniridia–genitourinary–mental retardation) is found in approximately seven to eight per 1000 individuals with WT. Forty percent develop renal failure by age 20. Heterozygous microdeletion of 11p13 (encompassing *WT1* and *PAX6)* results in Wilms tumor–aniridia syndrome, in which the *PAX6* gene deletion explains the aniridia. About 30% of individuals with aniridia have deletions that include *WT1*. Larger deletions of this region account for the full WAGR phenotype.

Frasier syndrome (OMIM #136680) consists of nephropathy, gonadal dysgenesis (including sex reversal in XY individuals), and gonadoblastoma. This is due to a splice site mutation in intron 9 of *WT1*, but does not include an increased risk of WT.

Incidence: Incidence of WT is one in 10 000 general population live births, and WT accounts for more than 90% of childhood renal tumors, with a median age of onset of 3–4 years and declining rapidly thereafter. Ninety-five percent of WT occur as a sporadic event in children with no recognizable syndromic findings. In this group, it is unclear how many are truly sporadic tumors vs the number having new (de novo) mutations or inherited predisposition of a gene of low penetrance. Only 1%–2% of patients with WT have a family history of WT (3). However, 2%–3% occur as part of a multiple congenital anomaly syndrome including WT–aniridia syndrome, WAGR syndrome, DDS, or an overgrowth syndrome such as Beckwith–Wiedemann syndrome, Simpson–Golabi–Behmel syndrome, or Fanconi anemia (2). Aniridia occurs in one in 70 000 persons in the general population, and Wilms tumor occurs in one in 70 children with aniridia.

Diagnosis: Approximately 10%–30% of affected children with WT present with bilateral or multifocal disease, a pattern suggestive of a predisposing genetic lesion. However, the familial aggregation of WT is rare, so the majority of bilateral or multifocal cases appear to represent new mutation dominant disease. Siblings of probands with WT have a twofold increased risk of cancer, all types combined, and a 14-fold increased risk of WT (4). WTs are usually seen in children younger than 5 years, but they are also reported in young adults. Males and females are at equal risk (5).

Laboratory features: Nephrogenic rests are the presumed precursor lesions in the kidneys. Intralobar rests are presumed to result from very early somatic mutation, whereas perilobar rests may represent a later insult. Nephrogenic rests are found in adjacent normal kidney in 40% of unilateral WT and nearly 100% of bilateral WT.

Associated malignant neoplasms: Wilms tumor in the case of *WT1* mutations.

Associated benign neoplasms: Nephrogenic rests.

Cancer risk management: In all individuals with a new diagnosis of WT, evidence for a genetic predisposition should be carefully sought—that is, a family history of Wilms tumor or other embryonal tumor, aniridia, a genitourinary disorder, the presence of multifocal disease, consideration of Beckwith–Wiedemann syndrome, isolated hemihypertrophy, *FA/BRCA2*-like history, or neurofibromatosis type 1. Those with bilateral or multifocal disease or nephrogenic rests should be considered to carry a germline mutation. Children whose tumors are found by ultrasound performed for suspicion of a syndrome usually have earlier stage cancer; therefore, it is felt that systematic surveillance should be undertaken. Recent expert guidelines suggest 1) offering screening to children at greater than 5% risk of WT, 2) implementing screening only after review by a clinical geneticist, 3) performing renal ultrasonography every 3–4 months, 4) continuing screening to age 7, 5) conducting ultrasound examination by an experienced pediatric radiologist, and 6) managing screen-detected lesions at a specialty center (6). The efficacy, risk, and benefits of screening in FWT are unknown.

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55. Xeroderma Pigmentosum (DeSanctis–Cacchione Syndrome; includes Complementation Groups A–G and XP Variant)

OMIM numbers and genes and chromosomal locations: Listed in Table 19. Xeroderma pigmentosum (XP) genes A through G are involved in nucleotide excision repair (NER). In XP variant, the molecular basis is an error-prone DNA polymerase, which continues replication of damaged DNA by bypassing UV-induced thymidine dimers.

Inheritance pattern: Autosomal recessive.

Mutations: A variety of mutations have been reported in each of the cloned genes, usually point mutations. Until recently, mutation analysis was available on a research basis only and then only when preceded by complementation group studies aimed at selecting the specific gene to be tested. Some clinical laboratories now offer *XPA* and *XPC* mutation analysis (see GeneTests).

Incidence: Approximately one in 1 000 000 live births in the United States, one in 40 000 in Japan (higher rates are observed in populations in which consanguinity is more prevalent).

Diagnosis: XP is a clinical diagnosis based on childhood onset of photosensitivity (blistering in 50% and/or freckling in 50%), with progressive degenerative changes leading to xerosis (dryness), poikiloderma (marble-like dyspigmentation), telangiectasiae of the skin and conjunctiva, photophobia, and early development of skin and eye cancers. Approximately half of XP patients are not hypersensitive to acute sunburn; their initial presentation tends to be very early-onset freckling (age <2 years) and multiple early-onset skin cancers (age <10 years). Skin changes in unprotected, sun-exposed areas are evident in 50%, 75%, and 95% of affected individuals by ages 18 months, 4 years, and 15 years, respectively. Ocular abnormalities include UV damage to the eyelids, conjunctivae, and cornea (cataract).

Approximately 30% of XP patients have associated progressive neurological abnormalities, the earliest signs of which include absence of deep tendon reflexes and high-frequency sensorineural hearing loss. In a series of neurologically abnormal patients, the following were reported: cognitive impairment, often progressive (80%); microcephaly (25%); progressive high-frequency sensorineural deafness (20%); hyporeflexia or areflexia (20%) with axonal or mixed neuropathy; spasticity, late-onset ataxia; choreoathetoid movements; and abnormal electroencephalogram (11%). Central nervous system imaging may show enlarged ventricles and cortical thinning. The nonneurological manifestations of XP are similar in those with and without neurological features. Neurological abnormalities are common in all XP complementation groups except groups C, E, F, and XP-variant (1,2). Those with XP-variant have the same skin and/or eye findings but have later disease onset (10–20 years).

Table 19. Xeroderma pigmentosum genes

XP complementation group[a]	Gene	Chromosome	OMIM number
A	*XPA*	9q22.3	278700
B	*ERCC3*	2q21	133510
C	*XPC*	3p25	278720
D	*ERCC2*	19q13.2–q13.3	126340
E	*DDB2*	11p11–p12	600811
F	*ERCC4*	16p13.13–p13.3	133520
G	*ERCC5*	13q33	133530
XP variant	*POLH*	6p12–p21.1	603968

[a]XP = xeroderma pigmentosum; OMIM = online Mendelian inheritance in man. Complementation refers to the capacity of cells from one XP cell line to correct the nucleotide excision repair defects of another cell line to which it is fused. Pairwise combinations are studied to identify novel complementation groups.

Note that some patients with trichothiodystrophy (OMIM 601675—cognitive impairment, sulfur deficient brittle hair, ichthyosis) have mutations in the *XPB* and *XPD* genes. Some patients with XP also have features of Cockayne syndrome (CS; OMIM 216400, 133540, 216411—the "XP/CS complex"—including cachectic dwarfism with microcephaly; premature aged appearance; progressive mental, neurological, and retinal degeneration; and pronounced photosensitivity) and mutations in the *XPB*, *XPD*, and *XPG* genes. These XP/CS complex patients have an increased risk of skin cancer. Cockayne syndrome and trichothiodystrophy are both UV-sensitive disorders that share many of the features of XP at both the phenotypic and molecular level. However, neither is associated with an increased risk of internal cancer, suggesting that there may be more to the carcinogenesis pathway in XP than simply an inability to repair UV-induced DNA damage (3). Finally, some patients with Cerebro–oculo–facial–skeletal syndrome (OMIM 214150) have mutations in the *XPD* and *XPG* genes. Each of these three disorders can also be caused by genes other than the XP-related genes (4).

Laboratory features: Cells from individuals with XP have defective NER and display reduced levels of unscheduled DNA synthesis when exposed to UV light. The synthesis step of NER can be assessed by measuring incorporation of thymidine into nondividing cells. This is reduced in cells with defective NER. These findings may not be evident in XP-variant cells. Heterozygous carriers of XP gene mutations do not have detectable abnormalities by these methods, although they may have reduced amounts of messenger RNA. Chromosomal analyses are generally normal.

Associated malignant neoplasms: There is a 1000-fold increased frequency of early-onset basal cell or squamous cell carcinomas and melanomas of the skin, often with multiple primary tumors, by age 20. The median age at first skin neoplasm diagnosis is 8 years, nearly 50 years younger than that found in the general population. A 5% risk of malignant melanoma is reported. Occasional sarcomas are observed. Ocular melanomas have been reported. The incidence of squamous cell carcinoma of the sun-exposed tip of the tongue is increased 10 000-fold.

A 10- to 20-fold increased risk of internal neoplasms has been reported, including brain tumors, cancers of the lung, uterus, breast, stomach, kidney, testicle, and leukemias. It is uncertain which of these cancers are truly manifestations of the XP syndrome. These cancers could theoretically result from unrepaired DNA damage caused by environmental carcinogens, such as those in tobacco smoke, or from endogenous metabolic oxidative DNA damage.

Associated benign neoplasms: Conjunctival papillomas, actinic keratoses, lid epitheliomas, keratoacanthomas, angiomas, and fibromas.

Cancer risk management: Parents and patients must be educated regarding rigorous methods of protection of all skin and eyes from UV light exposure (including that from artificial light sources) as early in life as the diagnosis is recognized. Compliance can be encouraged by use of UV light meters. Regular examination of the skin and eyes by parents and physicians, with baseline photography and early excision or treatment of premalignant tumors, is required. Cultured cells from XP patients are hypersensitive to mutagens found in cigarette smoke; consequently, patients should avoid exposure to tobacco smoke, both direct and sidestream. Oral isotretinoin may have a role in prevention of skin carcinoma, but it should be administered under the direction of an experienced dermatologist. Risks and benefits of cancer screening in this syndrome for cancers other than those arising in the skin are not established.

Comments: In the past, survival was generally reduced because of the high cancer incidence, with only a 70% probability of surviving to age 40. However, this may be modified by early diagnosis, aggressive photoprotection, and meticulous follow-up, with early diagnosis and aggressive treatment of skin cancers. This strategy has reduced the frequency of skin cancer.

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Notes

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Appendix 1: Clinical Cancer Genetics Resources for the Busy Health-Care Practitioner

General information regarding specific cancers and related topics such as genetic risk, prevention, support, and survivorship is available online. The following list includes links to only a few of the many Web sites and organizations providing information that may be of interest to health-care providers seeking more detailed information or referral sources related to clinical cancer genetic risk assessment and management.

Inclusion of any particular site outside of the National Cancer Institute (NCI) does not imply an endorsement of that site by the NCI, the National Institutes of Health, the Department of Health and Human Services, or the Mayo Clinic. Our intent is simply to bring to the reader's attention information sources at the national level, which, in our personal opinion, are likely to be of assistance.

National Cancer Institute Cancer Genetics Homepage

http://www.cancer.gov/cancertopics/prevention-genetics-causes/genetics. NCI's main information "gateway" to cancer genetics resources. At this site, one will find links to:

Glossaries of Genetic Terms: Definitions of commonly used terms and concepts used in genetic research and clinical care.

- NCI PDQ (Physicians Data Query) Cancer Genetics Web site glossary: http://www.cancer.gov/cancertopics/genetics-terms-alphalist.
- NHGRI (National Human Genome Research Institute) Web site glossary: http://www.genome.gov/glossary.cfm. A Spanish version of this Web site is available: http://genome.gov/sglossary.cfm.

Directory of Cancer Genetics Professionals: http://www.cancer.gov/search/geneticsservices/. List of professionals who provide services related to cancer genetics (cancer risk assessment, genetic counseling, genetic susceptibility testing).

NCI's PDQ Cancer Genetics Information Summaries: http://www.cancer.gov/cancertopics/pdq/genetics/. Contains modules related to general cancer genetics overview, principles of risk assessment and counseling, and selected syndrome-specific disorders.

Links to Official Policy Statements Regarding Cancer Genetic Issues: Including the American Society of Clinical Oncology and the American Society of Human Genetics policy statements on genetic testing for cancer susceptibility.

National Center for Biotechnology Information

Online Mendelian Inheritance in Man (OMIM): http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=OMIM. This is a catalog of human genes and genetic disorders created by Dr Victor A. McKusick and his colleagues at Johns Hopkins and elsewhere, which contains textual information and references, including direct links to cited articles in MEDLINE.

Genes and Disease: http://www.ncbi.nlm.nih.gov/books/bv.fcgi?call=bv.View..ShowSection&rid=gnd.preface.91. A collection of articles that discuss genes and the diseases that they cause. Organized by the parts of the body that they affect. For each disorder, the underlying mutations are discussed, along with clinical features and links to key Web sites.

National Library of Medicine Genetics Home Reference: http://ghr.nlm.nih.gov/. The National Library of Medicine's Web site for consumer information about genetic conditions and the genes or chromosomes responsible for those conditions.

Miscellaneous Resources

GeneTests (University of Washington): http://www.genetests.org/. A publicly funded medical genetics information resource developed for health-care providers. Includes expert-authored syndrome reviews, directories of genetic testing laboratories, and genetic diagnostic clinics, as well as an illustrated glossary.

National Human Genome Research Institute: http://www.genome.gov/PolicyEthics/LegDatabase/pubMapSearch.cfm. This site provides information on legislation for all states, related to genetic privacy, discrimination for insurance, and so on.

National Society of Genetic Counselors: http://www.nsgc.org/resourcelink.cfm. To assist in locating genetic counseling services. Can be searched by zip code, distance, counselor's name, institution, or areas of practice or specialization.

CDC (Centers for Disease Control) Office of Genomics and Disease Prevention: http://www.cdc.gov/genomics/. This site provides information about human genomic discoveries and how they can be used to improve health and prevent disease in populations. Includes information regarding CDC's Family History Initiative and their Genomics in Practice resource.