

# Contents

<b>Foreword</b>	<b>xi</b>
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Nicholas J. Petrelli

<b>Preface</b>	<b>xiii</b>
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Steven Gallinger

<b>Overview of Colorectal Cancer Genetics</b>	<b>573</b>
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Robert Gryfe

Cancer is a genetic disease in which the clonal accumulation of genetic alterations confers a cell with the malignant characteristics of uncontrolled growth, local invasiveness, and metastatic potential. Studies of colorectal cancer and its precursor lesion, the adenomatous polyp, have served as the cornerstone in advancing knowledge of cancer molecular genetics. The past 30 years have ushered in an era of revolutionary increases in understanding colorectal cancer genetics. In the future, it is hoped that the tremendous recent gains made in understanding colorectal cancer genetics will allow for significant, tailored chemoprevention and treatment of this common malignancy.

<b>Familial Adenomatous Polyposis</b>	<b>585</b>
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James Church

Patients with FAP are guaranteed to have one major abdominal surgery in their life. They are also subject to cancers and benign disorders in other organ systems, some of which can be life threatening. Steering a course through life while avoiding preventable disease and complications of treatment, and maintaining good quality of life is a challenge for health care givers, patients, and their families. A successful voyage calls for clinical cooperation between providers and patients, education and understanding, and expertise and experience. FAP patients and families should be involved in a registry or genetic center, not to the exclusion of local practitioners but to their benefit. In this way the best of care is given and the best of outcomes ensured.

<b>MUTYH-Associated Polyposis and Colorectal Cancer</b>	<b>599</b>
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Malcolm G. Dunlop and Susan M. Farrington

This article reviews the role of defective base excision repair, and MUTYH specifically, in colorectal cancer etiology and discusses the consequences of MUTYH gene defects, with particular emphasis on clinical relevance to

colorectal polyposis, colorectal cancer risk, and appraising the risk of extra-colonic malignancy. Evidence guiding clinical practice, in terms of surveillance recommendations and options for surgical and other prophylactic interventions, is reviewed.

### **The *hMSH2* and *hMLH1* Genes in Hereditary Nonpolyposis Colorectal Cancer**

611

Patrick M. Lynch

Hereditary nonpolyposis colorectal cancer (HNPCC) is the most common inherited colorectal cancer predisposing condition. HNPCC is an important problem for the surgeon because up to 60% of carriers of mismatch repair (MMR) gene mutations develop colorectal cancer (CRC), commonly before age 50 years. When CRC is diagnosed, the surgeon is in the ideal position to order appropriate tumor testing for microsatellite instability or immunohistochemical stains for loss of MMR gene associated protein, if this has not already been done. This article reviews the history of HNPCC, its clinical features, gene discovery, development of clinical genetic workup, and clinical surveillance, with an emphasis on the two major HNPCC genes, *hMSH2* and *hMLH1*. It is not always possible to discuss these specific genes without commenting on the broader problem of HNPCC diagnosis and management.

### **Role of *MSH6* and *PMS2* in the DNA Mismatch Repair Process and Carcinogenesis**

625

Mark A. Jenkins

In comparison with the mismatch repair genes *MLH1* and *MSH2*, the genes *MSH6* and *PMS2* are relatively understudied with respect to cancer risk. However, some recent large studies of data combined from several sources, using analytic methods that appropriately condition on the varying methods of ascertainment, are producing reasonably precise estimates, which can be used for risk estimation in patients. To identify modifiers for risk in such carriers, a goal for epidemiologists to improve the health of carriers, such collaborative studies need to continue and expand to include additional mutation carriers in which lifestyle factors and DNA samples are available for analysis.

### **Familial Colorectal Cancer Type X: The Other Half of Hereditary Nonpolyposis Colon Cancer Syndrome**

637

Noralane M. Lindor

Establishing the Amsterdam criteria, based on pedigrees, was essential for defining hereditary nonpolyposis colorectal cancer (HNPCC) syndrome in such a way that the underlying genetic cause could be identified. It is now known that about half of families that fulfill the original Amsterdam criteria have a hereditary DNA mismatch repair (MMR) gene mutation. These families may be said to have Lynch syndrome. The other half of families with HNPCC has no evidence of DNA MMR deficiency, and studies show that these families are different from families with Lynch syndrome. *Familial colorectal cancer type X* is the name used to refer to the "other half of HNPCC".

**Less Common Colorectal Cancer Predisposition Syndromes** 647

Thomas J. McGarrity and Christopher Amos

A variety of syndromes confer increased risk for intestinal polyp development, outside the more commonly occurring syndromes. Each of these uncommon syndromes predispose to pathognomonic histologies that are uncommonly observed. Accurate diagnosis of these syndromes is contingent on higher-level pathology review, evaluation of signs and symptoms beyond sole consideration of the polyps, and collection of a detailed family history. When a genetic mutation can be identified in the proband, the management of intestinal and extra-intestinal cancer screening can be more appropriately tailored.

**Genome-Wide Association Studies and Colorectal Cancer** 663

Loïc Le Marchand

Genome-wide association studies (GWAS) provide a powerful new approach to identify common, low-penetrance susceptibility loci without prior knowledge of biologic function. Results from three GWAS conducted in populations of European ancestry are available for colorectal cancer (CRC). These studies have identified 11 disease loci that, for the majority, were not previously suspected to be related to CRC. The proportions of the familial and population risks explained by these loci are small and they currently are not useful for risk prediction. However, the power of these studies was low, indicating that a number of other loci may be identified in new ongoing GWAS, and in pooled analyses. Thus, the risk prediction ability of susceptibility markers identified in GWAS for CRC may improve as more variants are discovered. This may, in turn, have important implications for targeting high-risk individuals for colonoscopy screening.

**Genetic Counseling for Hereditary Colorectal Cancer: Ethical, Legal, and Psychosocial Issues** 669

Melyssa Aronson

The impression that genetic testing for an inherited colorectal cancer syndrome involves a simple blood test masks the complex issues that surround this type of testing. This article explores the ethical, legal, and psychosocial implications of genetic testing and the role of genetic counseling through the genetic testing process.

**Genetic Testing for Hereditary Colorectal Cancer** 687

Heather Hampel

This article focuses on genetic testing for hereditary colorectal cancer syndromes. Genetic testing is now available in North America for all of the known hereditary colorectal cancer genes. In addition, most of these tests have improved significantly in the past few years with the inclusion of techniques to detect large rearrangements. As a result, clinicians are in a better position than ever to help families with these syndromes to identify the

underlying genetic cause. This identification will ensure that they receive appropriate management, and will enable their relatives to determine their precise risks and to tailor their cancer surveillance.

**Role of Surgery in Familial Adenomatous Polyposis and Hereditary  
Nonpolyposis Colorectal Cancer (Lynch Syndrome)**

705

Kerrington D. Smith and Miguel A. Rodriguez-Bigas

Surgery remains the mainstay of treatment for patients who develop colorectal cancer (CRC) in the setting of a hereditary CRC syndrome. In patients with a hereditary CRC syndrome, surgery can be prophylactic, therapeutic with curative intent, and, in some cases, palliative. The type and extent of surgical resection in familial adenomatous polyposis (FAP) and in the Lynch syndrome is influenced by differences in the natural history of carcinogenesis between the two syndromes and by the effectiveness of and patient compliance with available surveillance strategies. In this article, the surgical options for the management of patients with FAP and Lynch syndrome are discussed.

**Index**

717