Review Article

Integrating surgery and genetic testing for the modern surgeon

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Abstract: The field of cancer genetics is rapidly evolving and several genetic mutations have been identified in hereditary cancer syndromes. These mutations can be diagnosed via routine genetic testing allowing prompt intervention. This is especially true for certain variants of colorectal, breast, and thyroid cancers where genetic testing may guide surgical therapy. Ultimately, surgical intervention may drastically diminish disease manifestation or progression in individuals deemed as high-risk based on their genetic makeup. Understanding the concepts of gene-based testing and integrating into current surgical practice is crucial. This review addresses common genetic syndromes, tests, and interventions salient to the current surgeon.

Keywords: Breast cancer; familial adenomatous polyposis (FAP); genetic testing; hereditary nonpolyposis colorectal cancer (HNPCC); multiple endocrine neoplasms

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Introduction

Since the discovery of the DNA double helix in 1953, the study of the human genetic makeup has led to numerous breakthroughs in modern medicine. Genetic testing allows the identification of inherited or acquired mutations in a person's genome, which may have a variable impact on health. Importantly, gene mutations are believed to have a significant role in 5–10% of all malignancies. Although many diseases have yet to be addressed through genetic-tailored approaches, cancer genetics is becoming increasingly more prevalent. The last 20 years of genetic research has had a major impact on surgical practice. Several genetic mutations have been identified in hereditary cancer syndromes, and genetic testing can be utilized to diagnose these conditions. For the modern day surgeon, this is especially true for certain variants of colorectal, breast, and thyroid cancers where genetic testing may guide management. Screening of high-risk individuals can lead to a surgical intervention that might drastically diminish the chances of disease manifestation all together. Furthermore, specific genetic phenotypes may aid in optimizing surgical and surveillance protocols. This article highlights the current understanding of hereditary colorectal, breast, and thyroid cancer and the use of genetic testing in the field of surgery.

Familial adenomatous polyposis (FAP)

FAP is characterized by the development of multiple (at least 100 by definition) adenomatous polyps in the colon and rectum, usually beginning during adolescence, and defined as a mutation in the adenomatous polyposis coli (APC) tumor suppressor gene (1). Affecting 1–8 in 10,000 persons, the phenotypic finding of multiple colorectal polyps was initially recognized and first reported in 1721, but the characterization of a condition known as adenomatous polyposis was described in 1881. It was not until 1986 that Herrera *et al.* described a potential link between a deletion in the 5q chromosome and colorectal

polyposis (2-4). Discovery of the *APC* gene was then identified in 1987 on chromosome 5q21–22, and in 1991 it was characterized in detail (5-7).

The clinical disease process begins with adenoma formation within the gastrointestinal tract. Fifteen percent of individuals with FAP will develop polyps by age 10, and 90% by age 30 (8). Polyp emergence is seen on average at 16 years of age but can range from 8 to 34 years (4). Symptomatic presentation may include gastrointestinal bleeding, abdominal pain, or diarrhea, but the majority of patients are asymptomatic. Other polyps including duodenal and periampullary polyps occur in 30% to 100% of patients (9,10). Extraintestinal manifestations of FAP such as mucosal neuromas, soft tissue tumors, and medulloblastomas have also been described (10-12).

The identification of greater than 100 colorectal adenomas is sufficient for clinical diagnosis according to the American College of Gastroenterology. If the disease is suspected, it is important to verify the location, nature, and number of polyps present in the patient. The average age of malignant transformation into colorectal cancer is 42 years, markedly earlier than the average age of 63 years for developing a sporadic case of colorectal cancer. Although, exceedingly rare, the development of colorectal cancer before the age of 10 has been reported in several case reports, with the youngest presentation at 5 years old (13). Early diagnosis can be facilitated by gene based testing to identify patients prior to the development of symptoms or identification of polyps.

Genetic basis of diagnosis

FAP is caused by mutations in a single gene and follows a dominant inheritance pattern with nearly 100% penetrance (8). About 80–90% of patients with a clinical diagnosis of FAP will be found to have an identifiable mutation in the *APC* gene (14,15). The *APC* gene is a tumor-suppressor gene that encodes a large protein of 2,843 amino acids, and a germline mutation in the *APC* gene, as determined through genetic testing, is required for a definitive diagnosis of FAP (11,12,16). Commercially available testing, at clinical and academic laboratories, is readily available. Genetic testing for FAP most commonly involves DNA sequencing but may also be tested for protein truncation. Direct DNA sequencing is the most accurate test but also the most expensive. Large deletions and rearrangements can be identified using southern blot and karyotype analysis through primer annealing to specific genetic fragments. Karyotype analysis or fluorescent *in situ* hybridization can only be used for the largest gene deletions (14).

The American College of Gastroenterology has published the following recommendations for patients with expected or confirmed FAP (13): (I) patients with classic FAP (>100 adenomas) should pursue genetic counseling and genetic testing if they have siblings or children who could potentially benefit from this testing; (II) patients with known FAP or who are at risk of FAP based on family history (and genetic testing has not been performed), an annual flexible sigmoidoscopy or colonoscopy should be performed until a colectomy is deemed by physician and patient as the best treatment; (III) patients with a retained rectum after subtotal colectomy should undergo a flexible sigmoidoscopy every 6–12 months; (VI) patients with oligo-polyposis (<100 colorectal polyps) should undergo genetic counseling, with consideration of APC and MYH mutation testing, and individualized colonoscopy surveillance; (V) upper endoscopic surveillance is required for individuals with FAP due to the presence of upper gastrointestinal polyps.

Genetic basis for treatment

The key consideration in the treatment of a patient with FAP is the timing and type of surgery performed. Prophylactic surgery is the mainstay of treatment since 5% of patients with FAP develop colorectal carcinoma by age 20, with most patients developing colorectal cancer by age 40. Family history and patient preference may guide timing of surgery, but it is often deemed appropriate shortly after the time of diagnosis (8).

From the late 1940's until the 1970's, colectomy with ileorectal anastomosis or total proctocolectomy with end ileostomy were the surgical management options available to patients with FAP. In 1978, the restorative proctocolectomy was described and was used extensively for prophylactic treatment. This involves a staged procedure in which a proctocolectomy is completed with creation of an ileal reservoir. The subsequent stages ultimately result in an ileal pouch anal anastomosis. In patients with a diseased rectum, rectal preservation is avoided. However, in patients with limited rectal involvement who are willing to undergo lifelong screening every 6 months, total colectomy and ileorectal anastomosis is an option (14).

Reported cumulative incidence of rectal cancer is

about 13% at 26 years post-colectomy in FAP (17). A number of factors are associated with an increased risk of subsequent rectal cancer: presence of more than 100 rectal polyps, a retained rectal segment greater than 10 to 15 cm, inadequate endoscopic follow-up, and colon cancer at the time of colectomy (8). Additionally, the APC mutation loci can determine the risk of developing rectal cancer following surgery (18). Patients with a polyp-free rectum have been stratified into mild, intermediate, and severe risk categories. Those considered severe have a mutation between codons 1,250 and 1,464, especially codon 1,309 of the APC gene. The mild category has a mutation in the extreme ends of the APC gene and in the alternatively spliced exon 9. The intermediate category captures the remaining genome mutations (19). A cumulative risk for a secondary proctectomy following initial surgery is 10%, 39%, and 61% with APC mutations classified as mild, intermediate and severe, respectively (19). Mutation loci and the clinical presentation are crucial in counseling patients and selecting the appropriate surgical intervention for patients with FAP.

Hereditary nonpolyposis colorectal cancer (HNPCC)

HNPCC is the most common hereditary colorectal cancer. HNPCC was first described in 1913. An associated polyposis phenotype is absent in HNPCC. Two phenotypic variants of HNPCC have been described: Lynch syndromes I and II (20). Lynch syndrome I families manifest only colon cancer. Lynch syndrome II families manifest colon cancer in addition to endometrial (most commonly), ovarian, gastric, small bowel, liver and biliary tract, upper urologic tract, and/or central nervous system cancers. The development of either colorectal or endometrial cancer in HNPCC patients occurs between the ages of 39 to 46 (21). HNPCC occurs in 1–2 in 1,000 individuals, and of these 70–90% of individuals develop colorectal cancer, accounting for 10–15% of colorectal cancer overall.

The clinical criteria necessary for identifying a family as an HNPCC kindred were first established by an international collaborative conference in Amsterdam in 1990 and then later revised in 1999 (22). However, a proportion of individuals at risk for HNPCC were still missed, leading to the creation of the Bethesda criteria as an alternative screening system (23,24). Newer screening tools have also been developed and are available as online calculators: MMRpredict, MMRpro, PREMM.

Genetic basis for diagnosis

HNPCC is caused by in autosomal-dominant mutation in DNA mismatch repair genes leading to microsatellite instability (MSI). Microsatellites are regions of repetitive nucleotide sequences. DNA base substitutions, insertions and deletions in these regions result in dysregulation of the cell cycle and ultimately lead to carcinogenesis. MSI can also be caused by de novo hypermethylation of MLH1 gene promoter and is seen in 20% of sporadic cancer (25). Screening for MSI or DNA mismatch repair is the first step to diagnosis. Screening for MSI is performed by identifying the presence of at least two of five mismatch repair proteins (mononucleotide markers BAT25, BAT26, D2S123, D5S346, D17S250) in the tumor (26). Alternatively, immunohistochemistry evaluation of tumors showing loss in expression of MLH1, MLH2, MSH6, and/or PMS2 proteins can be used to screen for deficiency in DNA mismatch repair. Both have been shown to be equally effective at screening for Lynch syndrome, but immunohistochemistry is more feasible and widely available (27). A positive screen indicates the need for further germline analysis for MSH2/MLH1 gene abnormalities.

The American College of Gastroenterology recommends screening for mismatch repair deficiency in all newly diagnosed colorectal cancers using either MSI or immunohistochemistry. Tumors that demonstrate loss of MLH1 should undergo further BRAF testing (BRAF mutations are almost never present in HNPCC). Confirmatory genetic testing for MLH1, MSH2, MSH6, PMS2, and EPCAM genes should be performed in individuals who show evidence of mismatch repair in the absence of BRAF mutation, have a known family mutation associated with HNPCC, meet the Amsterdam or Bethesda criteria, or have a greater than 5% risk of HPNCC based on other screening methods (MMRpro, MMRpredict, PREMM) (13). Meeting these pretest criteria enhances the likelihood of an actionable result.

Genetic basis for treatment

Similar to FAP, genetic confirmation of HNPCC requires more frequent and earlier screening for colorectal cancer since malignancy is more aggressive than sporadic cancers and can develop within 2 years of a negative colonoscopy. A Finnish study showed that screening HNPCC families with colonoscopy at 3-year intervals decreased mortality by 65%

due to the early detection of colorectal cancer (28). The American College of Gastroenterology recommends those patients with positive genetic testing, or those at risk when genetic testing is unsuccessful, should undergo colonoscopy every 2 years beginning at age 20–25 years, until age 40 years, then annually thereafter (13,29).

Individuals who have difficulty with colonoscopy, do not wish to be regularly screened, or have a high prevalence of colon cancer in their family may elect to undergo surgical intervention (13). Prophylactic subtotal colectomy with ileorectal anastomosis can be offered but is rarely performed for patients with HNPCC. To date, no study has compared outcomes of prophylactic surgery versus surveillance. However, the risk of metachronous colorectal cancer with partial colectomy is eliminated if a subtotal colectomy is performed (30,31). Furthermore, younger patients may benefit from total proctocolectomy and ileal pouch anal anastomosis given the increased occurrence of metachronous colorectal cancer with age (25). Although segmental colectomy with adequate surveillance remains an option it should typically be reserved for elderly patients or those that cannot tolerate a subtotal colectomy due to the increased lifetime risk of developing a metachronous colorectal cancer.

BRCA

Breast cancer is the most common malignancy and second leading cause of cancer-related death in women in both the US and Europe. In the US, breast cancer accounts for over 230,000 cases each year and is responsible for over 40,000 deaths (32). Approximately 20–30% of patients have a family history of the disease. However, only 5–10% of patients have a mutation in a major breast cancer susceptibility gene (33).

Of the women with definitive genetic mutations, the majority of cases result from mutations in *BRCA1* and *BRCA2*. *BRCA1* is located on chromosome 17 and was the first major breast cancer associated gene discovered in 1990 using linkage analysis in families with suggestive pedigrees (34). *BRCA2* was mapped to chromosome 13 in 1994 (35). Women who carry a *BRCA1 or BRCA2* mutation have a 60–80% lifetime risk of developing breast cancer (36). Both cohorts have an increased risk for ovarian cancer with a greater risk in *BRCA1* mutation carriers. Additionally, *BRCA2* families carry an increased risk of male breast cancer, prostate cancer, and pancreatic cancer (37,38). Over the last 2 decades, these genetic mutations have drawn extensive attention in the media.

Genetic basis of diagnosis

Genetic testing for *BRCA1* and *BRCA2* mutations is now a commercially available option for women with a family history suggestive of a genetic mutation. As with all genetic testing, a counseling session should precede the test in which the complexities of genetic testing and the potential emotional and financial ramifications of test results are discussed. The information obtained from testing will be maximized by first testing a family member affected with breast or ovarian cancer, or both. If the affected person does not carry a mutation, testing an unaffected relative is unlikely to be informative.

Current guidelines from the National Comprehensive Cancer Network (NCCN) recommend genetic counseling and testing for hereditary breast cancer in the following high risk individuals: breast cancer at age 50 years or younger, bilateral breast cancer, triple-negative (estrogen receptor negative, progesterone receptor negative, Her2Neu negative) breast cancer, breast cancer occurring at any age when close relatives have breast/ovarian/pancreatic cancer, breast cancer with Ashkenazi Jewish ancestry, male breast cancer, women with breast cancer who have a known mutation for a breast cancer susceptibility gene within the family, and women with a history of ovarian cancer (39).

Prior to 2013, there was only one company in the US with commercially available BRCA testing, making the testing cost prohibitive for many. However, in June 2013 the Supreme Court ruled to allow other entities to offer testing for BRCA mutations, bringing down cost and increasing testing availability. Many companies now offer multi-gene panels. The most comprehensive of these is BRAC Analysis Large Rearrangement Test (BART). Panel testing has the ability to test for multiple cancer genes in patients that may test negative for a BRCA1/2 mutation using traditional methods. However, many of these panel genes are variants of unknown significance that make it challenging for patients and providers to interpret. Less familiar BRCA mutations may be discovered without a thorough understanding of the clinical implications. Nevertheless, an increased use of panel testing has lead to updated NCCN recommendations to now include adjusted screening protocols for ten additional genetic mutations aside for BRCA1/2 (40).

Genetic basis for treatment

According to the NCCN guidelines, women with *BRCA1*

and *BRCA2* mutations should have an annual MRI at age 30 or mammogram if MRI is unavailable starting at age 25. Commonly patients will alternate surveillance imaging (MRI and mammogram) every 6 months to meet this guideline. After the age of 75, continuation of screening should be determined on an individual basis (40).

Several risk-reducing interventions exist for BRCA patients. A prophylactic bilateral mastectomy has shown to decrease the lifetime risk of breast cancer up to 90% (41-43).

Moreover, nipple-sparing mastectomy has not shown any additional cancer risk in this patient population (44), but patients require lifelong screening and should be counseled accordingly prior to surgery (40). Bilateral salpingo-oophorectomy reduces the risk of ovarian cancer by 83% and combined with bilateral mastectomies reduces the risk of breast cancer by 95% (43,45). Typically it is recommended for patients to undergo such prophylactic measures by age 35–40. However, if there is a strong family history of ovarian cancer or childbearing is complete, earlier intervention is recommended (45). For patients electing not to pursue surgical intervention, the use of selective estrogen receptor modulators and aromatase inhibitors remains a chemopreventive, non-surgical option. Tamoxifen use for 5 years leads to a 50% and 62% reduction in breast cancer risk in women with a moderate to high risk of developing breast cancer and those that are *BRCA2* carriers, respectively (46,47). It has not been shown to have a beneficial effect for carriers of *BRCA1*, likely because *BRCA1* carriers commonly develop estrogen receptor-negative tumors.

Treatment of hereditary breast cancer is similar to that of sporadic breast cancer. The exception to this is women with early stage breast cancer. Women with a localized breast cancer are often candidates for breast-conserving therapy (lumpectomy combined with radiation therapy). However, similar to the prophylactic guidelines, treating women that are *BRCA1* or *BRCA2* carriers, who present with an early stage cancer, with a bilateral mastectomy has been shown to significantly decrease mortality (48).

MEN2

Multiple endocrine neoplasia (MEN) syndromes are autosomal dominant disorders that present with tumors occurring in two or more endocrine glands. MEN type 2 (MEN2) is composed of three variants (MEN2A, MEN2B, and FMTC), but all uniformly present with an increased risk of medullary thyroid carcinoma (MTC) (49). MEN2A accounts for 80% of hereditary MTC. Patients typically develop MTC or pheochromocytomas and more rarely develop parathyroid tumors. MEN2B accounts for 5% of hereditary MTC with patients developing MTC and pheochromocytomas. This variant is also often associated with a marfanoid habitus and mucosal neuromas (49). FMTC is not associated with any additional endocrine tumor, solely manifesting as MTC. This accounts for 15% of hereditary MTC.

Genetic basis of diagnosis

A mutation in the *RET* protooncogene is responsible for MEN2. This 21-exon gene located on chromosome 10 encodes a membrane-bound tyrosine kinase receptor. MEN2 patients have mutations involving exons 8, 10, 11, 13, 14, 15, and 16 (50). Variations in specific mutation loci have been found to correlate with tumor age of onset, aggressiveness of tumor biology, and overall phenotypic presentation.

Any patient with newly diagnosed MTC should undergo *RET* mutation testing. Interestingly, 50% of sporadic MTC tumors will have a *RET* mutation. However, diagnosis of this syndrome requires a germline mutation. Additionally, testing should be offered to first-degree relatives of individuals with known mutations. Finally, there is a known association with both Hirshprung's disease and cutaneous lichen amyloidosis, thus infants presenting with these disorders should be tested as well (51). Screening for pheochromocytoma and hyperparathyroidism, as discussed below, is critical in determining the sequence of treatment.

A targeted gene detection approach is the most cost effective screening method used for families with known mutation loci. When the specific mutation is unknown a two tier approach is performed, where first an attempted detection of a known mutation in exons 10, 11, 8, 13, 14, 15, and 16 is carried out and if a positive result is not obtained reflex sequencing of the entire *RET* gene is performed (51). Whole gene sequencing is currently the most expensive testing method.

Genetic basis for treatment

MTC is considered an aggressive cancer which is often bilateral and multi-centric requiring a total thyroidectomy and central lymph node dissection (52). Plasma levels of calcitonin and CEA serve as good markers of tumor persistence or recurrence of MTC following resection.

Early prophylactic total thyroidectomy to prevent MTC

is recommended in known carriers of the mutation. Because MTC metastasizes rapidly, early prophylactic treatment is imperative (53). Original guidelines recommended a prophylactic thyroidectomy between 5 and 10 years of age in MEN2A and FMTC families. However, the latest American Thyroid Association guidelines recommend thyroidectomy as early as a few months of life up to 5 years of age depending on the specific mutation present and corresponding plasma calcitonin levels. In patients with hereditary MEN2B, prophylactic thyroidectomy should occur by 6 months (51).

Pheochromocytomas in MEN2 often occur in the fourth decade of life, and present as benign, bilateral masses. Screening for pheochromocytoma with plasma or urinary metanephrines in addition to MRI imaging is required prior to thyroidectomy for MTC in MEN2A patients (52). If identified, adrenalectomy (laparoscopic or open) with preoperative alpha-adrenergic blockade must be performed prior to thyroidectomy (50). Additionally, annual screening for pheochromocytomas in patients with MEN2A and FMTC should begin at age 20, and in MEN2B patients it should start at age 8 (52).

Primary hyperparathyroidism is a less rare occurrence seen in some MEN2A patients. It is diagnosed concurrently with MTC in the presence of mild hypercalcemia, elevated PTH, and/or enlarged parathyroid glands. Primary hyperparathyroidism is managed via resection of the enlarged parathyroids at the time of thyroidectomy, with preservation of a small volume of parathyroid tissue (52). As discussed above, screening for and management of pheochromocytomas must precede neck surgery.

Discussion

It is evident that genetics plays an important role in the field of surgery. There is a clear benefit for genetic testing which continues to revolutionize the surgical management of hereditary colorectal, breast, and thyroid cancer. As the field of genetics evolves, the role for prophylactic surgery will expand. Interventions tailored towards a patient's individual genetic makeup will likely aid in adjuvant post-operative care as well.

The field of cancer genetics is rapidly evolving and panel testing is now readily available for rapid analysis of multiple genes. Use of panel testing can be of tremendous importance for screening patients that might be at high-risk for certain malignancies. This would allow the implementation of an intervention, whether surgical or medical, before phenotypic manifestation of disease, thus drastically impacting prognosis. However, the increasing number of commercially available genetic tests that are both affordable and accessible to the public will likely result in a surge in patients undergoing genetic screening who fall outside of these high risk groups. It remains unclear what impact this will have on the healthcare system.

Recently, direct-to-consumer (DTC) genetic testing has been marketed to the public, providing genetic information directly to the consumer with little to no interaction with a medical professional. Concerns regarding how to interpret the data obtained from these genetic tests and the implications of such information on patients, healthcare providers, and the healthcare system remain (54). A survey of customers from two DTC companies found that none of the participants received a positive test for a highly penetrant cancer susceptibility gene, and the majority of individuals did not change their lifestyle based on their test results (55). A systematic review examining primary care providers' knowledge, opinion, and use of genetic testing demonstrated the majority of providers were proponents of genetic testing, specifically for cancer risk. However, most providers felt their knowledge was lacking in determining when to order specific tests and how to interpret the results (56). Given this information, it seems unlikely that medically untrained consumers will be adequately suited to interpret the plethora of genetic data provided to them. Ultimately, adherence to pre-screening guidelines is paramount for optimization of genetic testing, interpretation of results and guiding surgical therapy. Maintaining evidence-based approaches towards surgical care will uphold the utility of genetic testing and role for surgical management of various hereditary oncologic diseases.

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Footnote

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