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Family Cancer Syndromes: Inherited Deficiencies in Systems for the Maintenance of Genomic Integrity **1**

Huferesh Darbary, Daniel L. Stoler, and Garth R. Anderson

Familial cancer syndromes have revealed important fundamental features regarding how all cancers arise through destabilization of the genome, such that somatic evolution can select for the disruption of critical cellular coordinating and regulatory features. The authors examine those cellular genes and systems whose normal role is to preserve genomic integrity and relate them to the genetic foundations of heritable cancers. By examining how these cellular systems normally function, how family cancer genes are able to affect the process of tumor progression can be learned. In so doing, a clearer picture of how sporadic cancers arise is additionally gained.

Genetic Risk Assessment, Counseling and Testing **19**

Thereasa A. Rich and Mary Salazar

Hereditary cancer risk assessment, counseling, and testing are becoming ever more complex as the understanding of the genetic components of disease grows. The demand for highly trained professionals with expertise in this field, such as genetic counselors, is also growing. Surgical oncologists are likely to encounter patients with hereditary cancer syndromes in their practice and should be able to identify patients appropriate for genetic assessment and counseling.

Thyroid Cancer Genetics: Multiple Endocrine Neoplasia Type 2, Non-Medullary Familial Thyroid Cancer, and Familial Syndromes Associated with Thyroid Cancer 39

Melanie L. Richards

Familial thyroid cancer accounts for 25% of medullary thyroid cancer (MTC) and 5% of non-medullary thyroid cancer. All patients who have familial MTC have one of three variants of multiple endocrine neoplasia type 2 that are defined by specific mutations in the rearranged during transfection (*RET*) proto-oncogene. Patients who have familial nonmedullary familial thyroid cancer most likely have a mutation that is autosomal dominant with reduced penetrance. Thyroid cancer also is associated with a number of familial syndromes. This article focuses on the genetics and management of familial thyroid cancers and the syndromes associated with thyroid cancer.

Genetic Issues in Patients with Breast Cancer 53

Victoria Sahadevan Fossland, Jennifer B. Stroop, Robin C. Schwartz, and Scott H. Kurtzman

Screening for genetic abnormalities is a relatively complex task requiring detailed training and knowledge. Analysis of a person's genetic makeup has implications not only for that individual but also for their progenitors, offspring, siblings, and spouses. There are potential insurance, employment, and other risks regarding disclosure of this information. With proper training, surgeons or nurses with advanced skills can be qualified to conduct this type of initial analysis. Geneticists may be the ideal professionals to counsel patients. In this article, we explore these and other issues. The goal is to provide the surgeon with the information needed to identify patients at risk for carrying identifiable mutations that might lead to the development of breast cancer.

Management of Familial Melanoma and Nonmelanoma Skin Cancer Syndromes 73

Alfredo A. Santillan, Basil S. Cherpelis, L. Frank Glass, and Vernon K. Sondak

The clinical manifestations of hereditary skin cancer syndromes depend upon the interplay between environmental and genetic factors. Familial melanoma occurs in the setting of hereditary susceptibility, with a complex phenotype of early age of onset, multiple atypical moles, multiple primary melanomas, multiple melanomas in the family, and in some instances pancreatic cancer. Identification of individuals who may have a hereditary susceptibility for the development of melanoma is essential to provide an opportunity for primary prevention, and to target high-risk groups for early diagnosis and treatment. Consequently, the surgeon as one of the primary caregivers should be familiar with hereditary skin cancer syndromes and their pathogenesis, diagnosis, management, and surveillance recommendations. This article discusses a practical approach for some of the issues likely encountered by the surgeon in the management of familial melanoma and nonmelanoma skin cancer.

The Recognition and Surgical Management of Heritable Lesions of the Pancreas 99

Michael P. Kim, Douglas B. Evans, Thuy M.Vu, and Jason B. Fleming

Our knowledge regarding the inherited factors that lead to the development of lesions within the pancreas is clearly incomplete. This article addresses clinical issues in patients at moderate-to-high risk for pancreatic malignancy, with special emphasis on the recognition and diagnosis of known genetic syndromes. Using the current available information, the authors attempt to equip the practicing surgeon with critical information to increase clinical suspicion for heritable syndromes and inform specific surgical management. Additionally, this article is meant to encourage the practicing surgeon to participate in the genetic testing/screening, cancer surveillance, and prevention activities of patients who have heritable cancer syndromes and associated pancreatic lesions that require surgery.

Hereditary Colorectal Cancer Syndromes and the Role of the Surgical Oncologist 121

Peter A. Learn and Morton S. Kahlenberg

The expanding understanding of the genetic basis to hereditary colon cancer syndromes is dismantling previously conceived categorizations and shedding light on why those schemes often failed in past. This review highlights evolving concepts regarding the genetic diagnosis and clinical management of the more commonly inherited colorectal cancer syndromes, including a discussion of recently described familial syndromes. This review also addresses clinician responsibilities in recognition of familial syndromes and provision of counseling.

Li-Fraumeni Syndrome: The Genetics and Treatment Considerations for the Sarcoma and Associated Neoplasms 145

Brandi Upton, Quyen Chu, and Benjamin D.L. Li

Li-Fraumeni syndrome is an autosomal dominant disorder first reported by Drs Li and Fraumeni in 1969. Malkin was the first to describe a germline mutation as an underlying defect of Li-Fraumeni syndrome. Cancer risk in mutation carriers has been estimated to be 50% by age 40 and 90% by age 60. Children of affected parents have an approximate 50% risk of inheriting the familial mutation. Functional assays have been established that allow for easy genetic testing for *TP53* mutation. Treatment goals center on early detection and surgical resection of affected organ. Targeted therapy for the *TP53* gene may hold promise for the future.

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Von Hippel-Lindau (VHL) disease is an autosomal dominant inherited tumor syndrome in which a genetic defect in the <i>VHL</i> gene is located on chromosome 3p25. The urologic surgeon is an integral part of the management team for patients who have VHL disease, because patients frequently have multiple urologic tumors. This article presents a cumulative review of the literature regarding the diagnosis and management of urologic tumors in patients who have VHL disease, along with the latest data regarding the genetics and molecular mechanisms of VHL disease.	
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Colin M. Parsons, Robert J. Canter, and Vijay P. Khatri	
Neurofibromatoses are a complex set of genetic diseases with a wide spectrum of clinical manifestations. Life-threatening complications may develop as the result of tumor progression. Surgical intervention is the only effective means of treatment for progressive pain, disfigurement, functional compromise, and malignancy. In the future, molecular advances should allow for the development of targeted therapies to treat patients who have neurofibromatosis in addition to those who have sporadic tumors. Tumor profiling should allow us to guide therapies and predict responses.	
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