TABLE 101e-3 CANCER PREDISPOSITION SYNDROMES AND ASSOCIATED GENES

Syndrome	Gene	Chromosome	Inheritance	Tumors
Ataxia telangiectasia	*ATM*	11q22-q23	AR	Breast
Autoimmune lymphoproliferative syndrome	*FAS*	10q24 1q23	AD	Lymphomas
	FASL			
Bloom syndrome	*BLM*	15q26.1	AR	Several types
Cowden syndrome	*PTEN*	10q23	AD	Breast, thyroid
Familial adenomatous polyposis	*APC*	5q21	AD	Intestinal adenoma, colorectal
Familial melanoma	*p16INK4*	9p21	AD	Melanoma, pancreatic
Familial Wilms' tumor	*WT1*	11p13	AD	Kidney (pediatric)
Hereditary breast/ovarian cancer	*BRCA1*	17q21	AD	Breast, ovarian, colon, prostate
	BRCA2	13q12.3		
Hereditary diffuse gastric cancer	*CDH1*	16q22	AD	Stomach
Hereditary multiple exostoses	*EXT1*	8q24	AD	Exostoses, chondrosarcoma
	EXT2	11p11-12		
Hereditary prostate cancer	*HPC1*	1q24-25	AD	Prostate
Hereditary retinoblastoma	*RB1*	13q14.2	AD	Retinoblastoma, osteosarcoma
Hereditary nonpolyposis colon cancer (HNPCC)	*MSH2*	2p16	AD	Colon, endometrial, ovarian, stomach, small bowel, ureter carcinoma
	MLH1	3p21.3		
	MSH6	2p16		
	PMS2	7p22		
Hereditary papillary renal carcinoma	*MET*	7q31	AD	Papillary kidney
Juvenile polyposis	*SMAD4*	18q21	AD	Gastrointestinal, pancreatic
Li-Fraumeni	*TP53*	17p13.1	AD	Sarcoma, breast
Multiple endocrine neoplasia type 1	*MEN1*	11q13	AD	Parathyroid, endocrine, pancreas, and pituitary
Multiple endocrine neoplasia type 2a	*RET*	10q11.2	AD	Medullary thyroid carcinoma, pheochromocytoma
Neurofibromatosis type 1	*NF1*	17q11.2	AD	Neurofibroma, neurofibrosarcoma, brain
Neurofibromatosis type 2	*NF2*	22q12.2	AD	Vestibular schwannoma, meningioma, spine
Nevoid basal cell carcinoma syndrome (Gorlin's syndrome)	*PTCH*	9q22.3	AD	Basal cell carcinoma, medulloblastoma, jaw cysts
Tuberous sclerosis	*TSC1*	9q34	AD	Angiofibroma, renal angiomyolipoma
	TSC2	16p13.3		
von Hippel–Lindau	*VHL*	3p25-26	AD	Kidney, cerebellum, pheochromocytoma

Abbreviations: AD, autosomal dominant; AR, autosomal recessive

Although the Mendelian forms of cancer have taught us much about the mechanisms of growth control, most forms of cancer do not follow simple patterns of inheritance. In many instances (e.g., lung cancer), a strong environmental contribution is at work. Even in such circumstances, however, some individuals may be more genetically susceptible to developing cancer, given the appropriate exposure, due to the presence of modifier alleles.

GENETIC TESTING FOR FAMILIAL CANCER

The discovery of cancer susceptibility genes raises the possibility of DNA testing to predict the risk of cancer in individuals of affected families. An algorithm for cancer risk assessment and decision making in high-risk families using genetic testing is shown in Fig. 101e-6. Once a mutation is discovered in a family, subsequent testing of asymptomatic family members can be crucial in patient management. A negative gene test in these individuals can prevent years of anxiety in the knowledge that their cancer risk is no higher than that of the general population. On the other hand, a positive test may lead to alteration of clinical management, such as increased frequency of cancer screening and, when feasible and appropriate, prophylactic surgery. Potential negative consequences of a positive test result include psychological distress (anxiety, depression) and discrimination, although the Genetic Information Nondiscrimination Act (GINA) makes it illegal for predictive genetic information to be used to discriminate in health insurance or employment. Testing should therefore not be conducted without counseling before and after disclosure of the test result. In addition, the decision to test should depend on whether effective interventions exist for the particular type of cancer to be tested. Despite these caveats, genetic cancer testing for some cancer syndromes already appears to have greater benefits than risks. Companies offer genetic testing for many of the cancer syndromes listed in Table 83-3, including FAP (*APC* gene), hereditary breast and ovarian cancer syndrome (*BRCA1* and *BRCA2* genes), Lynch's syndrome (mismatch repair genes), Li-Fraumeni syndrome (*TP53* gene), Cowden syndrome (*PTEN* gene), hereditary retinoblastoma (*RB1* gene), and others.

Because of the inherent problems of genetic testing such as cost, specificity, and sensitivity, it is not yet appropriate to offer these tests to the general population. However, testing may be appropriate in some subpopulations with a known increased risk, even without a defined family history. For example, two mutations in the breast cancer susceptibility gene *BRCA1*, 185delAG and 5382insC, exhibit a sufficiently high frequency in the Ashkenazi Jewish population that genetic testing of an individual of this ethnic group may be warranted.

As noted above, it is important that genetic test results be communicated to families by trained genetic counselors, especially for high-risk high-penetrance conditions such as the hereditary breast and ovarian cancer syndrome (*BRCA1/BRCA2*). To ensure that the families clearly understand its advantages and disadvantages and the impact it may have on disease management and psyche, genetic testing should never be done before counseling. Significant expertise is needed to communicate the results of genetic testing to families. For example, one common mistake is to misinterpret the result of negative genetic tests. For many cancer predisposition genes, the sensitivity of genetic