EDITORIAL

Genetic Testing and Early Onset Colon Cancer

See "Germline genetic features of young individuals with colorectal cancer," by Stoffel EM, Koeppe E, Everett J, et al, on page 000.

Although there have been encouraging decreases in the overall incidence of colorectal cancer (CRC) in the United States, a discouraging rise in incidence among those under 50 years has emerged.[1] This increase has ranged from 1.0% to 2.4% annually, and curiously, most of these early onset cases have been localized to the distal colon and rectum. The precise etiologic factors underlying this trend have yet to be elucidated.

Genetic risk factors can predispose to early onset colon cancer, and recognizing these hereditary colon cancer syndromes is critical to the management of affected individuals and their family members. Since the cloning of the APC gene that underlies the familial adenomatous polyposis syndrome in 1991, there has been an explosion in the number of genes (now >20) linked to hereditary colon cancer risk.[2] The best understood are the high-penetrance genes associated with the classic Mendelian syndromes: Lynch and familial adenomatous polyposis. Many other genes that exhibit moderate penetrance are not as well-understood, and the associated cancer risks remain incompletely defined. On a practical level, most known genes associated with increased CRC risk are now captured on gene "panel" tests, although even more comprehensive panels that include genes associated with all cancer types are also available.

Stoffel et al[3] sought to define the frequency of germline genetic alterations in patients diagnosed with CRC <50 years of age by retrospectively reviewing genetic test results at a large academic center. There were 430 individuals who attended a genetics clinic, and 315 underwent routine testing as clinically indicated. The testing strategies included syndrome-specific testing and/or panel testing, and 117 individuals participated in more comprehensive research-based testing. In aggregate, a germline mutation was identified in 20% of patients (85 of 430). Most mutations were associated with the high-penetrance syndromes: Lynch syndrome (58 of 85 [68%]) and familial adenomatous polyposis/MYH-associated polyposis (20 of 85 [24%]). A handful of mutations (7%) were seen in less common and/or moderate penetrance CRC genes: TP53 (n = 2), SMAD4 (n = 2), CHEK2 (n = 1), and POLE (n = 1). One mutation (1%) was identified in a non–CRC-related gene (BRCA1).

Of note, a family history of CRC was elicited in only one-half of all mutation carriers. One-fifth of mutation carriers did not meet National Comprehensive Cancer Network clinical criteria for the relevant syndrome.[3]

This important study reveals that a significant proportion (20%) of individuals with early onset CRC carry a germline cancer predisposition gene. A retrospective review of 193 patients with even younger onset CRC (≤ 35 years) identified a hereditary CRC syndrome in 35%,[4] and 19% had no family history of CRC. A prospective evaluation of 450 individuals with CRC <50 years of age who all underwent comprehensive gene panel testing identified mutations in 16%.[5] In this study, 13% were in genes associated with CRC risk, and nearly two-thirds of these were Lynch syndrome genes, 3% were in unexpected genes not traditionally associated with CRC risk, and 33% would not have met established clinical criteria for genetic testing.

The themes that consistently emerge are that genetic mutations are relatively common in early onset colon cancer, most cases are due to Lynch syndrome, and family history and clinical criteria will miss a significant fraction of cases. What are the implications for clinical practice? First, genetic testing is clearly indicated for early onset CRC. Syndrome-specific testing is appropriate if there is a high degree of confidence for a known syndrome based on family history or tumor testing (ie, immunohistochemistry/microsatellite instability for Lynch syndrome screening[6]). Given that clinical criteria are often unreliable, however, using a CRC gene panel would be sensible in many cases. With this strategy, one must recognize that some moderate penetrance genes such as ATM or CHEK2 are included on the panel even though their precise colon cancer risks and optimal surveillance guidelines are not well-defined in the literature.[2]

Opting for a comprehensive cancer panel instead of a CRC-specific gene panel is reasonable when there are overlapping syndromes under consideration, but unexpected findings become more likely. Among a cohort of 1058 patients with CRC of any age who underwent comprehensive panel testing, 14 (1.4%) had an unexpected mutation in a non-CRC gene such as BRCA1/2, PALB2, or CDKN2A.[7] This figure was higher (3%) among patients with early onset CRC.[5] There is general agreement around the value of incidentally discovering a mutation in a clinically actionable gene like BRCA1/2, because cancer risks are well-defined and risk-reducing measures can be effective.[8]

However, unexpected test results can also present significant challenges. When a mutation is identified in the absence of any corroborating family history, it is uncertain whether the cancer risks may indeed be as high as in families who do exhibit classic features. For example, uncovering a CDH1 mutation associated with the rare hereditary diffuse gastric cancer syndrome in a patient with no family history of gastric cancer would force a difficult discussion of whether to proceed with the recommendation for prophylactic total gastrectomy.

Because of the significant medical and emotional impact that such test results can have on patients and their families, genetic testing is best accompanied by formal genetic counseling. Such services are not widely available, and, even

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Table 1. Genes Associated With Inherited Risk of Colorectal Cancer[a]

Colorectal Cancer Genes	Syndrome
High penetrance	
APC	Familial adenomatous polyposis, attenuated familial adenomatous polyposis
MSH2, MLH1, PMS2, MSH6, EPCAM	Lynch syndrome
MUTYH (biallelic)	*MUTYH*-associated polyposis
SMAD4, BMPR1A	Juvenile polyposis
STK11	Peutz-Jeghers syndrome
PTEN	Cowden disease
TP53	Li-Fraumeni syndrome
POLE, POLD1	Polymerase proofreading-associated polyposis
Moderate penetrance	
ATM	
AXIN2	
CDH1	
CHEK2	
GALNT1	
GREM1	
MSH3	
MUTYH (monoallelic)	
NTHL1	

[a]These genes are commonly included on commercial gene panel tests.

when they are, rates of referral as well as rates of attendance are suboptimal. In a screening program for Lynch syndrome, baseline attendance rates at a genetic counseling session were as low as 32%.[9] Overcoming this barrier is essential for the successful integration of genetics into clinical care.

The number of new genetic risk factors for colon cancer continues to grow,[10,11] and the size of gene panel tests will similarly enlarge. Efforts to precisely define the clinical significance of these discoveries are necessary and ongoing. In the meantime, it is likely that the most common colon cancer syndromes that are highly penetrant have already been identified. Prompt recognition of these syndromes through state-of-the-art genetic testing is feasible, standard of care, and essential to further reduce disease-related morbidity and mortality.

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Conflicts of interest
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