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# SPECIAL ARTICLE

## The Concise Handbook of Family Cancer Syndromes

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See "Note" at the end of the article.

## INTRODUCTION

Some details are inevitably lost when attempting to simplify subjects involving complex medical genetics subjects. However, unless an attempt is made to distill such topics, busy clinicians who may only occasionally need access to these subjects may perceive the information to be inaccessible. With these considerations in mind, we have attempted to develop a clinically usable catalog of recognizable family cancer syndromes. Thirty-five different syndromes are included (shown in Tables 1–3). Thereafter, the subjects are listed in alphabetical order. For each disorder, the following template was used:

**OMIM number** (in the genetic database known as On-Line Mendelian Inheritance in Man, which can be accessed via the internet for collated up-to-date genetic information, at [www3.ncbi.nlm.nih.gov/Omim/searchomim.html](http://www3.ncbi.nlm.nih.gov/Omim/searchomim.html))

### **Inheritance pattern**

### **Gene and chromosomal location**

### **Mutations**

### **Incidence**

### **Diagnosis**

### **Laboratory features**

### **Associated malignant neoplasms**

### **Associated benign neoplasms**

### **Surveillance strategies**

### **Comment(s) (optional)**

### **References (selected)**

The surveillance strategies are offered with full acknowledgment that the efficacy of these strategies are, in all instances, unproved by controlled clinical trials. Only for hereditary non-polyposis colon cancer (HNPCC) and for BRCA1- and BRCA2-related hereditary breast cancer syndromes have consensus statements been published. Review of these statements reveals that, even for these three relatively common and well-studied disorders, the quality of evidence supporting the published screening

**Table 1.** Familial cancer syndromes: autosomal dominant disorders

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Adenomatous polyposis, familial (includes Gardner's syndrome)
Basal cell nevus syndrome (Gorlin's syndrome)
Breast/ovarian cancer: BRCA1
Breast/other cancer: BRCA2
Carney syndrome
Chordoma, familial
Colon cancer syndrome, hereditary nonpolyposis colon cancer (or Lynch syndrome—includes Muir-Torre syndrome)
Cowden syndrome
Esophageal cancer with tylosis
Gastric cancer, familial
Li-Fraumeni syndrome
Melanoma, familial, with or without dysplastic nevi
Multiple endocrine neoplasia type 1
Multiple endocrine neoplasia type 2
Neurofibromatosis type 1
Neurofibromatosis type 2
Osteochondromatosis, multiple (multiple exostoses)
Paraganglioma familial
Peutz-Jeghers syndrome
Prostate cancer
Renal cancer, familial (papillary and nonpapillary [clear cell adenocarcinoma])
Retinoblastoma
Tuberous sclerosis
von Hippel-Lindau disease
Wilms' tumor

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**Table 2.** Familial cancer syndromes: autosomal recessive disorders

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Ataxia-telangiectasia
Bloom syndrome
Fanconi's anemia
Rothmund-Thomson syndrome
Werner's syndrome
Xeroderma pigmentosum

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**Table 3.** Familial cancer syndromes: disorders of uncertain mode(s) of inheritance

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Carcinoid, familial
Hodgkin's disease, familial
Pancreatic cancer, familial
Testicular carcinoma, familial

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guidelines is still only that of expert opinion, with the one exception being some observational series of the efficacy of colonoscopy in HNPCC. For the less common disorders, even greater uncertainty exists regarding the efficacy of screening procedures. Uncertainty even exists as to which malignant neoplasms are truly associated with specific disorders. It is not the intent of this document to define these syndromes or to establish a standard of care. Clinicians and their patients need to be aware that screening methods and interventions in these disorders are still unproved. Nevertheless, it is our contention that cancer prevention efforts are warranted in individuals who are thought to have a predisposition to site-specific cancers, i.e., when early detection of those cancers may prevent morbidity and mortality.

This handbook is not intended to be an endorsement of genetic testing for familial cancer-predisposing disorders. The role of clinical genetic testing for cancer-predisposing disorders is a rapidly evolving area, and the appropriateness of such testing varies as a function of which disorder is thought to be present and the manner in which a genetic test result would influence clinical management. In general, if a test result would not change clinical management, testing may not be reasonable. If testing could conceivably alter clinical management, then comprehensive pretest genetic counseling is warranted prior to proceeding with formal predictive genetic testing. This counseling needs to include education about the scientific aspects of genetic testing, addressing (but not limited to) test sensitivity, test specificity, the possibilities of indeterminate test results, discussions of what action the patient may take given a positive or negative test result, and the cost of testing. Counseling also needs to address the psychologic aspects of testing, which can be powerful; consultation with a mental health care professional may be useful to explore these issues and to identify support systems and follow-up plans. Lastly, counseling needs to explain institutional policies regarding the confidentiality of test results, i.e., who would have access to those results (other health care providers, family members, and third party payers) and under what circumstances and with what possible ramifications. To assist clinicians in identifying an individual or a center near their practice where this type of pretest evaluation and counseling can be provided,

**Table 4.** Rare familial syndromes: cancer sites reported in association with specific familial cancer-predisposing disorders\*

Cancer or tumor site	Adenomatous polyposis	Ataxia-telangiectasia	Basal cell nevus	Bloom syndrome	Breast/ovarian	Breast/other	Carcinoid	Carney syndrome	Chordoma	Colon (HNPCC)	Cowden syndrome	Esophagus, with tylosis	Fanconi's anemia	Gastric	Hodgkin's disease	Li-Fraumeni syndrome	Melanoma	MEN1	MEN2	NF1	NF2	Osteochondromatosis	Pancreatic	Paraganglioma	Peutz-Jeghers syndrome	Prostate	Renal cancer	Retinoblastoma	Rothmund-Thomson syndrome	Testicular	Tuberous sclerosis	VHL	Werner's syndrome	Wilms' tumor	XP		
Acoustic neuroma																				Y	Y																
Adrenal cortical							Y								Y		Y																		Y		
APUDoma																	Y																	Y			
Basal cell, skin	Y	Y	Y																															Y	Y		
Biliary										Y																											
Bladder, urinary										Y																											
Breast, female	Y		Y	Y	Y						Y				Y									Y										Y	Y		
Breast, male						Y																															
Carcinoid							Y										Y		Y															Y			
Cervix			Y										Y											Y													
Chondrosarcoma																						Y					Y										
Chordoma									Y																												
Colon/rectum	Y			Y	Y	Y				Y														Y													
Endolymphatic sac tumor																																			Y		
Endometrium	Y									Y																											
Esophagus				Y								Y	Y																								
Fibrosarcoma			Y																									Y									
Hepatoblastoma	Y																																			Y	
Hepatocellular										Y			Y																						Y		
Hodgkin's disease															Y																						
Gastric	Y	Y								Y				Y											Y									Y	Y		
Germ cell															Y															Y					Y		
Glioma		Y								Y		Y	Y	Y	Y				Y	Y											Y				Y		
Larynx				Y											Y																						
Leukemias	Y		Y										Y		Y												Y							Y	Y		
Lung				Y											Y																					Y	
Lymphoma, NH		Y		Y											Y													Y									
Medulloblastoma	Y	Y	Y										Y																								
Melanoma																	Y											Y						Y	Y		
Meningioma																				Y	Y																
Neuroblastoma																				Y																Y	
Osteosarcoma															Y							Y						Y	Y					Y			
Ovarian			Y		Y	Y				Y					Y										Y												
Pancreas (ACA)	Y					Y				Y					Y	Y							Y	Y										Y			
Pancreas (islet cell)																	Y																		Y		

**Table 4 (continued).** Rare familial syndromes: cancer sites reported in association with specific familial cancer-predisposing disorders\*

Cancer or tumor site	Adenomatous polyposis	Ataxia-telangiectasia	Basal cell nevus	Bloom syndrome	Breast/ovarian	Breast/other	Carcinoid	Carney syndrome	Chordoma	Colon (HNPCC)	Cowden syndrome	Esophagus, with tylosis	Fanconi's anemia	Gastric	Hodgkin's disease	Li-Fraumeni syndrome	Melanoma	MEN1	MEN2	NF1	NF2	Osteochondromatosis	Pancreatic	Paraganglioma	Peutz-Jeghers syndrome	Prostate	Renal cancer	Retinoblastoma	Rothmund-Thomson syndrome	Testicular	Tuberous sclerosis	VHL	Werner's syndrome	Wilms' tumor	XP	
Paraganglioma																		Y	Y			Y								Y	Y					
Parathyroid																		Y	Y																	
Pheochromocytoma																		Y	Y	Y			Y									Y				
Pinealoblastoma																										Y										
Pituitary								Y										Y																		
Prostate					Y	Y										Y									Y											
Renal, clear cell										Y																Y					Y	Y				
Renal, papillary																										Y										
Renal, transitional										Y																										
Retinoblastoma																										Y										
Rhabdomyosarcoma															Y				Y														Y	Y		
Schwannoma							Y										Y		Y	Y																
Sebaceous gland									Y																											
Small bowel	Y									Y														Y												
Soft-tissue sarcoma															Y												Y							Y		
Squamous cell (skin)				Y								Y																Y					Y	Y		
Testicle							Y								Y									Y				Y								
Thyroid	Y						Y			Y																					Y	Y				
Thyroid, medullary																			Y																	
Tongue				Y								Y																								Y
Ureter									Y																											
Wilms' tumor																				Y															Y	

\*Most associations *have not* been subjected to rigorous statistical analysis. It is likely that additional tumor associations will be identified by further studies of these disorders, and conversely, some of the earlier reported associations will be disproved. This table is intended to assist clinicians in considering whether or not the presenting constellations of cancer types have been previously reported in the context of one or more familial cancer disorders. Abbreviations used are defined as follows: Y = yes; APUDoma = a tumor composed of APUD cells (amine precursor uptake and decarboxylation); NH = non-Hodgkin's; ACA = adenocarcinoma; HNPCC = hereditary nonpolyposis colon cancer; MEN = multiple endocrine neoplasia; NF = neurofibromatosis; VHL = von Hippel-Lindau disease; XP = xeroderma pigmentosum.

there is a voluntary listing of interested providers available through the National Cancer Institute Familial Cancer Risk Counseling and Genetic Testing Information Search Database, at <http://cancernet.nci.nih.gov/wwwprot/genetic/genesrch.html>

We have attempted to develop a concise table of disorders that are thought to be associated with particular tumors (*see* Table 4). This table provides a tool by which clinicians can rapidly consider whether the patient's presentation and family history might be suggestive of a familial disorder.

A glossary of terms that may not be familiar to clinicians is located at the end of the handbook. We have found this hand-

book to be useful in recognizing familial cancer syndromes in our daily practice and hope that others will also.

### Clinical Clues to Presence of Inherited Predisposition to Cancer

- A cancer occurring at an unusually young age compared with the usual presentation of that type of cancer
- Multifocal development of cancer in a single organ or bilateral development of cancer in paired organs
- Development of more than one primary tumor of any type in a single individual

- Family history of cancer of the same type in close relative(s)
- High rate of cancer within a family
- Occurrence of cancer in an individual or a family exhibiting congenital anomalies or birth defects

## DISORDERS

### 1. Adenomatous Polyposis, Familial (FAP) (Includes Gardner's Syndrome, Familial Multicentric Fibromatosis, and Hereditary Desmoid Disease)

**OMIM numbers:** 175100; 135290.

**Inheritance pattern:** Autosomal dominant.

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

**Mutations:** Protein truncation mutations comprise 70%–80% of mutations. Truncating mutations in the extreme 5' end of the gene may cause attenuated FAP; those in the extreme 3' end may cause familial desmoid disease only. One specific missense mutation (isoleucine-1307 to lysine) has been reported in 6% of Ashkenazi Jews and about 28% of Ashkenazim with a family history of colorectal cancer. This mutation has reduced disease penetrance, with a two-fold increased risk for colorectal cancer, and carriers do not manifest the polyposis coli phenotype that is characteristic of FAP.

**Incidence:** One in 6000 to one in 13000. The frequency of gene mutations in the general population is unknown.

**Diagnosis:** Based on characteristic polyposis (usually the presence of more than 100 colorectal polyps). One fourth to one third of cases represent new mutation dominant disease. Genetic testing is also available.

**Laboratory features:** Linkage-based predictive testing and mutational analysis (based on protein truncation assay) are available on a clinical service basis.

**Associated malignant neoplasms:** Colon adenocarcinoma, with risk of cancer in classical FAP approaching 100% by age 40 years unless the colon is removed; duodenal carcinomas, especially around the ampulla of Vater, occurring on the average 20 years later than the colon cancers; follicular or papillary thyroid cancer; childhood hepatoblastomas (approximately 1-in-250 risk to offspring of gene carriers); gastric carcinomas; and central nervous system tumors in some families, 79% of which were identified as medulloblastomas (Hamilton et al., 1995). The combination of multiple adenomatous colon polyps and a brain tumor has been called Turcot's syndrome. Turcot's syndrome can be seen in both FAP (medulloblastoma) and hereditary non-polyposis colon cancer (glioblastoma).

**Associated benign neoplasms:** Adenomatous polyps of the colon that appear before the age of 10 years in fewer than 10% of gene carriers but in more than 90% of gene carriers by the age of 20 years, also duodenal polyps (especially periampullary), sebaceous or epidermoid cysts, lipomas, congenital hypertrophy of the retinal pigment epithelium, osteomas (especially of mandible), supernumerary teeth, gastric polyps, and juvenile nasopharyngeal angiofibromas.

Desmoid tumors are reported in 30% of FAP kindreds, with overall lifetime risk of 8% for males with FAP and 15% for females; the risk of desmoid tumors is 25% if a first-degree relative with FAP has desmoid tumors and 8% if a third-degree relative has desmoid tumors.

**Surveillance strategies:** No randomized, controlled trials of screening efficacy or consensus statements exist for FAP. Mor-

ton et al. (1993) reported existing screening practices on 47 families in which 37 individuals had developed colon cancer before a diagnosis of FAP was established. Three of the individuals who developed colon cancer were among 51 family members who were having regular colon cancer screening. The remaining 34 individuals who developed colon cancer were among 53 family members who were unscreened (cancer proportions = 6% [three of 51] and 64% [34 of 53], respectively), suggesting great value in colon screening.

Genetics consultation is suggested to explore the utility of genetic testing in families with FAP and to determine which other relatives are at risk. Some families will be able to use linkage testing, and some may use direct testing. For those diagnosed by genetic testing or clinical examination, the initiation of discussions about colectomy should be undertaken as soon as the diagnosis is established. For those diagnosed by genetic testing, annual flexible sigmoidoscopy is indicated beginning at the age of 10–12 years, with discussion of colectomy once gene expression manifests itself as colon polyps.

A baseline screening with gastrointestinal tract upper endoscopy for gastric, duodenal, and ampullary polyps has been suggested at the time of diagnosis with repeat screening to be performed every 2–3 years unless upper intestinal tract symptoms occur. When the duration of polyposis disease reaches 15–20 years, or the patient reaches age 50, annual upper tract endoscopy has been advised (Marcello et al., 1996), although this remains controversial. When benign polyps are identified in the duodenum or the ampulla, these polyps may be removed and yearly follow-up examinations should be performed to look for dysplastic changes (although some would say that, if only small polyps or low-grade dysplasia is found, then observation is indicated). Dysplasia in a normal-appearing ampulla has not been reported, and biopsy examination of this area, therefore, is not advised if the ampulla appears normal. Polyps of the stomach, which are usually hyperplastic but can be antral adenomas, have been associated with a higher risk of gastric carcinoma in only selected populations (e.g., Korean [Park et al., 1992]); therefore, Marcello et al. (1996) do not advise altering screening intervals based on their presence.

Careful annual palpation for thyroid masses is advisable for gene carriers.

For those at risk of having FAP, flexible sigmoidoscopy beginning at the age of 10–12 years is suggested, to be repeated every 1–2 years until age 35, if negative. If polyps are found, consultation should be arranged to discuss the timing of colectomy and other investigations. Annual thyroid palpation is warranted. Ophthalmologic examination for congenital hypertrophy of the retinal pigment epithelium may help establish diagnosis (dilated pupils are needed to visualize these harmless congenital lesions in 80% of cases; in individuals with true FAP, 88% had four or more lesions, compared with control subjects who showed zero to two lesions in 92 of 94 cases).

For children at risk for FAP, serum  $\alpha$ -fetoprotein testing and abdominal palpation for hepatoblastoma every 6 months until the age of 6 years have been advised (Hughes and Michels, 1992).  $\alpha$ -Fetoprotein levels are elevated in two thirds of hepatoblastomas. The risk of hepatoblastoma in children of parents with FAP has been estimated at one in 305 person-years (Giardiello et al., 1991).

**Comments:** Attenuated cases of FAP can be very difficult to distinguish from hereditary nonpolyposis colon cancer, which is often associated with increased numbers of adenomatous polyps (despite its name). Some cases of attenuated FAP even manifest a right-sided predominance of polyps. Recent progress in the analysis of tumor microsatellite instability may help clinicians more accurately distinguish between FAP and hereditary nonpolyposis colon cancer, because tumors from FAP are negative for microsatellite instability. In addition, in individuals with more than one desmoid tumor or in families with desmoid tumors, evidence of FAP should be aggressively sought.

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## 2. Ataxia-Telangiectasia (AT) (Includes AT Complementation Groups A, C, D, E, and V1/V2 and Louis-Barr Syndrome)

**OMIM numbers:** 208900; 251260.

**Inheritance pattern:** Autosomal recessive.

**Gene and chromosomal location:** ATM gene at 11q22.3. Complementation groups A, C, D, and E show the following distribution worldwide: A = 55%, C = 28%, D = 14%, and E = 3%. The mutations in these complementation groups all map to a single gene. The V1/V2 variants (Nijmegen breakage syndrome and Berlin breakage syndrome) are both linked to 8q21, establishing that they are not allelic with AT.

**Mutations:** Homozygous germline mutations in a gene called NBS1 were recently reported in 12 of 14 patients with Nijmegen syndrome (Matsuura et al., 1998). Various ATM mutations have been reported, with more than 85% resulting in a truncated protein. Mutational analysis is not yet available on a clinical service basis, but it is being performed in research laboratories.

**Incidence:** One in 30 000 to one in 100 000. The frequency of gene mutations in the general population is around 1%.

**Diagnosis:** Cerebellar ataxia (present in 100% of cases) becomes evident around the time a child learns to walk. Initially this ataxia is truncal, but it evolves gradually to include ataxia of gait, intention tremor, choreoathetosis/dystonia (in 90% of cases), slurred speech, apraxia of eye movements, nystagmus, and strabismus. Most affected individuals are wheelchair bound by the age of 10 years, and they develop a progressive spinal muscular atrophy in their 20s and 30s. Dementia is not a feature of most AT patients, although severe impairment of short-term memory has been noted in adults. The neurologic features of AT dominate the clinical picture.

Telangiectasia generally begins in sun-exposed areas and conjunctiva and occurs later than the onset of ataxia symptoms (after age 7 years typically). 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 and hypogonadism.

A variable degree of immunodeficiency, with decreased levels of immunoglobulins IgG2, IgA, and IgE, is reported in most patients, which may account for the frequent sinopulmonary infections (reported in 50%-70% of cases). No one immunodeficiency is present in all AT patients; the most consistent immunodeficiencies are IgA deficiency, which is detected in 75% of cases, and IgE deficiency, which is detected in 85% of cases. Cellular immunodeficiency is also common. Patients with group V1/V2 variants have microcephaly, sometimes with mental retardation, and normal  $\alpha$ -fetoprotein levels.

Most people with AT live into their 30s. Cancer and infection account for 90% of all deaths.

**Laboratory features:**  $\alpha$ -Fetoprotein levels are elevated in about two thirds of cases. Characteristic cytogenetic features are acquired aberrations involving 10% of mitoses, commonly (about 80%) with chromosome breakpoints at sites for T-cell and B-cell receptors (7p14, 7q35, 14q11, 14q32, 2p11, and 22q11). Radioresistant DNA synthesis is the gold-standard test for this disorder and is available now in a few laboratories on a clinical basis.

**Associated malignant neoplasms:** One third of all AT patients will develop cancer during their lives and 15% will die of their cancer, although milder atypical forms of AT have been described (oldest reported patients with AT as of 1985 were 52 and 49 years old [Scriver et al., 1995]). Eighty percent of the associated malignant neoplasms involve lymphoreticular tissue, especially non-Hodgkin's lymphoma (usually B-cell), a feature

shared by other disorders exhibiting immunodeficiency, and leukemias (usually 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 and gliomas have been reported, and precocious onset of basal cell carcinomas and uterine cancers has also been noted.

Individuals who are heterozygous for ATM mutations were reported to have a 6.8-fold increased risk of breast cancer compared with control subjects (Swift et al., 1987). Epidemiologic studies have estimated that carriers of ATM mutations may account for 9% of all breast cancers in the United States. Other studies have disagreed with this conclusion, such as the one reported by FitzGerald et al. (1997), in which only 0.5% of 401 women with breast cancer diagnosed under the age of 40 years were heterozygous for ATM mutations, compared with 1% of the control subjects. These findings have been difficult to reconcile with earlier studies (Swift et al., 1987) that have reported that, overall, men and women who are heterozygous for ATM mutations have relative risks of developing cancer of 2.3 and 3.1, with excess risks of cancer mortality of 3.0 and 2.6, respectively.

**Associated benign neoplasms:** None reported.

**Surveillance strategies:** We suggest aggressive prevention of infection (beyond the scope of this summary). For heterozygous women, we suggest breast cancer screening beginning around age 30, with monthly breast self-examination, twice yearly clinical breast examinations, and annual mammograms. A similar plan may be reasonable for women affected with AT. We also suggest regular and thorough review of symptoms of hematologic cancers and suggest periodic blood cell counts and consideration of stomach imaging if upper gastrointestinal symptoms are reported. Aggressive evaluation of new symptoms that could indicate any cancer is warranted. The risks and benefits of cancer screening in AT have not been established.

**Comments:** AT patients are unusually sensitive to ionizing radiation, and treatment of cancer with conventional doses of radiation can be fatal.

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## 3. Basal Cell Nevus Syndrome (Gorlin's Syndrome)

**OMIM number:** 109400.

**Inheritance pattern:** Autosomal dominant.

**Gene and chromosomal location:** PTC gene on 9q22.3, a homologue of the *Drosophila* patched gene. (Self-healing squamous epithelioma and xeroderma pigmentosum group A map to the same region.)

**Mutations:** High new mutation rate (i.e., a gene mutation occurred at that person's conception but was not carried by either parent) in a clinical series (37 of 64 individuals [Shanley et al., 1994]). Germline mutations in patients include insertions, deletions, and point mutations leading to premature stops or frameshifts. Genetic testing by direct analysis and linkage analysis is available on a limited basis.

**Incidence:** One in 55 600 in the U.K. Frequency of gene mutations in the general population is unknown.

**Diagnosis:** One group (Evans et al., 1993) has used the following criteria, the specificity and sensitivity of which are unknown:

Diagnosis made when two major or one major and two minor criteria are fulfilled:

### Major criteria

- 1) Multiple (more than two) basal cell carcinomas, one basal cell carcinoma before 30 years of age, or more than 10 basal cell nevi
- 2) Any odontogenic keratocyst (proven on histology) or polyostotic bone cyst
- 3) Palmar or plantar pits (three or more)
- 4) Ectopic calcification, lamellar or early (<20 years of age) falx calcification
- 5) Family history of basal cell nevus syndrome

### Minor criteria

- 1) Congenital skeletal anomaly: bifid, fused, splayed, or missing rib or bifid, wedged, or fused vertebra
- 2) Head circumference >97th percentile, with frontal bossing
- 3) Cardiac or ovarian fibroma
- 4) Medulloblastoma
- 5) Lymphomesenteric cysts
- 6) Congenital malformation: cleft lip and/or palate, polydactyly, or eye anomaly (cataract, coloboma, or microphthalmia)

**Laboratory features:** The PTC gene encodes a transmembrane protein that in *Drosophila* acts in opposition to the Hedgehog signaling protein, controlling cell fates, patterning, and growth in numerous tissues. Data suggest that basal cell nevus syndrome conforms to the Knudson two-hit hypothesis model (Levanat et al., 1996) for carcinogenesis, and this model may also cause the developmental anomalies.

**Associated malignant neoplasms:** Multiple basal cell cancers (reported in 90% of affected individuals by age 40 years [Evans et al., 1993] and in 75% of affected individuals in an

Australian study by age 20 years [Shanley et al., 1994]), a medulloblastoma reported in 5% of affected individuals, ovarian carcinomas, and fibrosarcomas.

**Associated benign neoplasms:** Jaw cysts in 90% of affected individuals by age 40 years; congenital pits on the palms and soles (also seen in Cowden syndrome); cutaneous keratocysts and milia; ovarian fibromas, with or without calcification (in 24% of affected women); cardiac fibromas; lymphomesenteric cysts; and hamartomatous polyps of the stomach.

**Surveillance strategies:** Basal cell carcinomas seldom occur before puberty. Annual screening by an experienced dermatologist is suggested, beginning with puberty and more frequently as needed. Conservative early excision of basal cell tumors is recommended. Use of sunscreen is advised. Careful gynecologic examination should be conducted annually in adulthood. Clinicians should be aware of the possibility of medulloblastoma in affected children. The risks and benefits of cancer screening in patients with basal cell nevus syndrome have not been established.

**Comments:** Characteristic features of affected individuals include tall stature, large head with frontal bossing, ocular hypertelorism, broad nasal root, enlarged jaw, long fingers with short fourth metacarpals, cleft lip and/or palate (in 5% of cases), ophthalmologic abnormalities including strabismus or cataract (in 26% of cases), skeletal malformation of the spine and ribs, hydrocephalus, sellar bridging, mental subnormality (in 1%–10% of cases), and dominant inheritance with 97% penetrance.

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## 4. Bloom Syndrome

**OMIM number:** 210900.

**Inheritance pattern:** Autosomal recessive.

**Gene and chromosomal location:** BLM gene at 15q26.1, a putative DNA helicase.

**Mutations:** Multiple mutations responsible, with some founder mutations in Ashkenazi Jews.

**Incidence:** Unknown.

**Diagnosis:** Growth deficiency (prenatal and postnatal) with normal body proportions, sun-sensitive facial erythema/

**Table 5.** Cancer statistics from the Bloom Syndrome Registry, as of January 1, 1996 (reviewed by Ellis and German, 1996)

	No.	Age, y	
		Mean	Range
Persons under surveillance	168		
Alive	107	20.7	1–45
Dead	61	24.4	1–48
From cancer	50	26.4	4–48
From other causes	11	14.4	<1–48
Person who developed cancer(s)	71	21.3	2–46
Cancers diagnosed	100	24.5	2–48
Persons with >1 primary tumor	19		
Persons with >2 primary tumors	5		
Persons with >3 primary tumors	3		
Persons with >4 primary tumors	2		

telangiectasia (butterfly rash) with malar hypoplasia, nasal prominence, small mandible, and dolichocephalic skull. The specific diagnostic instability is increased frequency of sister chromatid exchange; demonstration of this feature requires special analytic techniques and will not be detected by routine chromosomal analysis.

**Laboratory features:** Strikingly elevated (10-fold above normal) sister chromatid exchange rates in all cell types examined and other somatic hyperrecombination mutations that give rise to chromosomal quadraradials and excess breakage are found, all of which may lead to loss of heterozygosity as a result of homologous recombination and duplications and deletions from unequal sister chromatid exchanges between repetitive elements or syntenic members of gene families.

**Associated malignant neoplasms:** Increased frequency at all ages, with acute leukemia and lymphoid neoplasms predominating before the age of 25 years; after the age of 20 years, carcinomas of the tongue, larynx, lung, esophagus, colon, skin, breast, and cervix are most notable, with the age of diagnosis often 20 or more years younger than that generally expected for each tumor type (Table 5).

**Associated benign neoplasms:** None known.

**Surveillance strategies:** Increased cancer surveillance after the age of 20 years is suggested to identify the precocious development of cancers that generally affect older age groups. The risks and benefits of cancer screening in Bloom syndrome have not been established.

**Comments:** Susceptibility to infection with subsequent bronchitis and bronchiectasis, frequent occurrence of diabetes, diarrhea and vomiting common in infants, café-au-lait with or without hypopigmented macules, high-pitched voice, and azoospermia. Learning disabilities are frequent but overall intellect is usually normal. Most common in Ashkenazi Jews whose ancestors were from the Ukraine or Poland.

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## 5. Breast/Ovarian Cancer, Hereditary (BRCA1)

**OMIM number:** 113705.

**Inheritance pattern:** Autosomal dominant.

**Gene and chromosomal location:** BRCA1 gene on chromosome 17q21, a tumor suppressor gene of unknown function.

**Mutations:** Several hundred distinct deletions, insertions, and point mutations in this very large gene have been identified in a heterogeneous population. It has been estimated that current gene mutation analyses have a sensitivity of approximately 80%. No clinically usable genotype–phenotype correlations have been established. Note that, in the Ashkenazi Jewish population, 1% carry the 185delAG mutation; in this population, this single mutation accounts for 21% of breast cancers diagnosed at or before the age of 40 years.

**Incidence:** Varies widely between populations; overall, BRCA1 and BRCA2 account for 6%–10% of all breast and ovarian cancers in patients unselected for family history, suggesting an overall carrier frequency of one of these two genes in one in 100 to one in 2500 across different populations. Szabo and King (1997) have summarized U.S. and international studies that showed that, in the United States, 39% of families with three or more cases of female breast and/or ovarian cancer had identifiable BRCA1 mutations. (The range was from 9% in Iceland to 79% in Russia.) Sixty-four percent of families with three or more cases of female breast and/or ovarian cancer had either BRCA1 or BRCA2 mutations. The cause of cancer in the remaining third of families is unknown. Eight percent of families in the United States with male and female breast cancer had BRCA1 mutations.

**Diagnosis:** Suspected on the basis of a family tree showing possible dominant inheritance of a predisposition to breast and/or ovarian cancer diagnosed at a younger age (often premenopausal) than sporadic cancers of the same type or suspected because of the presence of bilateral disease. A family tree is, however, not diagnostic (with the possible exception of those families with autosomal dominant, site-specific ovarian cancers, which, so far, have all been accounted for by BRCA1). DNA mutation analysis is offered on a clinical basis and can be used to supplement the clinical impression. Couch et al. (1997) and Shattuck-Eidens et al. (1997) have published useful models that provide estimates of the prior probability of detecting a BRCA1 mutation in families as a function of the average age at breast cancer diagnosis, bilaterality, the presence of ovarian cancer, and Ashkenazi Jewish heritage. These models may assist in deciding whether a family warrants predictive genetic testing or not.

**Laboratory features:** Adenocarcinoma of the breast and ovarian cancers of epithelial origin. There are no histologic findings specific to BRCA1-related cancer.

**Associated malignant neoplasms:** The cumulative risk of breast cancer is around 3% by age 30 years, 19% by age 40, 51% by age 50, 54% by age 60, and 85% by age 70. A 64% risk of contralateral breast cancer by age 70 is estimated. The risk for ovarian cancer of epithelial origin appears to vary between families, with most families manifesting a cumulative risk of 26% by age 70 but with an important subset exhibiting a risk of up to 85% by age 70 (summarized by Burke et al. [1997] and Greene et al. [1997]). There is concern that these risks, derived as they

are from rather extraordinary multiple case families, may be overestimated when applied to less striking families. Struwing et al. (1997) have estimated that the risks of breast and ovarian cancers by age 70 may be as “low” as 56% and 16%, respectively. A similar cautionary note regarding the precise magnitude of the cancer risks was sounded by Whittemore et al. (1997). After studying 374 women, Stratton et al. (1997) reported that mutations in BRCA1 occur in about 5% of all women in whom ovarian cancer is diagnosed before the age of 70 years.

The relative risk for colon cancer in BRCA1 gene carriers is 4.1, or 6%, by age 70, compared with a risk of 1%–2% in the general population. The risk for prostate cancer is 3.3, or 8%, by age 70 (Ford et al., 1994). These two cancers do not display the earlier than usual age at onset seen for the breast and ovarian cancers in these families. Additional work is under way to define other associated tumors.

**Associated benign neoplasms:** None known.

**Surveillance strategies:** Burke et al. (1997) reviewed the quality of evidence for the efficacy of screening recommendations in carriers of BRCA1 and BRCA2 mutations and suggested the following categories: E-1 was highest quality evidence (randomized control trials); E-2 was intermediate quality evidence (nonrandomized trials and observational studies); E-3 was lowest quality (expert opinion and case reports only). Consensus recommendations for breast cancer screening included breast self-examination monthly beginning by age 18–21 years (E-3), clinical breast examination annually or semiannually beginning by age 25–35 years (E-3), and mammography beginning by age 25–35 years (E-3).

Also recommended was annual or semiannual ovarian cancer screening with the use of transvaginal ultrasound and the measurement of serum CA-125 level beginning at age 25–35 years, with ultrasound examinations timed to avoid ovulation, to reduce false-positive results (E-3). Note that fewer than half of early stage ovarian tumors produce elevated serum levels of CA-125.

For prostate cancer surveillance in BRCA1 carriers only, rectal examination and serum prostate-specific antigen level testing should be offered annually, after the individual is informed about the uncertainty of benefit from early detection (E-3).

For colon cancer surveillance, fecal occult blood testing annually and flexible sigmoidoscopy every 3–5 years are recommended, beginning at age 50 (E-3, from population-based data of uncertain relevance).

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## 6. Breast/Other Cancer, Hereditary (BRCA2)

**OMIM number:** 600185.

**Inheritance pattern:** Autosomal dominant.

**Gene and chromosomal location:** BRCA2 on chromosome 13q12-q13, a tumor suppressor gene whose precise intracellular function is unclear, encoding a protein of 3418 amino acids.

**Mutations:** Numerous mutations, including deletions, insertions, and point mutations, have been reported, most of which lead to premature protein chain termination. A founder effect involving the 999del5 mutation was identified in Iceland; this mutation was present in 40% of 12 Icelandic men with breast cancer (Thorlacius et al., 1996). In Ashkenazi Jewish women, the 6174delT mutation may be present in 8% of women diagnosed with breast cancer before the age of 42 years (Berman et al., 1996) (compared with zero of 93 women in a non-Ashkenazi group [Neuhausen et al., 1996]). Thus, a single BRCA1 mutation (185delAG) and this common BRCA2 mutation may account for approximately one fourth of all early-onset breast cancers in the Ashkenazi Jewish population and two thirds of early-onset breast cancers in the setting of a personal or family history of ovarian cancer in Ashkenazi Jewish women.

**Incidence:** Varies widely between populations. Overall, BRCA1 and BRCA2 account for 6%-10% of all breast and ovarian cancers in patients unselected for family history, suggesting an overall carrier frequency of one of these two genes in one in 100 to one in 2500 across different populations. In a review by Szabo and King (1997), BRCA2 mutations have been identified in 25% of U.S. 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 U.S. families and in 90% of Icelandic families.

**Diagnosis:** Suspected on the basis of a family tree showing possible dominant inheritance of a predisposition to breast cancer diagnosed at a younger age (often premenopausal) than sporadic cancers of the same type or on the presence of bilateral disease. The presence of male breast cancer may be a clue pointing toward the involvement of BRCA2. The cumulative prob-

ability of male breast cancer in BRCA2 mutation carriers is approximately 6%. A family tree is, however, not diagnostic. DNA mutation analysis is offered on a clinical basis and can be used to supplement the clinical impression.

**Laboratory features:** No histologic features are specific for BRCA2-related tumors.

**Associated malignant neoplasms:** Adenocarcinoma of the breast, which may have an 80% penetrance by the age of 70 years. BRCA2 families are more likely to contain women with very early onset breast cancer ( $\leq 35$  years), and male breast cancer is more common in BRCA2 families than in BRCA1 families. The presence of pancreatic cancer in a breast cancer family was a significant predictor that a BRCA2 mutation would be found (Phelan et al., 1996). The role of BRCA2 in the development of pancreatic cancer has been studied (Ozcelik et al., 1997): Two of 41 patients had germline mutations in BRCA2. In 26 Jewish patients with pancreatic cancer, the 6174delT-BRCA2 mutation was found in three patients. Some studies have suggested increased rates of carcinomas of the colon and prostate, with some family histories similar to those reported in hereditary nonpolyposis colon cancer.

**Associated benign neoplasms:** None known.

**Surveillance strategies:** Burke et al. (1997) reviewed the quality of evidence for efficacy of screening recommendations in carriers of BRCA1 and BRCA2 mutations and suggested the following categories: E-1 was highest quality evidence (randomized control trials); E-2 was intermediate quality evidence (non-randomized trials and observational studies); E-3 was lowest quality (expert opinion and case reports only). Consensus recommendations for breast cancer screening included breast self-examination monthly beginning by age 18-21 years (E-3), clinical breast examination annually or semiannually beginning by age 25-35 years (E-3), and mammography beginning by age 25-35 years (E-3).

Annual or semiannual screening with transvaginal ultrasound and measurement of the serum CA-125 level beginning at age 25-35 years was recommended, with ultrasound examinations timed to avoid ovulation, to reduce false-positive results (E-3). Note that fewer than half of early stage ovarian tumors produce elevated serum levels of CA-125.

For prostate cancer surveillance in BRCA1 carriers only, rectal examination and serum prostate-specific antigen level testing should be offered annually, after the individual is informed about the uncertainty of the benefit from early detection (E-3).

For colon cancer surveillance, fecal occult blood test annually and flexible sigmoidoscopy every 3-5 years were recommended, beginning at age 50 years (E-3, from population-based data of uncertain relevance).

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## 7. Carcinoid, Familial

**OMIM number:** 114900.

**Inheritance pattern:** Uncertain, but autosomal dominant likely.

**Gene and chromosomal location:** Unknown.

**Mutations:** Gene not yet cloned.

**Incidence:** Unknown, rare. No large families have been reported, only groups of two and three individuals in one and two generations.

**Diagnosis:** Based on family history and clinical history. Carcinoid also occurs as a rare association in von Hippel-Lindau syndrome, neurofibromatosis, multiple endocrine neoplasia types 1 and 2, and hereditary nonpolyposis colon cancer, all of which need to be excluded.

**Laboratory features:** May have elevated urinary 5-hydroxyindoleacetic acid.

**Associated malignant neoplasms:** Multifocal carcinoid.

**Associated benign neoplasms:** Unknown.

**Surveillance strategies:** We suggest that regular screening of the urinary 5-hydroxyindole acetic acid level in first-degree relatives may be useful, starting by the age of 30 or at an age 10 years less than that of the first carcinoid diagnosis in a family. The risks and benefits of cancer screening in familial carcinoid have not been established.

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## 8. Carney Syndrome (Nevi, Atrial Myxoma, Myxoid Neurofibromas, and Ephelides [NAME] or Lentigines, Atrial Myxomas, Mucocutaneous Myxoma, and Blue Nevi [LAMB] Syndrome)

**OMIM number:** 160980.

**Inheritance pattern:** Autosomal dominant.

**Gene and chromosomal location:** Stratakis et al. (1996 and 1997) studied 101 patients from 11 North American kindreds and found linkage to markers on 2p16. Basson et al. (1997) studied one family with seven affected members in four generations, and linkage results strongly suggested that the disease in

this family was not linked to 2p16. Thus, Carney syndrome may be genetically heterogeneous.

**Mutations:** Gene not yet identified.

**Incidence:** Unknown. Fewer than 20 families have been reported worldwide.

**Diagnosis:** No diagnostic criteria have been suggested. Carney syndrome should be suspected on the basis of finding more than one of the characteristic lesions in an individual or one lesion in an individual and a characteristic lesion documented in a first-degree relative.

**Laboratory features:** Histologic features of the cutaneous myxomas of Carney syndrome include location in the dermis, subcutis, or both; sharp circumscription; hypocellularity; abundant myxoid stroma; and occasional presence of epithelial components.

**Associated malignant neoplasms:** Large-cell calcifying Ser-toli cell tumor and Leydig cell tumors. In one series of 53 affected patients from 12 families, two patients had thyroid carcinomas (one papillary and one follicular), one had colorectal carcinoma, and one had pancreatic cancer (Stratakis et al., 1997).

**Associated benign neoplasms:** Pigmented nodular adrenal cortical dysplasia with Cushing's syndrome occurred in 31% of 101 recognized patients (Stratakis et al., 1996). Pedunculated myxomas of the skin were reported in 62% of these patients; these myxomas appear at a mean age of 18 years, are multicentric in 71% of patients, and precede development of cardiac myxomas in 81% of patients (Carney et al., 1986). Pituitary adenomas are common and were found to secrete growth hormone in 8% of the above-mentioned 101 patients. Prolactinomas have also been noted. The presence of a calcifying, pigmented neuroectodermal tumor (psammomatous melanotic schwannoma) is highly characteristic and can occur in many locations. Cardiac myxomas (87% of which are atrial and 13% of which are ventricular) are multiple in half of the cases and recurrent in 18% of the cases. Myxoid uterine leiomyomas can be seen. 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 had clinical and biochemical euthyroidism, showed 60% with hypochoic, cystic, solid, or mixed lesions.

Spotty cutaneous pigmentation is common, especially of the face, eyelids, vermilion 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 Carney syndrome, the pigmented lesions include tiny black-brown macules, café-au-lait macules, blue nevi, and other pigmented lesions. In some individuals, it has been observed that pigmented lesions have faded with age.

Ophthalmic features in 63 patients (Kennedy et al., 1987) included eyelid myxomas in 16% of the cases, facial and eyelid lentigines in 70% of the cases, and pigmented lentigines on the caruncle or semilunar fold in 27% of the cases.

**Surveillance strategies:** No screening procedures have been published for Carney syndrome. We suggest that an individual with possible Carney syndrome or first-degree relatives of an individual with probable Carney syndrome who are over the age of 14 years should have a careful evaluation for associated features of the disease. This evaluation may include an echocardiogram (repeated every 3-5 years if normal), careful examination of the skin and mucous membranes with biopsy of papular le-

sions if diagnosis needs confirmation, checking serum cortisol after a dexamethasone suppression test to look for autonomous adrenal cortical function, checking serum levels of insulin-like growth factor-I and prolactin, careful and regular testicular examination (perhaps with sonography), thyroid examination, and careful endocrine review of systems with aggressive evaluation of symptoms suggestive of dysfunction.

**Comments:** Dr. Aidan Carney is also known for the identification of a clinical triad that consists of multicentric gastric leiomyosarcomas (which look like gastric autonomic nerve tumors by electron microscopy), pulmonary chondromas, and extra-adrenal paragangliomas. This disorder, which affects primarily young women, is called Carney's triad, and it is not related to Carney syndrome. The genetic underpinnings, if any, for Carney's triad are unknown (Carney, 1983).

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## 9. Chordoma, Familial

**OMIM number:** 215400.

**Inheritance pattern:** Autosomal dominant.

**Gene and chromosomal location:** Unknown.

**Mutations:** No gene cloned.

**Incidence:** Extremely rare.

**Diagnosis:** Based on family history and medical history. Stepanek et al. (1998) reported a family with three generations affected, with male-to-male transmission, indicating autosomal dominant inheritance. Some affected individuals were asymptomatic into their 60s but showed lesions by magnetic resonance imaging.

**Laboratory features:** None known.

**Associated malignant neoplasms:** Tumors arising anywhere along the path of the embryonic notochord, becoming symptomatic in the teens or much later in adulthood.

**Associated benign neoplasms:** Single cases of testicular teratoma and pituitary adenoma in individuals with chordomas

have been reported. One case has been identified in an individual with tuberous sclerosis.

**Surveillance strategies:** None have been defined. However, based on the reported cases, we suggest magnetic resonance imaging of the head and entire spinal cord region. A baseline examination is advised in childhood, with the frequency of repeated examinations uncertain (perhaps every 3-5 years in asymptomatic individuals).

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## 10. Colon Cancer, Hereditary Nonpolyposis (HNPCC) (Includes Lynch Syndrome and Muir-Torre Syndrome)

**OMIM numbers:** 120435; 120436; 600259; 600258; 158320; 600678.

**Inheritance pattern:** Autosomal dominant.

**Gene and chromosomal location:** hMLH1 at 3p21.3; hMSH2 at 2p22-p21; hPMS1 at 2q31-q33; hPMS2 at 7p22; hMSH6 (guanosine/thymidine mismatch binding protein [GTBP]) at 2p16. The products of these five genes all participate in a multimeric DNA mismatch repair complex. Other genes also participate in this complex, but germline mutations in those genes have not yet been reported.

**Mutations:** hMLH1 and hMSH2 account for more than 90% of the germline mutations in HNPCC families studied to date. Mutations in the above-mentioned five genes have been of all conceivable types, with no frequently occurring specific mutations identified. In Finland, two specific hMLH1 mutations were reported to account for 63% of that country's HNPCC kindreds (Nystrom-Lahti et al., 1995), suggesting a founder effect. Overall, approximately 70% or more of the characterized mutations would be predicted to yield a truncated protein product.

**Incidence:** HNPCC may account for 6%-10% of all colorectal cancers.

**Diagnosis:** Relies on a pedigree assessment. The Amsterdam criteria (Vasen et al., 1991) were developed to assist in the definition of HNPCC and are still widely used. They are generally recognized to be overly restrictive for clinical purposes, because up to 20% of true HNPCC families (as determined by germline mutation identification) will not meet these criteria. The Amsterdam criteria are met if all four of the following conditions are fulfilled: 1) three cases of colon cancer in which two of the affected individuals are first-degree relatives of the third, 2) colon cancers occurring in two generations, 3) one colon cancer diagnosed before the age of 50 years, and 4) familial adenomatous polyposis not diagnosed in the family.

At a recent National Cancer Institute workshop (Rodriguez-Bigas et al., 1997), new guidelines, the Bethesda guidelines, were proposed to expand the consideration of possible HNPCC if the following features were noted: 1) individuals with cancer in families that meet the Amsterdam criteria; 2) individuals with two HNPCC-related cancers, including synchronous and metachronous colorectal cancers or associated extracolonic cancers (defined as endometrial, ovarian, gastric, hepatobiliary, small

bowel, or transitional cell carcinoma of the renal pelvis or ureter); 3) individuals with colorectal cancer and a first-degree relative with colorectal cancer and/or HNPCC-related extracolonic cancer and/or a colorectal adenoma with one of the cancers diagnosed before age 45 years and the adenoma diagnosed before age 40 years; 4) individuals with colorectal cancer or endometrial cancer diagnosed before age 45 years; 5) individuals with right-sided colorectal cancer having an undifferentiated pattern (solid/cribriform) on histopathologic diagnosis before age 45 years; 6) individuals with signet-ring-cell-type colorectal cancer diagnosed before age 45 years; and 7) individuals with adenomas diagnosed before age 40 years. For such individuals, testing the colorectal tumor for microsatellite instability was suggested as the next step to identifying HNPCC (noting, however, that microsatellite instability is not specific for HNPCC).

**Laboratory features:** Mutation analysis is now available on a clinical basis, although current assays are costly and the sensitivity is estimated at only 70%. The histologic appearance of the tumors is nondiagnostic. Nearly all tumors show a mutator phenotype, i.e., widespread microsatellite instability, which is also called replication error; however, this tumor phenotype is not specific for germline mutations in the HNPCC genes. Tumors homozygous for somatic mutations in DNA mismatch repair genes will also manifest a phenotype showing microsatellite instability. Some laboratories are now offering testing for microsatellite instability in tumors as an adjunct to diagnosing HNPCC. Nontumor tissue from individuals with HNPCC does not show microsatellite instability.

**Associated malignant neoplasms:** Colorectal cancer, with average age at diagnosis of 45 years. Two thirds of the cancers occur in the right colon. The lifetime risk of colorectal cancer is at least 80%. Endometrial adenocarcinomas are also found, with the average age at diagnosis of 45 years; the lifetime risk of endometrial adenocarcinoma is 30%–60% in different studies. Relative risks are increased for ovarian cancer, transitional cell cancers of the renal collecting system, ureter, and bladder, and cancers of the stomach, small bowel, hepatobiliary tract, and pancreas. Sebaceous carcinomas are also found. (Benign or malignant sebaceous skin tumors in combination with internal cancer have been called Muir-Torre syndrome; linkage and mutational analyses of both hMSH2 and hMLH1 have demonstrated that Muir-Torre syndrome is a form of HNPCC.) There is probable increased risk for basal cell cancers and squamous cell cancers of the skin. Glioblastoma multiforme is associated with HNPCC. (The brain tumor in combination with colorectal tumors is also called Turcot's syndrome.) The glioblastomas show an early age at diagnosis (typically <20 years) and demonstrate microsatellite instability. In contrast, patients with familial adenomatous polyposis display an increased risk of medulloblastoma (Paraf et al., 1997), and this, too, has been called Turcot's syndrome. Additional tumors (breast and hematopoietic) are reported in HNPCC families, but the statistical significance of these associations remains to be demonstrated.

**Associated benign neoplasms:** Colonic adenomas, keratoacanthomas, sebaceous adenomas, and epitheliomas.

**Surveillance strategies:** Burke et al. (1997) developed a consensus statement for the care of individuals with HNPCC, noting that the efficacy of cancer surveillance or other risk-reducing measures has not been determined in controlled clinical trials.

For asymptomatic, suspected, or known gene carriers, the following two recommendations were made: 1) Full colonoscopy to the cecum is recommended every 1–3 years beginning at age 20–25 years, based on nonrandomized trials and observational studies. (Some studies have suggested that every 2 years is preferable; alternatively, the pros and cons of prophylactic subtotal colectomy can be considered [evidence of efficacy unavailable].) 2) Annual screening for endometrial cancer beginning at age 25–35 years is recommended, based on expert opinion of presumptive benefit. (Choices for screening include endometrial aspirate or transvaginal ultrasound, with the optimal method not established; prophylactic hysterectomy and oophorectomy after childbearing is completed may be considered [efficacy uncertain and risk not fully eliminated].) We make the following additional recommendations: 1) annual urinalysis and cytologic examination beginning at age 25; 2) annual skin surveillance; 3) in families in which gastric cancer has occurred, periodic upper gastrointestinal endoscopy starting at age 35; and 4) careful adherence to other American Cancer Society guidelines.

For at-risk family members, colonoscopy every 2 years beginning at age 25 is suggested. We also suggest endometrial biopsy and urinalysis with cytologic examination every 2 years after the age of 35.

**Comments:** The role of aspirin or sulindac in the reduction of adenomas has not been assessed in HNPCC. No data are available on the effect of lifestyle modification on cancer risk in HNPCC gene carriers.

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## 11. Cowden Syndrome (Gingival Multiple Hamartoma Syndrome)

**OMIM number:** 158350.

**Inheritance pattern:** Autosomal dominant.

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

**Mutations:** Mutations in PTEN, including four different non-sense or missense mutations predicted to disrupt the protein tyrosine/dual-specificity phosphatase domain of this gene, have been found in 80% of Cowden syndrome families reported (Liaw et al., 1997).

**Incidence:** Unknown.

**Diagnosis:** The International Cowden Syndrome Consortium Operational Criteria have been published and are revised on a continuous basis (Eng, 1997). The 1996 version is shown in Table 6. Cowden syndrome is probably most often recognized on the basis of skin lesions and intestinal hamartomas. Cranio-megaly and mental subnormality are found in approximately 50% of affected individuals; coarse, dark hair and massive, rapid overgrowth of breasts are observed in some. In a subgroup, a glial mass in the cerebellum leading to altered gait and seizures (Lhermitte-Duclos disease) is found.

**Laboratory features:** None known.

**Associated malignant neoplasms:** Breast cancer is observed in 30% of female gene carriers. Thyroid adenomas and carcinomas are also observed, but the risk is not defined. Various other cancers have been reported in the context of Cowden syndrome, but it is not clear if the overall risk for these cancers is different from that in the general population. These unproven cancer types/sites include colon, kidney, ovary, endometrium, melanoma, Merkel cell skin cancer, lung, and retinal glioma.

**Table 6.** International Cowden Syndrome Consortium Operational Criteria for the diagnosis of Cowden syndrome

Pathognomonic criteria

- Mucocutaneous lesions
  - Trichilemmomas, facial
  - Acral keratoses
  - Papillomatous papules
- Mucosal lesions

Major criteria

- Breast carcinoma
- Thyroid carcinoma, especially follicular thyroid carcinoma
- Macrocephaly (megalencephaly) ( $\geq 97$  percentile)
- Lhermitte-Duclos disease

Minor criteria

- Other thyroid lesions (e.g., adenoma or multinodular goiter)
- Mental retardation (intelligence quotient  $\leq 75$ )
- Gastrointestinal hamartomas
- Fibrocystic disease of the breast
- Lipomas
- Fibromas
- Genitourinary tumors (e.g., uterine fibroids) or malformations

Operational diagnosis in an individual

- 1) Mucocutaneous lesions alone if
  - (a) Six or more facial papules, of which three or more must be trichilemmoma
  - (b) Cutaneous facial papules and oral mucosal papillomatosis
  - (c) Oral mucosal papillomatosis and acral keratoses
  - (d) Six or more palmoplantar keratoses
- 2) Two major criteria but one must include macrocephaly or Lhermitte-Duclos disease
- 3) One major and three minor criteria
- 4) Four minor criteria

Operational diagnosis in a family where one individual is diagnostic for Cowden syndrome

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

**Associated benign neoplasms:** Verrucous skin lesions of the face and limbs and cobblestone-like hyperkeratotic papules of the gingiva and buccal mucosa. Biopsy examination of 29 of 53 skin lesions revealed facial trichilemmomas, all oral mucosal lesions were fibromas, and all hand and foot lesions were hyperkeratoses (Brownstein et al., 1979). Sixty percent of affected individuals had hamartomatous polyps of the stomach, small bowel, and colon. Also common are lipomas, giant fibroadenomas of the breast, cerebellar gangliocytomatosis, and hemangiomas.

**Surveillance strategies:** We suggest careful surveillance for thyroid masses. Aggressive breast cancer surveillance should begin at age 20; alternatively, prophylactic mastectomy for women at risk should be considered. The risks and benefits of cancer screening in Cowden syndrome have not been established.

**Comments:** May be underascertained; recently shown to be allelic with Ruvalcaba-Myhre syndrome. Also, Olschwang et al. (1998) reported finding PTEN germline mutations in juvenile polyposis coli; thus, mutations in the PTEN gene may cause an unexpectedly broad range of phenotypic presentations.

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## 12. Esophageal Cancer, Tylosis With (Nonepidermolytic Palmoplantar Keratosis [PPK] and Howel-Evans' Syndrome)

**OMIM number:** 148500.

**Inheritance pattern:** Autosomal dominant.

**Gene and chromosomal location:** 17q23-ter by linkage mapping, distal to the keratin 1 gene cluster. The gene has been named TEC (tylosis with esophageal cancer).

**Mutations:** Unknown because the gene is not yet cloned.

**Incidence:** Very rare. A limited number of large families has been reported.

**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 non-epidermolytic forms, the latter being known as tylosis. 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. At present, cancer risk does not appear to be elevated in other types of PPK, which are thought to be genetically distinct, although this remains to be proven. The hyperkeratosis in patients with tylosis is "late onset" (i.e., 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 (Howel-Evans et al., 1958). The average age at diagnosis of esophageal cancer was 45 years, and 95% of the affected individuals developed the cancer by age 65. There may be a synergistic interaction between tobacco smoking and a mutant TEC gene because, in one family, seven of eight esophageal carcinomas occurred in smokers.

**Laboratory features:** None known.

**Associated malignant neoplasms:** Squamous cell carcinoma of the esophagus.

**Associated benign neoplasms:** Mucosal leukoplakia.

**Surveillance strategies:** Although the mean age at esophageal cancer onset is 45 years, the youngest reported case patient was 20 years old (Howel-Evans et al., 1958). We suggest that annual upper gastrointestinal endoscopy commence at age 20 in family members with tylosis. The risks and benefits of cancer screening in this syndrome have not been established.

**Comments:** Abstinence from tobacco exposure may reduce the risk of esophageal cancer. Families with severe gastroesophageal reflux with subsequent Barrett's esophagus may also present with more than one case of esophageal cancer in the family. Antireflux therapy is indicated in that group. 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.

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## 13. Fanconi's Anemia (FA) (Includes Pancytopenia, Fanconi's Type)

**OMIM numbers:** 227650 (FA complementation group A [FA-A]); 227660 (FA complementation group B [FA-B]); 227645 (FA complementation group C [FA-C]); 227646 (FA complementation group D [FA-D]); 600901 (FA complementation group E [FA-E]).

**Inheritance pattern:** Autosomal recessive.

**Gene and chromosomal location:** FA-A at 16q24.3; FA-B, unmapped; FA-C at 9q22.3; FA-D at 3p26-p22; FA-E, unmapped.

**Mutations:** Mutations for FA-C have been found, with a common founder mutation noted in 19 of 23 individuals with Ashkenazi ancestry (Whitney et al., 1993). Several FA-A mutations have been found.

**Incidence:** Heterozygote frequency is estimated at one in 300 to one in 600, with one in 100 in Ashkenazi carriers. FA is associated with approximately 20% of all cases of childhood aplastic anemia.

**Diagnosis:** Progressive pancytopenia and chromosome breakage, worsened by exposure to alkylating agents. Most children present in early to middle childhood (mean age at diagnosis is 6 years) with hematologic abnormalities, including anemia, bleeding, and easy bruising. Multiple congenital anomalies may occur in 60% of individuals; these anomalies include low birth weight, abnormal skin pigmentation (76% with hyperpigmentation, café-au-lait spots, or both), skeletal deformities (50% with thumb anomalies, such as aplasia, hypoplasia, and supernumerary and 30% with microcephaly), renal malformation (31% with aplasia, duplication, ectopia, and horseshoe), neurologic abnormalities (23% with strabismus, 20% with hyperreflexia, and 18% with mental retardation), microphthalmia (19%), ear anomalies/deafness (12%), congenital heart disease (7%), and hypogonadism (20%). Note that 25% of individuals with FA have no dysmorphic features.

Enhancement of chromosome breakage with the mitomycin C chromosome stress test or diepoxybutane *in vitro* reliably identifies homozygotes but not heterozygotes. These tests show excess chromatid breaks, gaps, formation of radial chromosomes, endoreduplications, and other types of nonhomologous recombination in comparison with controls. Standard karyotyping does not demonstrate these features.

**Laboratory features:** Anemia, macrocytosis, poikilocytosis, anisocytosis, leukopenia, thrombocytopenia, reticulocytopenia, and hypocellular marrow.

**Associated malignant neoplasms:** Leukemia in around 10%, usually acute nonlymphatic type, hepatocellular carcinoma in around 5% (often after anabolic steroid therapy for aplastic anemia), and squamous cell carcinomas especially of the head and neck region, esophagus, cervix and vulva, and anus (Alter, 1996). Heterozygotes have no apparent increased risks. Myelodysplastic syndromes affect around 5%. There may be increased risks for primary brain tumors as well.

**Associated benign neoplasms:** Hepatic adenomas.

**Surveillance strategies:** 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 (1996) has suggested serial bone marrow aspirations, regular liver enzyme assessment, and frequent oral scrutiny by a dentist. Imaging of esophagus, lower pharynx, and stomach can also be considered.

**Comments:** In older reports, the average life expectancy is about 12 years, with most deaths due to bleeding, infection, or cancer. Bone marrow transplantation is a potential treatment, but extreme care is required, since Fanconi's anemia patients are unusually sensitive to chemotherapeutic agents and are prone to graft-versus-host disease.

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## 14. Gastric Cancer, Familial

**OMIM number:** 137215.

**Inheritance pattern:** Autosomal dominant.

**Gene and chromosomal location:** CDH1 gene on chromosome 16q22.1 recently identified in three Maori families. E-cadherin is an epithelial-type calcium-dependent adhesion protein. Germline mutations in non-Maori families have not yet been reported.

**Mutations:** The three germline mutations in CDH1 included a substitution in a donor splice consensus sequence of exon 7, a frameshift mutation in exon 15, and a premature stop codon interrupting exon 13.

**Incidence:** Unknown; uncommon.

**Diagnosis:** Two or more first-degree relatives with gastric adenocarcinoma. Case-control studies suggest that family members of probands with gastric adenocarcinoma are two to three times more likely to develop gastric cancer themselves. In families with germline E-cadherin mutations, an autosomal dominant pattern with incomplete penetrance was evident.

**Laboratory features:** It is currently unclear whether or not E-cadherin germline mutations will account for familial gastric cancer in ethnic groups outside the Maoris. Blood type A has been frequently associated with an increased risk of gastric cancer. Patients with gastric cancer display a 2%-8% excess of this blood type compared with the general population. A report (Scott et al., 1990) has described a strong association between *Helicobacter pylori* and gastric cancer in one family. It was hypothesized that this family might be carrying a genetic predisposition to the epithelial metaplasia/dysplasia/neoplasia sequence leading to invasive cancer, with *H. pylori* acting as a tumor promoter. Nonspecific immunologic abnormalities have been reported in several families.

**Associated malignant neoplasms:** Gastric adenocarcinoma.

**Associated benign neoplasms.** Possible intestinal metaplasia of the gastric mucosa.

**Surveillance strategies:** We suggest annual upper gastrointestinal endoscopy for at-risk family members beginning at an age that is 5-10 years younger than the age at diagnosis for the youngest individual with reported gastric cancer in that family. The risks and benefits of cancer screening in this syndrome have not been established.

**Comments:** Gastric cancer appears to be part of the tumor spectrum of hereditary nonpolyposis colon cancer and familial adenomatous polyposis, so these possibilities should be considered in any family with two or more cases of gastric cancer. In the Maori gastric cancer families, the majority of cases occurred in individuals under the age of 40 (the youngest subject being 14 years of age), in contrast to the general New Zealand population in which 80% of gastric carcinomas occur after the age of 60 years.

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## 15. Hodgkin's Disease, Familial

**OMIM number:** 236000.

**Inheritance pattern:** Uncertain mode (autosomal recessive?).

**Gene and chromosomal location:** 6p (major histocompatibility complex?).

**Mutations:** None known.

**Incidence:** Rare.

**Diagnosis:** Two or more first- or second-degree relatives with Hodgkin's disease.

**Laboratory features:** Numerous familial aggregations of Hodgkin's disease have been reported, with a variety of non-specific abnormalities in cellular and humoral immunity. No reproducible abnormality of clear etiologic significance has been found. There is a strong association between Hodgkin's disease and evidence of exposure to or infection with Epstein-Barr virus. DNA from this virus can be identified in at least half of all Hodgkin's disease tumor biopsies; however, the relationship between Epstein-Barr virus and Hodgkin's disease remains unclear. Studies have suggested an association between specific human leukocyte antigen (HLA) (i.e., histocompatibility) phenotypes and Hodgkin's disease on the basis of comparisons between individuals from Hodgkin's disease families and the general population. In such families, there is a higher than expected concordance of HLA haplotypes (Chakravarti et al., 1986; Hors et al., 1983; Marshall et al., 1977).

**Associated malignant neoplasms:** Hodgkin's lymphoma.

**Associated benign neoplasms:** Unknown.

**Surveillance strategies:** No consensus. Periodic medical history and physical examination, with more detailed studies as indicated, would be a reasonable starting point. The risks and benefits of cancer screening in this syndrome have not been established.

**Comments:** Epidemiologic studies have documented a significant familial component to the etiology of Hodgkin's disease (Grufferman et al., 1977; Kerzin-Storarr et al., 1983). The increased risk clusters among relatives of patients under the age of 45 at diagnosis; such relatives experience a sevenfold increased risk of Hodgkin's disease compared with the general population. No excess risk is observed among relatives of patients who are older than 45 at diagnosis. This excess is affected by the sex of the case subjects. Brothers of an affected male have a ninefold increased risk of Hodgkin's disease, compared with sisters, for whom the risk is only fivefold. If the proband is female, the reverse holds true. This pattern is thought to provide support for an infectious rather than a genetic etiology for Hodgkin's disease. One hypothesis regarding the pathogenesis of early-onset Hodgkin's disease is that it represents an uncommon outcome secondary to exposure to a common infectious agent, with age at exposure and other factors modifying the outcome. The significant concordance of HLA haplotypes in affected individuals from Hodgkin's disease families has suggested the presence of a susceptibility gene in or near the major histocompatibility complex. An analysis of 41 Hodgkin's disease families supported this hypothesis and provided evidence favoring an autosomal recessive mode of inheritance (Chakravarti et al., 1986). A study of Hodgkin's disease in monozygotic and dizygotic twin pairs revealed concordance in 10 of 179 pairs versus none of 187 pairs, respectively (Mack et al., 1995). This finding was interpreted as favoring the existence of genetic factors in early-onset Hodgkin's disease.

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## 16. Li-Fraumeni Syndrome

**OMIM number:** 151623.

**Inheritance pattern:** Autosomal dominant.

**Gene and chromosomal location:** Approximately half of Li-Fraumeni families have identifiable mutations in the p53 gene (also known as TP53), which is located at 17p13.1. Most mutations occur in exons 5 through 8 of the gene.

**Mutations:** Families with this syndrome are likely to be a genetically heterogeneous group. Among those with identified p53 mutations, 75% (six of eight) of the mutations were point mutations involving exons 5 through 8, one was a nonsense mutation in exon 6, and one was a splice site mutation in intron 4. Each mutation generated truncated p53 protein.

**Incidence:** Unknown.

**Diagnosis:** The classical definition requires one patient with sarcoma under the age of 45, a first-degree relative under the age of 45 with cancer (type not specified), and a third affected family member (first- or second-degree relative) with either sarcoma at any age or cancer (type not specified) under the age of 45 years. Studies based on modified Li-Fraumeni-like inclusion criteria resulted in only four (8%) of 53 individuals with identifiable p53 mutations (Eeles et al., 1994). Analysis of p53 mutation is available on a clinical basis and on a research basis with proper pretesting genetic counseling.

**Laboratory features:** None specific.

**Associated malignant neoplasms:** Risk of developing any invasive cancer (excluding skin cancer) was almost 50% by age 30 (compared with 1% in the general population) and almost 90% by age 70. The tumor spectrum includes rhabdomyosarcoma, osteogenic sarcoma, breast cancer, brain cancer, leukemia, and adrenal cortical carcinoma. Also reported (but not proven) are melanoma and laryngeal, lung, gonadal germ cell, pancreatic, stomach, and prostate cancers. There may be an increased susceptibility to radiation-induced cancers within the treatment field of a prior cancer.

**Associated benign neoplasms:** None known.

**Surveillance strategies:** We suggest annual mammography, clinical examination of the breasts every 6 months, and monthly breast self-examination beginning in adulthood. We also advise annual blood cell counts with a manual review of peripheral blood smears (leukemia) and a careful annual physical examination with attention and high index of suspicion to sites known to be potentially affected, beginning in infancy. The risks and benefits of cancer screening in this syndrome have not been established.

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## 17. Melanoma, Familial With or Without Dysplastic Nevi (Includes Dysplastic Nevus Syndrome, Familial Atypical Mole-Malignant Melanoma Syndrome, and Melanoma-Astrocytoma Syndrome)

**OMIM numbers:** 155600; 155601; 123829; 155755.

**Inheritance pattern:** Autosomal dominant.

**Gene and chromosomal location:** At least three melanoma-susceptibility genes have been identified. CMM1 has been mapped to 1p36, with melanoma and dysplastic nevi seeming to be pleiotropic effects of this gene. This linkage finding is controversial, and no candidate gene has yet been identified. CMM2 maps to 9p21, and the gene appears to be p16<sup>INK4a</sup> (also known as MTS1 and CDKN2). Around 20%–25% of melanoma-prone kindreds are linked to p16<sup>INK4a</sup>. Recently, germline mutations in the CDK4 gene (chromosome 12q14) have been reported, and this gene likely represents a third melanoma-susceptibility gene. Mutation of CDK4 is quite rare, with only three affected families identified in several hundred screened for CDK4 abnormalities. Although p16<sup>INK4a</sup> functions as a tumor suppressor gene, CDK4 appears to operate as a dominant oncogene. Mutation analysis of p16<sup>INK4a</sup> is available for clinical use, but its utility is uncertain.

**Mutations:** Various mutations have been identified in p16<sup>INK4a</sup>, including nonsense, splice donor site, missense, insertion, and others that impair the function of this gene. Only one germline CDK4 mutation has been identified to date, i.e., Arg24Cys (due to a cytosine to thymidine transition at nucleotide 297 of the protein coding region of the published complementary DNA sequence [Zuo et al., 1996]).

**Incidence:** It is estimated that 5%–7% of melanoma patients are from genetically high-risk families. Gene and mutation frequencies are unknown.

**Diagnosis:** Ten to 100 moles on the upper trunk and limbs,

with variability in mole size (5–15 mm), outline, and color. Family history of invasive melanoma in at least two first-degree relatives. Early age at melanoma diagnosis and a tendency to develop multiple primary melanomas characterize these families. Germline mutations in p16<sup>INK4a</sup> have been reported in some patients with multiple primary melanomas and a negative family history of melanoma. *Note:* There are clearly familial melanoma kindreds that do not manifest the dysplastic nevus syndrome.

**Laboratory features:** Histologically, moles show readily recognizable cytologic atypia of melanocytes with lymphocytic infiltration, delicate fibroplasia, and new blood vessel formation.

**Associated malignant neoplasms:** Kindreds with disabling p16<sup>INK4a</sup> mutations have a melanoma risk that is increased by a factor of 75. The risk of pancreatic cancer is increased by a factor of 13. Kindreds without this type of mutation have a risk of melanoma that is increased by a factor of 38. (However, the difference in melanoma risk was not statistically different because the series was small [Goldstein et al., 1995].) The average age at diagnosis of melanoma in dysplastic nevus syndrome families is 34 years, compared with 54 years for melanoma diagnosed in the general population. Astrocytomas occur with melanomas in rare families.

**Associated benign neoplasms:** Dysplastic nevi.

**Surveillance strategies:** We suggest monthly skin self-examination, twice yearly dermatologic evaluation with photography of entire skin, and early excision of suspicious lesions. The role of pancreatic screening remains to be defined. Affected individuals should avoid sunburn, and regular use of ultraviolet A/B-blocking sunscreens is advised. The risks and benefits of cancer screening in this syndrome have not been established, but the striking preponderance of thin, biologically early melanomas among prospectively screened subjects strongly suggests a favorable impact of screening.

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## 18. Multiple Endocrine Neoplasia Type 1 (MEN1) (Wermer Syndrome Includes Zollinger-Ellison Syndrome)

**OMIM number:** 131100.

**Inheritance pattern:** Autosomal dominant.

**Gene and chromosomal location:** 11q13.

**Mutations:** MEN1 encodes a 10-exon, 2.8-kilobase (kb) transcript termed "menin" from a 9-kb segment of DNA. Various different frameshift, nonsense, missense, and in-frame deletion mutations have been reported. The encoded protein does not resemble any known polypeptide, and its function is unknown. Linkage-based predictive testing is currently available.

**Incidence:** Unknown.

**Diagnosis:** This autosomal dominant disorder is characterized by a high frequency of peptic ulcer disease and endocrine abnormalities, especially of the pituitary (44% of affected individuals), parathyroid (95% of affected individuals), pancreas (73% of affected individuals), and adrenals (16% of affected individuals). Hyperparathyroidism either is the presenting symptom or is diagnosed simultaneously with the presenting symptom in 94% of cases. Genetic linkage analysis is available clinically for selected families. Penetrance of MEN1 is high, with more than 80% of mutant gene carriers affected by the fifth decade of life.

**Laboratory features:** One may find hypoaminoacidemia, elevated adrenocorticotrophic hormone, an abnormal secretin test, hypoglycemia, hypergastrinism, hyperparathyroidism, and glucose intolerance.

**Associated malignant neoplasms:** Duodenal, thymic, and bronchial carcinoids; bronchial carcinoma; malignant schwannoma; ovarian tumors; pancreatic islet cell carcinomas; and adrenocortical carcinomas.

**Associated benign neoplasms:** Pancreatic islet cell adenomas; parathyroid hyperplasias or single or multiple adenomas; pituitary adenomas that are either nonsecreting or that secrete prolactin most often but that also secrete growth hormone, adrenocorticotrophic hormone, and luteinizing hormones; multiple adrenocortical adenomas; gastrinomas (usually of the duodenum, but also seen in the pancreas); Cushing's syndrome; pheochromocytomas; prolactinomas; glucagonomas; insulinomas; vasointestinal peptide tumors; and lipomas.

**Surveillance strategies:** No consensus has been established, but in one 10-year study of four MEN1 kindreds, hyperparathyroidism was found in 90% of MEN1-affected relatives, and pancreatic endocrine tumors were found in 75%. Annual evaluation is recommended for known gene carriers or at-risk individuals older than 15 years of age, with testing for prolactin, cortisol, glucose, calcium, and phosphorus. In addition, a physical examination should be performed, including a careful review of endocrinologic systems. Assessment every 1-2 years is suggested for gastrin, parathyroid hormone, 5-hydroxyindole acetic acid, urinary metanephrine, human pancreatic polypeptide, insulin-like growth factor-I, insulin, proinsulin, and glucagon lev-

els. Periodic (every 3-5 years) magnetic resonance imaging of the pituitary and the pancreas should be considered. The clinical efficacy of these screening recommendations remains to be proven. The age at which testing can be discontinued for at-risk individuals is unknown. The risks and benefits of cancer screening in this syndrome have not been established.

**Comment:** Significant intrafamilial consistency of clinical manifestations has been noted (which might help guide the type and frequency of clinical investigations).

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## 19. Multiple Endocrine Neoplasia Types 2A and 2B (MEN2A and MEN2B) and Familial Medullary Thyroid Cancer (FMTC)

**OMIM number:** 171400.

**Inheritance pattern:** Autosomal dominant.

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

**Mutations:** The mutations found in more than 95% of cases of MEN2A lie in exons 10 and 11 of RET and involve one of five cysteines in the extracellular binding domain of the encoded protein. Eight-six percent of cases of FMTC have mutations in the same exons. MEN2B is characterized by a single mutation in codon 918, which is located in exon 16 in all cases studied so far. Direct mutation and linkage analyses are available on a clinical basis.

**Incidence:** Five percent to 10% of all thyroid cancers in clinical practice are of the medullary type. Among these, 20% are due to germline RET mutations. Those resulting from germline RET mutations differ from sporadic tumors by being multifocal. The gene mutation frequency is unknown.

**Diagnosis:** Based on DNA results, biochemical results, family history, and physical diagnosis (in MEN2B).

**Laboratory features:** Mutations in RET, elevated calcitonin after pentagastrin stimulation, elevated metanephrines if pheochromocytoma present, and possible elevation in serum parathyroid hormone and calcium levels.

**Associated malignant neoplasms:** Medullary thyroid cancer (MTC), with the earliest age at diagnosis reported for a 2.7-year-old child with MEN2A. By use of biochemical screening, 40% of children under the age of 5 years who were treated with surgery had invasive carcinoma at the time of their diagnosis, compared with virtually 100% of individuals who were diag-

nosed at an age older than 20 years (Ledger et al., 1995). Disease onset in MEN2B can occur at a younger age and can be more aggressive. MTC is almost always diagnosed before the age of 40 in MEN2A and MEN2B. MTC in FMTC is a more indolent disease, with onset often after the age of 50 years.

Pheochromocytomas are present in 10%–50% of individuals with MEN2A and MEN2B.

**Associated benign neoplasms:** Hyperparathyroidism is found in 10%–20% of individuals with MEN2A; however, this condition is rare in individuals with MEN2B and is never found in FMTC (by definition). Ganglioneuromas of the gastrointestinal tract and mucosal neuromas are present in nearly all patients with MEN2B.

**Surveillance strategies:** Genetic testing for at-risk individuals is an established clinical procedure. For those who test positive, planning for thyroidectomy should be addressed. Once the diagnosis is established, additional screening for pheochromocytomas and hyperparathyroidism is indicated. These complications of MEN nearly always occur later than the MTC, and prophylactic surgery for these conditions has not been suggested.

Biochemical screening with pentagastrin-stimulated calcitonin evaluation can be diagnostic in 80% of cases of MEN2A and 85% of cases of MEN2B, but 82% of the individuals diagnosed in this manner had invasive carcinoma and 10% already had metastatic disease. For this reason, aggressive pursuit of genetic testing offers the best chance for proactive management.

**Comments:** Some genotype/phenotype information suggests that certain mutations in specific codons of RET are strongly associated with the development of pheochromocytomas. At this time, the association is not strong enough to offer prophylactic surgery to those with the high-risk mutations or to omit pheochromocytoma screening for those without the mutations.

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## 20. Neurofibromatosis Type 1 (NF1)

**OMIM number:** 162200.

**Inheritance pattern:** Autosomal dominant.

**Gene and chromosomal location:** NF1 at 17q11.2 encodes a guanosine triphosphatase-activating protein known as NF1-

GAP-related protein or neurofibromin. NF1 is a very large gene with 59 exons.

**Mutations:** Unique from family to family. By 1994, 70 different mutations from 78 individuals had been reported; 70%–80% of the mutations result in a truncated protein. Entire gene deletions are associated with dysmorphism and mental retardation (probably a contiguous gene syndrome).

**Incidence:** One in 3000; one third to one half of cases represent new mutation dominant disease.

**Diagnosis:** National Institutes of Health Consensus Development Conference (1988) criteria require two or more of the following to diagnose: 1) café-au-lait macules (in children, five or more that are 0.5 cm or more in diameter; in adults, six or more that are 1.5 cm or more in diameter); 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 (with or without pseudoarthrosis); 5) bilateral optic nerve gliomas; 6) two or more iris Lisch nodules (iris hamartomas); and 7) first-degree relative with NF1 by these criteria.

NF1 can present at any age in any organ system. Café-au-lait macules are sometimes present at birth but more often appear in late infancy and early childhood and increase in number and size over time. Freckling of the axilla and the groin is seldom seen before puberty. Neurofibromas can be cutaneous, subcutaneous, or deep plexiform, and they may be few or myriad in numbers. Neurofibromas are not specific for NF1. Seizures are reported in 3%–5% of affected individuals, and learning disabilities are reported in 25%–40%, with frank mental retardation in 5%–10%. Short stature is reported in 15%–20% of affected individuals; scoliosis is reported in 10%; visceral arterial aneurysms and pulmonary fibrosis occur in an unknown percent. Iris Lisch nodules are present in only 10% of children under the age of 10; they are present in 50% of affected individuals by the age of 29 and in approximately 100% by the age of 60.

Genetic testing by an *in vitro* transcription-translation assay (i.e., protein truncation test) is clinically available and, if positive, is virtually diagnostic; if negative, the diagnosis cannot be ruled out.

**Laboratory features:** The histopathology of any given lesion is nondiagnostic for NF1. Skin biopsy examination of café-au-lait macules reveals giant melanosomes or melanin macroglobules, which are nonspecific. Neurofibromas are composed of Schwann cells, fibroblasts, mast cells, and vascular elements.

**Associated malignant neoplasms:** Neurofibrosarcomas (malignant schwannomas) develop in 3%–15% of affected individuals, most often associated with deep neurofibromas. Conversely, it has been estimated that 50% of individuals with neurofibrosarcomas have NF1. Also, there is increased risk for astrocytomas, carcinoids (usually duodenal), pheochromocytomas, neuroblastomas, ependymomas, primitive neuroectodermal tumors, rhabdomyosarcomas (especially of the genitourinary tract), and undifferentiated sarcomas, as well as for Wilms' tumor and leukemia (juvenile chronic myelogenous). Affected individuals may have multiple primary cancers.

**Associated benign neoplasms:** Neurofibromas, pheochromocytomas (risk of 0.1%–1.0%), meningiomas, and optic or acoustic neuromas.

**Surveillance strategies:** Guidelines for management of the

non-neoplastic complications of NF1 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 and pheochromocytoma.) Patients should be educated to report any lesion that shows rapid enlargement, pain, or new itching. New onset of headaches, hearing loss, visual change, or other neurologic deficits should be carefully sought and fully evaluated. The risks and benefits of cancer screening in this syndrome have not been established.

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## 21. Neurofibromatosis Type 2 (NF2)

**OMIM number:** 101000.

**Inheritance pattern:** Autosomal dominant.

**Gene and chromosomal location:** NF2 at 22q12.2.

**Mutations:** Various mutations have been identified; none are common. Genetic testing by direct mutation analysis or by linkage analysis is available clinically.

**Incidence:** One in 35 000, of which 50% have new mutation dominant disease.

**Diagnosis:** National Institutes of Health consensus conference criteria for NF2 require one of the following two major criteria to be met:

- 1) Bilateral 8th nerve masses seen by magnetic resonance imaging with gadolinium
- 2) First-degree relative with NF2 plus one of the following:
  - (a) Computed tomography or magnetic resonance imaging evidence of a unilateral 8th nerve mass
  - (b) A plexiform neurofibroma
  - (c) Neurofibromas (two or more)
  - (d) Gliomas (two or more)
  - (e) Posterior subcapsular cataract at a young age
  - (f) Meningioma (two or more)
  - (g) Imaging evidence of an intracranial or a spinal cord tumor

The clinical features vary widely between and within families. Evans et al. (1992) reported on 150 affected individuals. In this

group, the mean age of onset was 21.6 years, with no patient presenting with a new diagnosis after the age of 55. Forty-four percent presented with hearing loss, which was unilateral in 35%. Tinnitus was present in 10%. Muscle weakness and wasting were the presenting symptoms in 12% (due to spinal cord tumors or peripheral neuropathy). Forty-three percent showed café-au-lait spots that tended to be few, large, and pale. Only 1% had six or more café-au-lait macules (*see* NF1 criteria). Cataracts were present in 34 of 90 individuals in this group for whom this information was available. Bouzas et al. (1993) reported on 54 patients. Eighty percent had posterior subcapsular cataracts, which remained minor in many instances. Retinal hamartomas are present in 22% of individuals with NF2. Twenty percent of affected individuals have intradermal neurofibromas, with 33% showing a palpable spherical tumor involving a peripheral nerve and 47% having a raised, rough pigmented area with excess hair.

Neurilemmomatosis, previously called NF3, is characterized by multiple cutaneous neurilemmomas and spinal schwannomas without acoustic neuromas or other sign of NF1 or NF2. Mutation analysis of NF2 identified germline mutations in the NF2 gene in two of three tumors studied in individuals, suggesting that "NF3" is really a form of NF2 (Honda et al., 1995).

**Laboratory features:** None specific. Predictive testing based on linkage or mutation analysis is available.

**Associated malignant neoplasms:** Gliomas.

**Associated benign neoplasms:** Vestibular schwannomas (acoustic neuromas), meningiomas, and spinal cord schwannomas.

**Surveillance strategies:** We suggest regular audiologic and ophthalmologic examination for those at risk or known to be affected. Annual neurologic physical examination, with imaging of any region manifesting new neurologic signs or symptoms, is recommended. The risks and benefits of cancer screening in this syndrome have not been established.

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## 22. Osteochondromatosis, Multiple (Includes Hereditary Multiple Exostoses [EXTs], Enchondromatosis, and Ollier's Disease)

**OMIM numbers:** 133700 (EXT1); 133701 (EXT2); 166000 and 600209 (EXT3).

**Inheritance pattern:** Autosomal dominant.

**Gene and chromosomal location:** Legeai-Mallet et al. (1997) studied 29 families with multiple exostoses for linkage to the three known disease loci, and results of modeling have sug-

gested that 44% are linked to 8q24.11–q24.13 (EXT1), 28% are linked to 11p12–p11 (EXT2), and 28% are linked to chromosome 19q (EXT3). Philippe et al. (1997) obtained similar results with a mutation screening method that examined EXT1 and EXT2 in 17 probands. Cook et al. (1993) had concluded that 70% of multiple exostoses families showed linkage to the 8q24 region. The gene sequences of EXT1 and EXT2 show striking similarity, defining a new multigene family encoding proteins with potential tumor suppressor activity. EXT3 has not yet been cloned.

**Mutations:** Fewer than 20 germline mutations have been reported to date in EXT1, and most lead to a truncated or non-functional EXT1 protein (supporting a tumor suppressor function of the gene product). Fewer than 10 mutations have been reported to date in EXT2, again, most leading to a truncated or nonfunctional EXT2 protein.

**Incidence:** One in 90 000 visits to a general hospital.

**Diagnosis:** Osteochondromatosis 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 resulting in deformity. This disorder is often associated with mildly short stature, and its penetrance is 100%. It may be detectable at birth, and 80% of affected individuals are diagnosed by 10 years of age. Around 40% of case patients have no family history (new mutation disease presumed).

**Laboratory features:** None are specific.

**Associated malignant neoplasms:** Chondrosarcomas or osteosarcomas may develop in the exostoses. No other cancers are associated. Wicklund et al. (1995) reviewed 43 probands with multiple osteochondromatosis (molecular type not specified) and 137 of their affected relatives; the investigators reported that 2.8% of the 180 individuals had experienced exostosis-related cancer. Other reports (Hennekam, 1991; Ochsner et al., 1978) suggest a 0.5%–2% risk of malignant degeneration per person, with a mean age of onset of 31 years, seldom occurring before the age of 10 or after the age of 50, with a predilection for the proximal femur and the pelvis.

**Associated benign neoplasms:** Multiple exostoses, which may cause a variety of compressive problems. When associated with multiple hemangiomas, the disorder is called Maffucci syndrome (OMIM number: 166000), nearly all cases of which are sporadic. The genetic basis for Maffucci syndrome is unknown.

**Surveillance strategies:** It may be useful 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 pre-existing lesion. The risks and benefits of cancer screening in this syndrome have not been established.

**Comments:** The Langer-Giedion syndrome is a rare disorder characterized by laxity of skin in infancy, dysmorphic facies, mental deficiency (in 70% of affected individuals), sparse hair, and multiple exostoses indistinguishable from those seen in EXT1 families. This disorder has been shown to be associated with a large deletion in the 8q24 region that contains EXT1 and a number of other genes (McKusick, 1994). Similarly, McGaughran et al. (1995) reported a patient with the WAGR syndrome [see “Wilms’ Tumor (Nephroblastoma)” section] plus

multiple exostoses, resulting from the deletion del(11)(p14.2p11.2). Potocki and Shaffer (1996) described a different contiguous gene syndrome with multiple exostoses, mental retardation, dysmorphic features, and parietal foramina, known as Catlin marks, in a patient who was found to have a *de novo* 11(p11.2p12) deletion.

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## 23. Pancreatic Cancer, Familial

**OMIM number:** 260350.

**Inheritance pattern:** Uncertain, but likely autosomal dominant.

**Gene and chromosomal location:** Unknown.

**Mutations:** No gene cloned.

**Incidence:** Rare families have been reported with multiple individuals affected with pancreatic cancer. A family history of pancreatic cancer was reported by approximately 7.8% of individuals with the disease but by only 0.6% of control subjects who did not have the disease. Lynch et al. (1995) estimated that 3%–5% of pancreatic cancers had a hereditary origin, but transmission appears to be complex and familial pancreatic cancer may not truly be a single-gene mendelian disorder.

**Diagnosis:** Two or more first-degree relatives with pancreatic adenocarcinoma and no evidence for alternative explanations (see “Comments” section *below*).

**Laboratory features:** None diagnostic.

**Associated malignant neoplasms:** Pancreatic adenocarcinoma.

**Associated benign neoplasms:** Unknown.

**Surveillance strategies:** We suggest consideration of imaging studies of the pancreas for those at risk, beginning at an age that is 10 years younger than the age of diagnosis for the youngest affected family member. Periodic assessment of amylase for those at risk should also be considered. The efficacy of these recommendations is unknown.

**Comments:** Exclusion of von Hippel-Lindau syndrome, hereditary breast cancer (BRCA2), ataxia-telangiectasia, hereditary nonpolyposis colon cancer, familial dysplastic nevus-melanoma syndrome, multiple endocrine neoplasia type 1, and hereditary pancreatitis as causes of familial pancreatic cancer is important (see Table 4). A genetic basis for pancreatic cancer has been suspected on the basis of frequent somatic mutations in both tumor suppressor genes and oncogenes, including KRAS, p53, DCC, MTS1, and DPC4, but germline mutations in candidate genes have not yet been demonstrated.

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## 24. Paraganglioma, Familial

**OMIM number:** 168000.

**Inheritance pattern:** Autosomal dominant; however, a unique parent of origin effect is consistently reported. Offspring of female gene carriers do not develop disease, whereas 50% of offspring of male gene carriers do develop disease. This observation indicates genomic imprinting of the associated gene.

**Gene and chromosomal location:** PGL gene located at 11q23 by linkage analysis in all families except one, in which a locus at 11q13.1 has been suggested.

**Mutations:** Gene not yet cloned.

**Incidence:** Very rare. Nine kindreds with 38 affected members seen at the Mayo Clinic from 1950 to 1992. Grufferman et al. (1980) reviewed case reports for 916 carotid body tumors and found 88 tumors that were believed to be familial. In the familial group, 31.8% were bilateral (compared with 4.4% of the presumed sporadic group). van Baars et al. (1981) found bilaterality in 37.5% of familial paragangliomas.

**Diagnosis:** No criteria. Should be considered in any individual with multiple paragangliomas, glomus tumor, or chemodectoma or in an individual with a single paraganglioma, glomus tumor, or chemodectoma with a relative who reported having a paraganglioma, glomus tumor, or chemodectoma and in whom no other disorder was evident, such as von Hippel-Lindau disease, multiple endocrine neoplasia, neurofibromatosis, or Carney's triad (see "Comments" section under "Carney Syndrome").

**Laboratory features:** Linkage to 11q on a research basis only. Clinical gene testing is not routinely available. This disorder has been associated with a combined deficiency in clotting factors VII and X in one large family.

**Associated malignant neoplasms:** Paragangliomas can be clinically malignant despite being histologically benign.

**Associated benign neoplasms:** Carotid body tumors in 89% of affected individuals, with glomus jugulare or glomus vagale in 38% and adrenal paragangliomas (pheochromocytomas) in an unknown percent.

**Surveillance strategies:** We suggest ultrasound imaging of the carotid region annually beginning at age 18, screening of urinary metanephrines annually beginning at age 18, and imaging of the adrenals if metanephrines are high, blood pressure is high, or a family history of intra-abdominal tumors exists. The risks and benefits of cancer screening in this syndrome have not been established.

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## 25. Peutz-Jeghers Syndrome (PJS)

**OMIM number:** 175200.

**Inheritance pattern:** Autosomal dominant.

**Gene and chromosomal location:** A serine threonine kinase gene, STK11, at 19p13.3.

**Mutations:** Mutations found in five PJS families or individuals, including a deletion, three nonsense mutations, and one acceptor splice site mutation (Jenne et al., 1998).

**Incidence:** One in 120 000 births.

**Diagnosis:** 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). Malignant transformation of these polyps is not common but can occur and may account for the increased risk of colon cancer reported in patient with PJS. Pigmentation begins in infancy or childhood, with 1- to 5-mm melanotic macules, most often on the lips and buccal mucosa but also on the face, forearms, palms, soles, digits, and perianal area and rarely on the intestinal mucosa. The pigmentation may fade with age. Pigmentation of this type occurs in greater than 95% of affected individuals. Definition of this syndrome, proposed by Giardiello et al. (1987), requires histopathologic confirmation of hamartomatous gastrointestinal polyps and two of the following three features: 1) small-bowel polyposis; 2) family history of PJS; and 3) pigmented macules of the buccal mucosa, the lips, fingers, and toes.

**Laboratory features:** None are specific. Clinical genetic testing not yet available.

**Associated malignant neoplasms:** The overall risk of any cancer is estimated at 50%, with 60% of deaths over the age of 30 attributed to cancer in one study (Spigelman et al., 1989). PJS is thought to be associated with breast cancer (bilateral reported), cervical cancer, benign and malignant ovarian tumors (especially granulosa cell cancer), testicular cancer, and pancreatic cancer. Boardman et al. (1998) reported that 26 noncutaneous cancers developed in 18 (53%) of 34 PJS patients, yielding a relative risk for cancer of 18.5 in women and 6.2 in men. In that series, there were 10 gastrointestinal cancers (including seven in the colon with a mean age of 39 years at diagnosis) and 16 extra-intestinal cancers (including six breast cancers with a mean age of 39 years at diagnosis).

**Associated benign neoplasms:** Multiple hamartomatous polyps throughout the gastrointestinal tract, including the ileum and the jejunum, are found in nearly all patients and in the colon and rectum in one third of patients. These polyps range in size from 1 mm to 4 cm. They can also occur in the nose, bronchi, renal pelvis, ureters, and bladder. The polyps may cause symptoms beginning in or before the third decade of life, with the average age at diagnosis being 22.5 years.

Ovarian tumors in affected individuals are "sex cord tumors with annular tubules," which are now considered characteristic of PJS, and are present in almost all affected females.

**Surveillance strategies:** The optimal screening strategy for PJS has not been determined. Substantial morbidity arises from short-gut syndrome, which is related to recurrent intestinal resections for intussusception; therefore, removal of polyps, if feasible, is advised. Upper and lower gastrointestinal endoscopy with polypectomy and small-bowel x-ray examination should be performed when gastrointestinal symptoms develop in an individual at risk for PJS. Surgery has been recommended for removal of symptomatic small-bowel polyps or small-bowel polyps larger than 1.5 cm. Some have advised intra-operative small-bowel endoscopy, when laparotomy is necessary, to remove all possible polyps. After reviewing the PJS literature, Tomlinson and Houlston (1997) have offered the following surveillance

plan for those with known PJS: 1) every other year upper gastrointestinal endoscopy from age 10, sooner if clinically indicated, and removal of any polyp larger than 1 mm; 2) every third year colonoscopy from age 25, sooner if clinically indicated, and removal of any polyp larger than 1 mm; 3) small-bowel follow-through screening from age 10, sooner if clinically indicated; 4) breast surveillance from age 25 with mammography beginning at age 35; 5) annual abdominal and pelvic ultrasound from age 25; and 6) every other year cervical smear.

In addition, we advise regular breast and gynecologic screening for at-risk and affected women; pelvic ultrasound could be considered after the age of 20. Regular testicular examination is advised for at-risk and affected men. Periodic colon cancer screening by colonoscopy after the age of 35 may also be reasonable. Mammography should be offered to at-risk or affected women who are 20–30 years of age and should be repeated every 2–3 years. These recommendations will likely need revision as additional information is gained about the tumor spectrum and risks associated with PJS.

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## 26. Prostate Cancer, Familial

**OMIM numbers:** 176807 (PRCA1); 601518 (HPC1).

**Inheritance pattern:** Autosomal dominant.

**Gene and chromosomal locations:** PRCA1 on 10q25 and HPC1 on 1q24–q25 (see "Comments" section below).

**Mutations:** Germline mutations unknown.

**Incidence:** Prostate cancer is the most common cancer in U.S. males and the number 2 cause of cancer mortality. A segregation analysis (Carter et al., 1992) has suggested that a highly penetrant autosomal dominant mutant gene might account for 9% of all prostate cancers and 40% of early-onset (age <55 years) prostate cancers. The frequency of such a gene is estimated to be 0.003. The estimated cumulative risk for gene car-

riers is 88% by age 85, compared with 5% for noncarriers. Twin studies support the hypothesis that genetic factors are important in prostate cancer (Gronberg et al., 1994).

**Diagnosis:** Based on three or more first-degree relatives with prostate cancer. Men with one second-degree relative with prostate cancer have a relative risk of prostate cancer equal to 1.7. The risk increases with the number and the degree of relatedness of affected family members. For one first-degree relative, the relative risk is 2; for two first-degree relatives, the relative risk is 5; for more than two first-degree relatives, the relative risk is 11. Schaid et al. (1997) reported that cumulative risk for prostate cancer to age 80 in men with a first-degree relative with prostate cancer was 35%, 30%, and 23% when the proband was diagnosed under the age of 60, between the ages of 60 and 70, and over the age of 70, respectively.

**Laboratory features:** Unknown.

**Associated malignant neoplasms:** Prostate cancer. An increased risk of central nervous system tumors has been observed in families exhibiting linkage to the HPC1 allele (Isaacs et al., 1995).

**Associated benign neoplasms:** None known.

**Surveillance strategies:** Regular screening by digital rectal examination, measurement of serum prostate-specific antigen level, and transrectal ultrasound would be prudent in members of high-risk families. The efficacy of this approach is unproven, and appropriate screening intervals and starting ages are unknown. Screening annually beginning at age 40 may be reasonable in high-risk families. The role of random sextant biopsies of the prostate is being explored; clearly, this technique will detect otherwise occult cancers, but whether there is a net benefit to this approach remains to be determined.

**Comments:** The risk of prostate cancer is increased threefold to fourfold in carriers of mutations in BRCA1 and BRCA2, which are associated with hereditary breast and/or ovarian cancer. The family tree should be evaluated for these possibilities. The HPC1 gene locus at 1q24–q25 was identified by linkage analysis of 91 families with at least three affected first-degree relatives (Smith et al., 1996). In that study, prostate cancer susceptibility in 34% of the families was linked to this locus, indicating that other genes accounted for disease susceptibility in the remainder of the families. Prostate cancers developing in families exhibiting linkage to the HPC1 allele are characterized by younger age at diagnosis, higher grade tumors, and more advanced clinical stage when compared with cancers in noncarrier families (Gronberg et al., 1997). A study of treatment outcome in patients with localized prostate cancer suggested that familial prostate cancer may have a more aggressive clinical course than nonfamilial prostate cancer (Kupelian et al., 1997). A confirmatory study (Cooney et al., 1997) suggested that African-American families contributed disproportionately to the evidence of linkage. The gene encoding MAX-interacting protein 1, which has been mapped to 10q25, has been shown to be deleted in some prostate cancers, and mutations have been identified in the retained allele, suggesting a tumor suppressor role for this gene. The androgen receptor gene has also been implicated in prostate cancer pathogenesis; the level of receptor activity increases with decreases in the length of exon 1 CAG and CGC microsatellite sequences in the encoding gene. Microsatellite length is shortest in populations at highest risk of prostate cancer

(African-American men), it is intermediate in intermediate-risk white men, and it is longest in low-risk Asian men.

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## 27. Renal Cell Carcinoma (RCC) (Includes Familial Papillary and Familial Nonpapillary Types, the Latter Also Known as Clear Cell Adenocarcinoma of the Kidney)

**OMIM numbers:** 144700 (nonpapillary); 179755 (papillary).

**Inheritance pattern:** Autosomal dominant.

**Gene and chromosomal location:** MET proto-oncogene at 7q31.1–34 for papillary RCC; 3p14.2 for nonpapillary/clear cell RCC.

**Mutations:** Mutations have been found in four of seven families with papillary RCC (Schmidt et al., 1997). The gene for the nonpapillary/clear cell type has not yet been cloned, but it is thought to be distinct from the von Hippel-Lindau gene, which is involved somatically in most clear cell renal carcinomas.

**Incidence:** Papillary renal cell cancer accounts for 15%–20% of all RCCs and can be sporadic or familial, the proportions of which have not been determined. The incidence of the familial nonpapillary/clear cell type is unknown.

**Diagnosis:** For papillary RCC, either bilateral or multifocal tumors and no family history or a single tumor or multifocal tumors and a first- or second-degree relative with papillary renal cell cancer. Zbar et al. (1995) studied 10 families with hereditary papillary RCC, showing male-to-male transmission. The diagnosis of familial nonpapillary/clear cell RCC is also based on history, family history, and ruling out von Hippel-Lindau disease and tuberous sclerosis.

**Laboratory features:** RCC can be divided into papillary and nonpapillary/clear cell tumors (adenocarcinomas). Clear cell

RCC is characterized genetically by frequent abnormalities of chromosome 3p, whereas papillary RCC does not show 3p loss of heterozygosity. A specific translocation between chromosome X and chromosome 1, t(X;1)(p11.2;q21.2), has been reported (Meloni et al., 1993) as a recurrent rearrangement in papillary RCC. This translocation fuses a transcription factor, TFE3, which is located on the X chromosome, with a novel gene, PRCC, located on chromosome 1.

**Associated malignant neoplasms:** Papillary RCC. Information is too limited at present to state whether or not gene carriers are at increased risks for other site-specific tumors. The following cancers were reported in seven papillary RCC families by Zbar et al. (1994): A gene carrier had stomach cancer at age 45, bilateral papillary renal carcinoma at age 56, and rectal cancer at age 60; other gene carriers had breast cancer (one individual), squamous cell cancer of the lung (one individual), pancreatic cancer (two individuals), and adenocarcinoma of the bile duct (one individual).

In familial nonpapillary/clear cell RCC, cancer occurs at the average age that is 10 years younger than that observed for the sporadic counterpart (which occurs between the ages of 50 and 70 years), and the cancers are often multifocal and bilateral.

**Associated benign neoplasms:** None known.

**Surveillance strategies:** von Hippel-Lindau disease and tuberous sclerosis should be ruled out in cases of nonpapillary/clear cell RCC. We suggest consideration of renal imaging every 1–2 years, beginning at age 35 or at an age that is 10 years younger than the age at which the youngest member of the family was diagnosed with renal cancer. The risks and benefits of cancer screening in this syndrome have not been established.

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## 28. Retinoblastoma

**OMIM number:** 180200.

**Inheritance pattern:** Autosomal dominant.

**Gene and chromosomal location:** RB1 at 13q14. This gene has 27 exons, extending over 180-kilobases (kb) of genomic DNA and producing a 4.7-kb transcript that encodes a protein of 928 amino acids. The RB1 gene product is a negative regulator of cellular growth; it does so by sequestering various nuclear proteins (DNA transcription factors) that are required to move the cell forward through the cell cycle.

**Mutations:** An array of large and small deletions and point mutations that are distributed widely across the gene has been reported. Lohmann et al. (1997) reported finding germline mutations in 17% of patients with isolated unilateral retinoblastoma, including one patient with somatic mosaicism. A rare, low-penetrance mutation (61% disease in gene carriers) has been reported by Bremner et al. (1997).

**Incidence:** Retinoblastomas have an incidence of one in 13 500 to one in 25 000. Approximately 60% are unilateral and nonhereditary, approximately 15% are unilateral and hereditary, and approximately 25% are bilateral and hereditary. Males and females are equally affected. Approximately 20%–30% of individuals with germline mutations have new germinal mutations. The frequency of gene mutation carriers in the general population is unknown.

**Diagnosis:** Based on strabismus and/or leukocoria. However, various atypical presentations have been recorded. Approximately 90% of all retinoblastomas are diagnosed before the age of 3 years, with the average age at diagnosis of 12 months in the case of bilateral disease and 18 months in unilateral disease. Genetic testing, including direct mutation analysis and linkage-based testing, is clinically available.

**Laboratory features:** Chromosomal deletions of 13q14 have been reported in a minority of families and as a mosaic abnormality in some affected individuals, although no deletion is usually evident by examination of G-banded metaphase chromosome spreads or by fluorescent *in situ* hybridization with an RB1-specific probe.

**Associated malignant neoplasms:** Hereditary retinoblastoma is an autosomal dominant disorder with more than 90% penetrance. Approximately 49% of the offspring of bilaterally affected parents develop retinoblastoma, whereas 42% of the offspring of unilaterally affected parents with hereditary disease are affected, suggesting variability in gene penetrance. Age at onset has some predictive value with respect to the development of bilateral disease, with bilateral disease developing in 85% of cases that present under the age of 6 months, in 82% of cases that present between the ages of 6 and 11 months, in 44% of cases that present between the ages of 12 and 23 months, and in 6% of cases diagnosed over the age of 24 months.

Second malignant tumors were originally attributed to radiation induction; however, in some analyses, they occurred with increased frequency both within and outside the field of irradiation in individuals with hereditary retinoblastoma, and they occurred with increased frequency even in those who had not received radiation therapy. The incidence of second nonocular tumors in hereditary bilateral retinoblastoma has been reported as 4.4% at 10 years, 18.3% at 20 years, and 26.1% at 30 years after diagnosis (Roarty et al., 1988). Among those who develop second nonocular tumors, 10% do so by 10 years, 50% do so by 20 years, and 90% do so by 30 years after being treated for retinoblastoma. The second nonocular tumor observed most

commonly was osteosarcoma (risk increased by 500-fold). Fibrosarcomas, chondrosarcomas, epithelial malignant tumors, Ewing's sarcomas, leukemias, lymphomas, melanomas, brain tumors, and pinealoblastomas were also reported. The combination of bilateral retinoblastoma and pinealoblastoma has been referred to as "trilateral retinoblastoma." Moll et al. (1997) reviewed 11 different studies on second primary tumors in patients with retinoblastoma and reported the cumulative incidence of second primary tumors as 15.7% by age 20 years and 19% by age 35 years. Among the second primary tumors, 37% were osteosarcomas, 7.4% were melanomas, 6.9% were soft-tissue sarcomas, and 4.5% were brain tumors; other individual tumor types occurred less frequently.

**Associated benign neoplasms:** Retinomas, benign retinal tumors, and lipomas (Li et al., 1997).

**Surveillance strategies:** According to expert opinion (not controlled trials), high-risk individuals should have an ophthalmologic examination at birth and every 8–12 weeks thereafter up to the age of 2 years. Examination requires pupillary dilation, and the patient may need anesthesia during this procedure. After age 2 years, examinations should be repeated every 6 months until the age of 12 years, and then they should be repeated annually. A high index of suspicion should exist for sarcomas in individuals at risk or who have had retinoblastomas. The role of genetic testing in at-risk individuals should be considered. In patients with a negative family history, the parents and all siblings should undergo a baseline examination. Sometimes a parent will show evidence of a spontaneously regressed tumor (a well-documented occurrence in retinoblastoma), in which case the prognosis and screening guidelines will be modified accordingly. A high index of suspicion for second primary tumors is warranted, but specific screening is not advised. The risks and benefits of cancer screening in this syndrome have not been established.

**Comments:** The following empiric risks of recurrence are used for genetic counseling:

- 1) For offspring of an individual with unilateral disease where the family history is clearly negative and before any affected children have been born, the risk is one in 20.
- 2) For the siblings of an individual with sporadic unilateral disease where the family history is clearly negative, the risk is one in 20.
- 3) For the offspring of an individual with bilateral disease where the family history is positive or negative, the risk is two in five.
- 4) For the siblings of an individual with sporadic bilateral disease where the family history is clearly negative, the risk is one in 10.
- 5) For the additional siblings of an individual with bilateral or unilateral disease where a second member of the sibship is also affected (either unilaterally or bilaterally) but no other relatives are affected, the risk is two in five.

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## 29. Rothmund-Thomson Syndrome

**OMIM number:** 268400.

**Inheritance pattern:** Autosomal recessive.

**Gene and chromosomal location:** Unknown.

**Mutations:** Not yet identified.

**Incidence:** Very rare; around 200 cases worldwide have been reported.

**Diagnosis:** Based on clinical gestalt. Skin atrophy, marbled pigmentation ("poikiloderma"), and telangiectasia, especially of extensor surfaces, begin appearing in the 3rd to 6th month of life; cataracts may develop in the 4th to 7th year. Hypogonadism is observed in 25% of affected individuals, and nail dystrophy is observed in 25%. Short stature and normal intellect are observed. Some individuals have radial ray anomalies, and microdontia may be found.

**Laboratory features:** No consistent findings. Five patients were reported (McKusick, 1994) with clonal and nonclonal cytogenetic rearrangements, often involving chromosome 8, representing acquired mosaicism. There are inconsistent reports of reduced DNA repair after exposure of cells to ultraviolet C and  $\gamma$ -irradiation. Lindor et al. (1996) have reported a normal response to mitomycin C *in vitro*, normal sister chromatid exchange, normal bleomycin-induced breakage, no evidence of microsatellite instability, and normal p53 expression.

**Associated malignant neoplasms:** Among the 200 or so individuals described in the world's literature, eight cutaneous cancers have been reported; they include four squamous cell carcinomas (diagnosed at the ages of 32, 32, 91, and 92 years), two Bowen's disease (diagnosed at the ages of 14 and 49 years), one basal cell carcinoma (diagnosed at age 25 years), and one spinocellular carcinoma (diagnosed at age 32 years).

Approximately 12 individuals with Rothmund-Thomson syndrome have had osteosarcomas reported (tibia, n = 8; calcaneous, n = 1; humerus, n = 2; fibula, n = 1; and femur, n = 2), including an 18-year-old with three metachronous lesions. The other cases were diagnosed at the following ages: 5, 6, 11, 11, 12, 13, 14, 19, 19, 31, and 32 years. One case has been

reported for each of the following: parathyroid adenoma (diagnosed at age 36 years), Hodgkin's "sarcoma" (diagnosed at age 16 years), fibrosarcoma (age at diagnosis unknown), and gastric carcinoma (diagnosed at age 28 years).

**Associated benign neoplasms:** Warty dyskeratosis.

**Surveillance strategies:** None known. There should be an increased index of suspicion for cancer, especially involving the skin and bones. The risks and benefits of cancer screening in this syndrome have not been established.

**Comments:** Reduction of standard chemotherapy doses was required in the siblings reported by Lindor et al. (1996) because of excessive marrow suppression. With no diagnostic criteria or laboratory markers, it is difficult to know if all patients reported have the same disorder or if this group is heterogeneous. Accurate risks for cancer are not known because this disorder may be underdiagnosed on the one hand, and there may be ascertainment bias for reporting the cases with cancer. Lindor et al. (1996) have speculated that Rothmund-Thomson syndrome may be biologically related to, or perhaps even allelic with, Werner's syndrome, the gene for which has been recently cloned.

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## 30. Testicular Carcinoma, Familial

**OMIM number:** 273330.

**Inheritance pattern:** Possible autosomal dominant.

**Gene and chromosomal location:** Gene unknown. Involvement of 12q22 is suggested by cytogenetic studies.

**Mutations:** No information.

**Incidence:** Rare. Surveys have documented a positive family history of testicular cancer in 2%–6% of cases. Standardized incidence ratios were 10.2 for brothers, 4.3 for fathers, and 5.7 for sons.

**Diagnosis:** Based on clinical history only. Bilateral cancers are three to four times more common in familial cases than in nonfamilial cases. The median age at diagnosis is significantly younger in familial cases than in nonfamilial cases. The cumulative risk to a brother of a case patient is reported variably to be 2.2% by age 50 years and 4.1% by age 60 years.

**Laboratory features:** None.

**Associated malignant neoplasms:** Both seminomatous and nonseminomatous germ cell tumors occur in high-risk families. Several families have included females with ovarian germ cell tumors.

**Associated benign neoplasms:** None known.

**Surveillance strategies:** The risks and benefits of cancer screening in this syndrome have not been established. We sug-

gest that monthly testicular self-examination and annual clinical examination plus testicular ultrasound starting 10 years prior to the age at diagnosis of the youngest case in the family may be prudent. The role of tumor markers, such as  $\alpha$ -fetoprotein and human chorionic gonadotropin- $\beta$ , is undefined.

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## 31. Tuberous Sclerosis

**OMIM numbers:** 191100 for TSC1; 191092 for TSC2.

**Inheritance pattern:** Autosomal dominant.

**Gene and chromosomal location:** According to Povey et al. (1994), approximately 50% of families show linkage to TSC1 at 9q34 and the remainder show linkage to TSC2 at 16p13.3. Linkages to both 11q and 12p were reported earlier, but there is a growing consensus that no tuberous sclerosis-associated genes are encoded on either of these latter chromosomes and that the identified sites account for all tuberous sclerosis. The TSC1 gene has 23 exons, encoding a protein called "hamartin." Most reported mutations have been of the protein-truncating type. The TSC2 gene at 16p13.3 encodes a widely expressed transcript whose gene product, "tuberin," shows homology to the guanosine triphosphatase-activating protein GAP3. Wienecke et al. (1995) reported that the loss of tuberin leads to constitutive activation of Rap1, an RAS-related protein. Wilson et al. (1996) reported finding germline TSC mutations in nine of 26 apparently sporadic cases of tuberous sclerosis.

**Mutations:** Various mutations scattered throughout these genes have been reported. Most TSC1 mutations have been truncating in type.

**Incidence:** Estimated at approximately one in 30 000 individuals under the age of 65 years and one in 15 000 under the age of 5 years. Up to 60% of cases represent new mutational disease.

**Diagnosis:** Genetic testing is not yet clinically available. Table 7 shows the diagnostic criteria currently used for the tuberous sclerosis complex (Gomez, 1988).

**Laboratory features:** Linkage-based predictive testing has limited availability. Mutational analysis is not yet available on a clinical service basis.

**Associated malignant neoplasms:** There is a 5%–14% incidence of childhood brain tumors in patients with tuberous sclerosis, of which more than 90% are subependymal giant-cell astrocytomas. Tuberous sclerosis is associated with renal cell cancer, which was diagnosed in three of 139 patients assessed by Cook et al. (1996). (This observation does not imply a known

**Table 7.** Diagnostic criteria for tuberous sclerosis complex (TSC)

Primary features
Facial angiofibromas*
Multiple unguinal fibromas*
Cortical tuber (histologically confirmed)
Subependymal nodule or giant cell astrocytoma (histologically confirmed)
Multiple calcified subependymal nodules protruding into the ventricle (radiographic evidence)
Multiple retinal astrocytomas*
Secondary features
Affected first-degree relative
Cardiac rhabdomyoma (histologic or radiographic confirmation)
Other retinal hamartoma or achromic patch*
Cerebral tubers (radiographic confirmation)
Noncalcified subependymal nodules (radiographic confirmation)
Shagreen patch*
Forehead plaque*
Pulmonary lymphangiomyomatosis (histologic confirmation)
Renal angiomyolipoma (radiographic or histologic confirmation)
Renal cysts (histologic confirmation)
Tertiary features
Hypomelanotic macules*
“Confetti” skin lesions*
Renal cysts (radiographic evidence)
Randomly distributed enamel pits in deciduous and/or permanent teeth
Hamartomatous rectal polyps (histologic confirmation)
Bone cysts (radiographic evidence)
Pulmonary lymphangiomyomatosis (radiographic evidence)
Cerebral white-matter “migration tracts” or heterotopias (radiographic evidence)
Gingival fibromas*
Hamartoma of other organs (histologic confirmation)
Infantile spasms
Definite TSC: One primary feature, two secondary features, or one secondary feature plus two tertiary features
Probable TSC: One secondary feature plus one tertiary feature or three tertiary features
Suspect TSC: One secondary feature or two tertiary features

\*Histologic confirmation is not required *if* the lesion is clinically obvious.

lifetime risk.) The age at diagnosis of renal cell cancer has been reported to be younger than that of sporadic renal cell cancer. Wilms' tumor has been reported in the context of tuberous sclerosis, but whether this is a true association or not is unknown. Hürtle cancer of the thyroid has also been reported.

**Associated benign neoplasms:** Cortical tubers, subependymal nodules, retinal hamartomas, and facial angiofibromas (the latter in 80% of postpubertal patients; also called “adenoma sebaceum”). Cook et al. (1996) reported renal lesions in 85 (61%) of 139 patients. Among these 85 patients with renal lesions, 40 had only angiomyolipomas, 17 had only renal cysts, and 28 had both. The angiomyolipomas were multiple in 91% and bilateral in 84%. Cardiac rhabdomyomas may present prenatally or perinatally. (It is estimated that 51%–86% of cardiac rhabdomyomas may be associated with tuberous sclerosis.) Shagreen patches are present in 54%–55% of affected individuals. Ungual fibromas are usually not present in children under the age of 5 years; however, they are found in 23% of affected children between the ages of 5 and 14 years and in 88% of patients older than 30 years of age. Multiple dental enamel pits in secondary dentition are seen in 71% of patients with tuberous sclerosis, compared with 0.88% in control subjects. Adrenal angiomyolipomas, adrenal adenomas and paragangliomas, pancreatic adenomas, and parathyroid adenomas are also reported.

**Surveillance strategies:** The general management of patients with tuberous sclerosis is beyond the scope of this handbook. Specific cancer screening has not been defined, and the value of recurrent imaging of the head and the kidneys in an individual with known tuberous sclerosis is unknown and perhaps should be reserved for individuals with new signs or symptoms suggestive of a change in the organs. A survey (Gomez, 1988) of 355 patients at the Mayo Clinic showed that 49 were deceased, nine from causes unrelated to tuberous sclerosis, 13 from status epilepticus or pneumonia with severe mental retardation, four from pulmonary lymphangiomyomatosis, one from cardiac rhabdomyoma, one from thoracic artery rupture, 10 from brain tumors, and 11 from renal disease that included two cancers.

**Comment:** Evaluation and care of individuals with tuberous sclerosis require a multidisciplinary approach, involving neurologists, ophthalmologists, dermatologists, geneticists, cardiologists, nephrologists, developmental specialists, pulmonologists, and others.

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## 32. von-Hippel-Lindau (VHL) Disease

**OMIM number:** 193300.

**Inheritance pattern:** Autosomal dominant.

**Gene and chromosomal location:** VHL gene at 3p25–p26, which contains three exons and encodes a 213-amino acid protein product. This protein appears to play a role in the transduction of growth signals generated by changes in ambient oxygen tension.

**Mutations:** In one series of 469 VHL families, 137 distinct mutations were found, including a variety of missense, nonsense, and deletion mutations.

**Incidence:** One in 36000, with nearly complete penetrance by the age of 65 years and an average life expectancy of 49 years. The age at onset of symptoms ranges from 11 to 65 years, with means ranging from 23 to 33 years in different studies.

**Diagnosis:** Based on clinical criteria as follows:

- 1) Central nervous system plus retinal hemangioblastoma  
*or*
- 2) Central nervous system or retinal hemangioblastoma plus one of the following:
  - (a) Multiple renal, pancreatic, or hepatic cysts
  - (b) Pheochromocytoma
  - (c) Renal cancer*or*
- 3) Definite family history plus one of the following:
  - (a) Central nervous system or retinal hemangioblastoma
  - (b) Multiple renal, pancreatic, or hepatic cysts
  - (c) Pheochromocytoma
  - (d) Renal cancer

**Laboratory features:** Mutation analysis is now available on a clinical basis. Linkage analysis is clinically available in suitable pedigrees. In some cases, these tests render clinical criteria unnecessary.

**Associated malignant neoplasms:** Three distinct cancer phenotypes have been identified as follows: 1) renal cell carcinoma without pheochromocytoma, 2) renal cell carcinoma with pheochromocytoma, and 3) pheochromocytoma alone. Malignant renal cell carcinoma 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. The mean age at diagnosis in various studies was 41–45 years (range, 20–69 years). The average age at death from renal cell cancer is 44.5 years. Pancreatic cystadenocarcinoma or islet cell tumors tend to cluster in certain families, where the incidence ranges from 7.5% to 25%. APUDomas (a tumor composed of APUD [amine precursor uptake and decarboxylation] cells) that produce vasoactive intestinal peptide and cause hypercalcemia have been reported. Overall, pancreatic cancer is not common in VHL. Carcinoid has been reported in at least two VHL patients (one in the common bile duct) (Michels, 1987).

**Associated benign neoplasms:** Retinal angiomas may result in visual loss. These angiomas have been detected in children as young as the age of 4 years, but typically they become evident between the ages of 21 and 28 years.

Also found are central nervous system hemangioblastomas, retinal angiomas, and renal cysts and adenomas, as noted above. In addition, pancreatic cysts, which can be multiple and occasionally large, are detected in 9%–29% of patients by computed tomography imaging; pancreatic angiomas or cystadenomas are found in 7% of patients; and hemangioblastomas are rare. Central nervous system 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 symptoms of VHL in 40% of cases and cause more than 50% of the deaths. The average age at the first symptom of hemangioblastoma is 30 years (range, 9–62 years). The location of the hemangioblastomas is cerebellar in 60%–75% of affected individuals, but spinal hemangioblastomas occur in 10%–35% of cases (can be asymptomatic). Supratentorial lesions are rare (rule out metastatic renal cell carcinoma if lesion seen).

Twenty percent to 100% of patients have renal lesions, in-

cluding simple cysts (in 76%, most often multiple and bilateral), hemangiomas (in 7%), benign adenomas (in 14%), and malignant renal cell carcinomas (in 35%–75% in autopsy series, often multiple and bilateral).

Pheochromocytomas occur in 3.5%–17% of VHL patients, but they tend to cluster in certain kindreds; 26%–34% of these lesions are bilateral, with an average age at diagnosis in various studies between 25 and 34 years. Malignant pheochromocytomas are very rare in VHL. Benign adenomas and paragangliomas of the sympathetic chain are infrequently found in VHL.

Epididymal cysts are found in 7%–27% of patients and range in size from 0.5 cm to 2.0 cm. Benign epididymal papillary cystadenomas are found in 3%–26% of males on autopsy series. Hepatic cysts (in 17% of patients), hemangiomas (in 7% of patients), and adenomas (in 3% of patients) have been reported in autopsy series. Angiomas and cysts of the spleen have been reported in 3%–7% of autopsied patients. Endolymphatic sac tumors have been reported to cause hearing loss. In general, cysts and hemangiomas can occur in a wide variety of tissues in rare patients with VHL.

**Surveillance strategies:** We suggest the following guidelines: 1) annual physical examination with neurologic evaluation for signs of cerebellar or spinal cord lesions; 2) annual ophthalmologic examination; 3) red blood cell count for polycythemia (caused by erythropoietin from renal cysts and cerebellar hemangioblastoma); 4) annual urinalysis, urine cytologic examination, urinary metanephrine analysis, and vanil mandelic acid measurement; 5) initial imaging of the central nervous system and the spinal cord by magnetic resonance imaging with gadolinium around age 11 years (the value of further imaging in asymptomatic individuals is unclear; biennial imaging may be reasonable); 6) annual imaging for the kidneys and the pancreas by computed tomography and/or ultrasound beginning no later than age 18 years. The optimal screening program in VHL disease and the risks and benefits of cancer screening in this syndrome have not been established.

**Comments:** All affected patients should have genetic counseling, and evaluation of all first-degree relatives is advised. The age at which screening of at-risk family members can be safely discontinued has not been determined. The VHL locus has recently been shown to be involved in patients with the constitutional chromosome translocation t(3;8)(p14;q24) who have renal cell cancer only.

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## 33. Werner's Syndrome ("Adult Progeria")

**OMIM number:** 277700.

**Inheritance pattern:** Autosomal recessive.

**Gene and chromosomal location:** WRN gene, which encodes a DNA helicase, at 8p12–p11.2 (identified in both Japanese and Caucasians). The gene has 35 exons, and the encoded protein contains 1432 amino acids. Mutations in WRN trigger premature expression of inhibitors of DNA synthesis and inhibitors of the expression of other genes. The net result is early cellular senescence.

**Mutations:** Ten distinct mutations have been reported (Yu et al., 1997); all of these mutations create a stop codon or cause frameshifts, leading to premature polypeptide termination.

**Incidence:** Estimated at one in 50 000 to one in 1 000 000. It may be more common in Japan.

**Diagnosis:** Clinical gestalt. Growth arrests at puberty; cataracts occur in the second and third decades. Premature graying and balding, scleroderma-like changes of the limbs, diminution of muscle mass and of subcutaneous tissue, chronic pressure ulcers over the feet and ankles, premature arteriosclerosis, adult onset diabetes (in 44% of cases), endocrine failure, and localized soft-tissue calcification also occur. The average lifespan is 47 years. Intellect is normal. Old age appearance is evident by age 30–40 years.

**Laboratory features:** No diagnostic finding. Chromosomal variegated translocation mosaicism has been reported (Hoehn et al., 1975). Microsatellite instability is absent.

**Associated malignant neoplasms:** Goto et al. (1996) reported on 34 non-Japanese case patients with WRN (13 from the United States) with 30 cancers and on 124 Japanese case patients with WRN with 127 cancers. The cancers were diagnosed between the ages of 25 and 64 years, except for one 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 feet), nine osteosarcomas, and 14 hematologic disorders. In addition, there were 63 epithelial cancers recorded, including 20 thyroid cancers (10 follicular, eight papillary, and two anaplastic), six gastric cancers, six breast cancers, three hepatocellular cancers, four biliary cancers, and a variety of other tumors reported less frequently.

Among the 30 cases among non-Japanese, there were seven soft-tissue sarcomas, four osteosarcomas, three melanomas, and four hematologic disorders. Eleven nonepithelial tumors were reported, the most notable including seven nonmelanotic skin cancers and two thyroid cancers. The ratio of epithelial (carcinoma) and nonepithelial (sarcoma) cancers in Werner's syndrome is 1 : 1, in striking contrast to the 10 : 1 ratio in the general population.

**Associated benign neoplasms:** Sixteen of the 124 Japanese case patients had benign meningiomas (multiple in only one patient), and seven of the 30 non-Japanese case patients had benign meningiomas (multiple in one patient).

**Surveillance strategies:** The risks and benefits of cancer screening in this syndrome have not been established. On the basis of the new observations of Goto et al. (1996), we suggest that regular clinical surveillance for melanomas (including intranasal examination) and thyroid masses is warranted beginning in adolescence. Regular hematologic surveys may also be useful. A high index of suspicion for neoplasia in general should be maintained.

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## 34. Wilms' Tumor (Nephroblastoma)

**OMIM numbers:** 194070 (WT1); 194071 (WT2); 194090 (WT3).

**Inheritance pattern:** Autosomal dominant.

**Gene and chromosomal location:** At least three different genetic entities are associated with Wilms' tumor, i.e., the WT1 gene at 11p13, a second predisposing locus (WT2) at 11p15.5, and a third locus (WT3) that is suggested by the existence of familial cases with no linkage to the other two sites.

**Mutations:** The WT1 gene has been cloned, and the protein binds p53 and suppresses transcription initiated from the epidermal growth factor receptor 1 and insulin-like growth factor-II promoters. Mutation analysis is not yet available as a clinical test.

Tumor development requires two "hits" to the WT1 gene; one is inherited (germline), and the other is somatic (acquired). Unlike other tumor suppressor genes, which do not manifest a loss of function in the heterozygous state, hemizygoty for WT1 causes developmental anomalies of the genitourinary tract, including cryptorchidism or hypospadias. (Aniridia, which demonstrates a nonrandom association with Wilms' tumor, is due to alterations involving a homeobox gene that is contiguous with WT1.) The cause of the retardation in WAGR (Wilms' tumor–aniridia–genitourinary anomalies–retardation) syndrome is unknown.

Certain point mutations in the zinc-finger domains of WT1 that affect the DNA-binding domains have a dominant negative effect, producing severe genitourinary malformations, with pseudohermaphroditism and mesangial sclerosis of the kidney that may lead to renal failure in early childhood (Drash syndrome).

The gene(s) at 11p15 related to Wilms' tumor predisposition have not yet been clearly identified. Candidate genes in this region include p57<sup>KIP2</sup>, H19, and IGF2.

**Incidence:** Wilms' tumor occurs in one in 10 000 children. Among these, 10%–30% are thought to have a germline mutation in WT1 (one in 30 000 to one in 100 000). Overall, it has been estimated that less than 1% of all cases of Wilms' tumor result from a gene mutation inherited from a parent. Most germline mutations, therefore, are due to new germline mutations.

Aniridia occurs in one in 70 000, but Wilms' tumor occurs in one in 70 children with aniridia.

**Diagnosis:** Ten to thirty percent of affected children with Wilms' tumors present with bilateral or multifocal disease, sug-

gestive of a predisposing genetic lesion. However, it appears that the familial tumor is rare, so the majority of bilateral/multifocal cases appear to represent new mutation dominant disease. Bilateral tumors have an age of onset that is 1–2 years earlier than that of unilateral cancers, and they may be associated with a positive family history for Wilms' tumors. Wilms' tumors are usually seen under the age of 5 years, but they are also reported in young adults. Males and females are equally at risk for Wilms' tumors.

In individuals with a diagnosis of Wilms' tumor, evidence for a genetic predisposition should be carefully sought, i.e., a family history of Wilms' tumor or other embryologic tumor, aniridia, a genitourinary disorder, the presence of multifocal disease, and consideration of Beckwith-Wiedemann syndrome (*see below*).

In 2% of cases, Wilms' tumor arises in the context of the WAGR syndrome, which is a contiguous gene-deletion syndrome incorporating the 11p13 locus.

Wilms' tumor is also seen in association with Beckwith-Wiedemann syndrome, a disorder characterized by hemihypertrophy or generalized macrosomia, enlarged organs (particularly the tongue and the abdominal viscera), umbilical hernia, prominent eyes, posterior helical pits and other craniofacial characteristics, and neonatal hypoglycemia in one third to one half of cases (related to pancreatic overgrowth). A 7.5% incidence of cancer in patients with Beckwith-Wiedemann syndrome has been reported (Scriver, 1995); these cancers include hepatoblastomas, adrenocortical carcinoma, gonadoblastoma, and Wilms' tumor. Beckwith-Wiedemann syndrome is related to complex events involving a second locus on chromosome 11p15. The precise gene or genes have not been determined. On the basis of family studies, Beckwith-Wiedemann syndrome appears to be caused by gene mutations inherited from a carrier mother, by segmental paternal uniparental disomy, or by paternally derived duplications of the 11p15 region. (The underlying theme in this disease is a relative excess of paternally contributed genes in the Beckwith-Wiedemann syndrome-associated region.) The relative contribution of Beckwith-Wiedemann syndrome to all cases of Wilms' tumor is unknown because this condition is underdiagnosed and is not usually diagnosable with currently available laboratory techniques. Fig. 1 shows the relationship of Wilms' tumor to the gene loci and syndrome diagnoses.

**Laboratory features:** None are specific.

**Associated malignant neoplasms:** Wilms' tumor in the case of WT1 mutations; other embryologic tumors in Beckwith-Wiedemann syndrome as noted above. Increased rates of a variety of non-Wilms' genitourinary tumors in first- and second-

degree relatives of children with Wilms' tumor have been reported (Hartley et al., 1994) in a population-based series of 218 children with renal tumors, including 192 with Wilms' tumor, suggesting some common underlying genetic factors even in families without more than one case of Wilms' tumor.

**Associated benign neoplasms:** None known.

**Surveillance strategies:** For Beckwith-Wiedemann syndrome, some have advocated abdominal palpation, abdominal ultrasound, and serum  $\alpha$ -fetoprotein measurement every 6 months until the age of 6 years.

For others believed to be at risk for the development of first or recurrent Wilms' tumors, renal ultrasound every 4–6 months through age 6 years may be reasonable. The risks and benefits of cancer screening in familial Wilms' tumor of any type have not been established.

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## 35. Xeroderma Pigmentosum (XP) and Its Multiple Complementation Groups (A–G)

**OMIM numbers:** 278700 (XPA gene in group XP-A); 133510 (ERCC3 gene in group XP-B); 278720 (XPC gene in group XP-C); 278730 (ERCC2 gene in group XP-D); 278740 (XPE gene in group XP-E); 278760 (ERCC4 gene in group XP-F); 278780 (ERCC5 gene in group XP-G).

**Inheritance pattern:** Autosomal recessive.

**Genes and chromosomal locations:** The genes are involved in excision repair of ultraviolet radiation-induced DNA pyrimidine dimers. XP is genetically heterogeneous. XP-A is on 9q34.1; XP-B is on 2q21; XP-C is on 3p25.1; XP-D is on 19q13.2; XP-E is on 11p12–p11; XP-F is on 16p13.2–p13.1; and XP-G is on 13q32–q33.

**Mutations:** Various mutations have been reported in each of the cloned genes, usually point mutations. Mutation analysis is not available clinically.

**Incidence:** One in 1 000 000 in the United States, one in 40 000 in Japan, and higher where consanguinity is high.

**Diagnosis:** Based on childhood onset of photosensitivity (blistering in 50%) and/or freckling (in 50% by 18 months), with progressive degenerative changes leading to poikiloderma, irregular pigmentation, telangiectasia, photophobia, and early development of skin and eye cancers. Skin changes in sun-exposed areas are evident in 50% of affected individuals by age 18 months, in 75% by age 4 years, and in 95% by age 15 years.

Approximately 20% of reported patients with XP have associated neurologic abnormalities. In a series of 154 neurologically abnormal patients, the following characteristics were reported

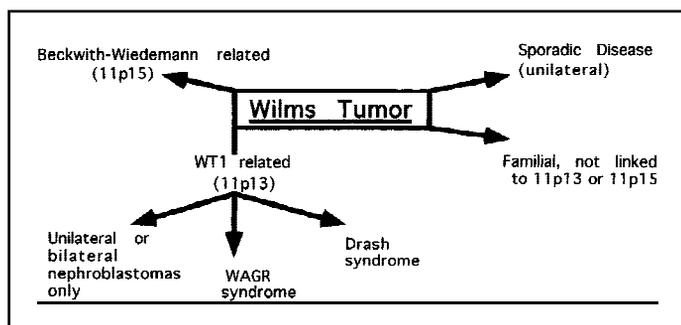


Fig. 1. Depiction of the Wilms' tumor association detailed in the text.

(Scriver et al., 1995): mental subnormality, often progressive (in 80%); microcephaly (in 25%); progressive sensorineural deafness (in 20%); hyporeflexia or areflexia (in 20%); spasticity, late-onset ataxia, and choreoathetoid movements in a few; and abnormal electroencephalogram (in 11%). Other XP features of these patients were not different from the features of patients without neurologic abnormalities. Neurologic abnormalities are present in four of the XP complementation groups and are generally absent in groups C, E, and F.

Recently, complementation studies have assigned a few Cockayne's syndrome patients to the rare XP groups B, D, and G. Cockayne's syndrome is characterized by cachectic dwarfism with microcephaly; premature aged appearance; progressive mental, neurologic, and retinal degeneration; and pronounced photosensitivity, with the onset of symptoms prenatally (type II) or after 6–12 months of normal development (type I).

**Laboratory features:** Cellular hypersensitivity to ultraviolet radiation, with defective DNA excision repair. This hypersensitivity is the basis for laboratory confirmation of XP, which is performed in only a few specialized laboratories. Chromosomal analyses are generally normal; heterozygotes are not detectable.

**Associated malignant neoplasms:** There is a 2000-fold increased frequency of basal cell and squamous cell carcinomas of the skin, often with multiple tumors, by age 20 years. The median age of onset of first skin neoplasm 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 10000-fold.

A 10-fold to 20-fold increased risk of internal neoplasms, including brain tumors, lung cancers, gastric cancers, and leukemias, has been reported.

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

**Surveillance strategies:** Rigorous protection from ultraviolet light exposure; regular examination of the skin and eyes by parents and physicians, with baseline photography and early excision of tumors. Cultured cells from patients with XP are hypersensitive to certain DNA-binding chemical carcinogens, including derivatives found in cigarette smoke and in charbroiled foods. Avoidance of these exposures may be desirable. The risks and benefits of cancer screening in this syndrome have not been established.

**Comments:** Survival is generally reduced because of neoplasms, with a 70% probability of survival to the age of 40 years, which represents a 28-year reduction in lifespan relative to the general population of the United States. Improved survival may be achievable with early diagnosis and modern means of ultraviolet light protection.

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## GLOSSARY

**Complementation:** In genetics, refers to restoration of the wild-type function (normal function) due to the presence of two distinct mutations. If two same-type mutations were present in a cell, the cell would be homozygously defective for the corresponding gene product.

**Exon:** Transcribed region of a gene that is present in mature messenger RNA and that usually contains protein-coding information.

**Germline mutation:** A change in a gene that was present in the zygote (fertilized ovum) and in all subsequent cells arising from that zygote. The offspring of carriers of germline mutations are at risk for inheritance of that mutation.

**Intron:** Transcribed region of a gene that is spliced out in mature messenger RNA and, thus, does not contribute in formation to the final gene product.

**Knudson two-hit hypothesis:** General concept involving tumor suppressor genes, in which both genes must be incapacitated (“hit”) for loss of growth suppressor function to be important. In inherited cancer-predisposing syndromes, such as hereditary retinoblastoma, the first hit is the inherited (germline) mutation, which is present in every cell of the body. The second hit could be a point mutation, a chromosomal nondisjunction, or another event that could occur anytime in a person's life (and would be classified as a somatic mutation).

**Linkage:** Co-inheritance of two or more nonallelic genes; because their loci are in such close physical proximity on the same chromosome, they remain associated after meiosis more often than 50% of the time, the probability for physically unlinked genes.

**Proto-oncogene:** Normal growth-promoting genes that are found in normal eukaryotic cells and are concerned with various aspects of cell division. If amplified, mutated, or rearranged, they may give rise to carcinogenic oncogenes.

**Somatic mutation:** A change in a gene that occurred after conception and that involves only some of a person's cells; e.g., somatic mutations may be found in tumor cells. The offspring of individuals with somatic mutations (i.e., a somatic APC [adenomatous polyposis coli] gene mutation in a tumor) are not at risk for inheritance of that mutation because it does not involve the person's germ cells (egg or sperm).

## Note

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