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Abstract

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Developing Optimal Decision Matrices for Determining Who Is and Who Is Not a Proper Candidate for Genetic Testing

All decision-making begins with the selection of subjects who are clinically affected, usually but not always straightforward. Difficult cases include those with a phenotype mildly suggestive of attenuated FAP, such as patients undergoing screening colonoscopy and found to have 10 to 20 adenomas. If no family history is present, such a presentation might indicate the colonoscopy and found to have 10 to 20 adenomas. If no family history is present, such a presentation might indicate the presence of MYH-associated polyposis or “MAP” in which case evaluating the MYH gene will be more informative than testing the APC gene. Cases without any appreciable polyp burden generally point to HNPCC and are characterized by early onset and/or right-sided colorectal cancer, commonly with mucinous, poorly differentiated histology and “tumor-infiltrating lymphocytes” or “Crohn’s” reaction, multiple primary cancers involving colon or selected associated sites (endometrium, other gastrointestinal tract, sebaceous skin tumors, uroepithelial tumors). A family history of similar features greatly strengthens the likelihood of HNPCC and of a MMR mutation being detectable. In practice, the presence of the much more liberal Bethesda guidelines provide a threshold for testing that increases the sensitivity of the next screening measures, but at the cost of lowered specificity.

Whether FAP, one of its variants, or HNPCC is being considered, it is always helpful to have access to and to review as much family history information as possible. Although the presenting clinical features for a particular patient may be compelling, properly targeted decision-making can only benefit from the opportunity to assess the presence or absence of patterns of disease expression within the family. Obtaining a detailed family history at the time of initial interview helps establish the presence or absence of a pattern. Depending on the nuances of this history, a case may or may not be made for taking the additional step of trying to retrieve records from additional relatives. Because such an undertaking is beyond the scope of most clinical practices, the perceived need for such work may constitute an additional argument in favor of referral to a “full-service” genetic counseling program.

In all likelihood, the most controversial questions have to do with HNPCC, specifically, where to set the cut-point for consideration of performance of at least MSI and/or immunohistochemical testing of tumor tissue, as opposed to “merely” recommending more intensive clinical surveillance, as for “positive family history, not otherwise specified.” The Bethesda guidelines actually do a good job of this, although such liberal criteria for MSI, such as age below 50, are likely not acted on with any regularity in clinical practice. Considerably greater awareness of both the liberality of these guidelines and the ready availability of appropriate testing is warranted. Once a decision has been made to consider such testing, the key, incompletely resolved issue is whether to do sequential or parallel MSI/immunohistochemistry or, in selected cases (unequivocal Amsterdam Criteria family), skip these and go straight to mutational testing. The National Comprehensive Cancer Network guidelines recommend the use of either MSI or immunohistochemistry of all four commonly involved MMR genes (hMLH1, hMSH2, hMSH6, hPMS2) when tumor tissue is available. When evaluable tissue is not available, direct mutation testing is regarded as an appropriate alternative, but only if Amsterdam Criteria are met. The National Comprehensive Cancer Network does not address the issue of whether there might be circumstances in which mutational testing may be considered, notwithstanding normal results of immunohistochemistry, MSI, or both. Pathologic mutations are rare in these situations and decision-making in such a circumstance must certainly be tailored individually and upon the advice of truly expert consultation.

In the case of HNPCC, it is known from population studies that even the rather broad Bethesda guidelines do not identify every case of colorectal cancer in which MSI is present and a pathologic germ line mutation is found (15, 16). However, because it is probably not practical to conduct MSI or

| Table 1. Relevant colorectal cancer screening practice guidelines |
| Society | Guidelines |
| American Cancer Society | Guidelines on screening/surveillance |
| National Society of Genetic Counselors | Genetic cancer risk assessment and counseling |
| American Gastroenterology Association | Hereditary colorectal cancer and genetic counseling |
| New Zealand Guidelines Group | Surveillance and management of groups at increased risk of colorectal cancer |
| American Society of Colon and Rectal Surgeons | Practice parameters FAP/HNPCC |
| Institute for Clinical Systems Improvement | Colorectal cancer screening |
| U.S. Preventive Services Task Force | Screening for colorectal cancer: recommendations and rationale |
| Several other sources representing interest groups and organizations with published practice guidelines (some labeled as such and others not) | Clinical practice guidelines |
| National Comprehensive Cancer Network Clinical Practice guidelines (see http://www.nccn.org) | Genetic testing for colon cancer |
| American College of Medical Genetics/American Society of Human Genetics | Policy update—genetic testing of cancer susceptibility |
| American Society of Clinical Oncology | Follow-up care in HNPCC (28) |

NOTE: Available at the National Guideline Clearinghouse web site (http://www.guideline.gov/); for additional information, search on “colon cancer”.

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immunohistochemical studies on every case of colorectal cancer, good clinical judgment must be called upon to determine who should be considered for mutational testing (17).

### Educating and Marketing to Providers and Consumers

However effective it may be to follow an algorithm for selecting and testing patients for inherited colorectal cancer susceptibility, the patient must present for such evaluation. This may be the single greatest challenge in accomplishing the goal of genetic diagnosis in all who would benefit from such testing. HNPCC, FAP, Peutz-Jeghers syndrome, and juvenile polyposis syndrome are all rare diseases. In the case of classic FAP, Peutz-Jeghers syndrome, and juvenile polyposis syndrome, clinical presentation is most often diagnostic. In such cases, the diagnosing clinician should have no trouble determining the clinical diagnosis, even if the patient has no grasp of the significance of the condition or its straightforward genetic basis. The challenge to the clinician is the need to extend management beyond the individual patient and to provide for genetic counseling and testing. Strictly speaking, genetic counseling and testing are not required for disease management. Rather, genetic counseling and testing provide the basis for identifying family members at risk, accomplishing genetic diagnosis in these individuals, and arranging proper surveillance. Tenuous barriers exist, even in the most straightforward of situations. Because the diseases are rare, the individual practitioner will rarely know which laboratory performs what diagnostic test. Referral to a specialty center with genetic counselors who routinely deal with such patients will generally suffice, but the clinician must first be willing and able to make the referral. For this process to work, the patient and family must appreciate the importance of submitting to such an evaluation. A genetics evaluation may be necessary for making an appropriate diagnosis in individuals with suspicious, yet subtle features, as in attenuated FAP and in HNPCC. The World Wide Web could be instrumental in providing guidance to both providers and patients (Table 2). For example, the National Guideline Clearinghouse1 offers a well-indexed and curated list of guidelines for diseases, including familial colorectal cancer. Detailed recommendations for management (extending from recognition of suggestive clinical pictures, through genetic counseling and testing, to clinical surveillance) have been provided by a Gastrointestinal Consortium Panel (18) comprised of members of the American Gastroenterology Association, American College of Gastroenterology, and American Society of Gastrointestinal Endoscopy. Similar guidelines have been promulgated by the National Comprehensive Cancer Network (19), American Cancer Society (20), American Society of Clinical Oncology (21), and American Society of Colorectal Surgery (22).

As an example of the content of clinical practice guidelines, consider those of the National Comprehensive Cancer Network. Among the various cancer management guidelines is a set that pertains to colorectal cancer screening, including details for approaching patients with known or suspected inherited susceptibility to colorectal cancer. These guidelines are more detailed than many other organization guidelines and are most familiar to the current author, who served on the screening guideline development committee. In general, these guidelines very much mirror our approach to any given patient in the clinic. One begins with the presenting circumstance, whether colorectal cancer (typically early onset) or adenomas (typically multiple). One then tries to identify the patient’s goal in seeking counseling and to collect additional background information (e.g., status of affected and unaffected relatives). A provisional clinical diagnosis and recommendation for consideration of a formal genetic counseling session is made. A genetic counselor, usually with the assistance of a clinician having an interest in such disorders, obtains additional information and makes a recommendation for or against genetic testing, influenced by the patient’s wishes. Algorithms exist for FAP, attenuated FAP, and HNPCC. Due to the rarity of Peutz-Jeghers and juvenile polyposis syndromes, no algorithm is provided; referral to a specialty center is recommended.

### Delivering and Interpreting State-of-the-Art Genetic Testing

After a patient has been identified as definitely or possibly having polyposis or HNPCC susceptibility, referral for genetic counseling can be properly initiated. Identifying a gastroenterologist, colorectal surgeon, medical oncologist, or medical geneticist in one’s region who has a specific interest in these conditions is challenging; thus it may be convenient to identify genetic counselors. The National Society of Genetic Counselors’ web site3 enables a simple search within a specified radius of a zip code of interest and is narrowed by area of specialization, in this case “cancer.” A search beginning with the Google entry

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1 http://www.guideline.gov/
2 http://www.nccn.org/
3 http://www.nsgc.org

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### Table 2. Selected web sites with information on hereditary colorectal cancer, genetic testing, and counseling

<table>
<thead>
<tr>
<th>Web site</th>
<th>Information</th>
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<tbody>
<tr>
<td><a href="http://www.guideline.gov/">http://www.guideline.gov/</a></td>
<td>Lists annotated practice guidelines</td>
</tr>
<tr>
<td><a href="http://www.CGAICC.com">http://www.CGAICC.com</a></td>
<td>Collaborative Group of the Americas on Inherited Colorectal Cancer</td>
</tr>
<tr>
<td><a href="http://www.nsgc.org">http://www.nsgc.org</a></td>
<td>National Society of Genetic Counselors</td>
</tr>
<tr>
<td><a href="http://www.insight-group.org">http://www.insight-group.org</a></td>
<td>International Society for Gastrointestinal Hereditary Tumors</td>
</tr>
<tr>
<td><a href="http://www.genetests.org">http://www.genetests.org</a></td>
<td>Lists available tests, laboratories, and disease-specific clinical and testing updates</td>
</tr>
<tr>
<td><a href="http://www.cancer.gov/cancertopics/pdq/genetics/colorectal/healthprofessional">http://www.cancer.gov/cancertopics/pdq/genetics/colorectal/healthprofessional</a></td>
<td>Updated synthesis of current literature on inherited colon cancer</td>
</tr>
</tbody>
</table>
“National Society of Genetic Counselors” quickly generated a list of 12 cancer genetic counselors in the Los Angeles area, all with e-mail addresses and phone numbers listed. Once a counselor is identified, a query regarding services provided, ideally directed by a thumbnail sketch of the case under consideration, generally leads to an appropriate referral. Other websites that can lead to resources for colon cancer genetic services include the Collaborative Group of the Americas for Inherited Colorectal Cancer,4 with 15 affiliated centers in the United States and one center in Canada, and the International Society of Gastrointestinal Hereditary Tumors.5 The National Cancer Institute also has a helpful listing, which can be found at its web site.6 Finally, the American College of Medical Genetics provides a list of geneticists, accessible at the ACMG web site.7

Providing Preventive Health Services, Including Endoscopic and Other Surveillance

It is widely accepted that intensive endoscopic surveillance is appropriate for the familial colorectal cancer syndromes. Key decision points involve the point at which, short of invasive cancer, prophylactic surgery should take place. The threshold for prophylactic colectomy differs dramatically in FAP, the hamartomatous polyposes, and HNPCC. In FAP, even a minimal rectal adenoma burden may warrant early prophylactic colectomy. Proctectomy and ileal pouch construction may be warranted at the same surgery, depending on rectal adenoma burden. However, many surgeons are willing to wait until there is more frank colonicoscopic evidence of adenoma progression, with a trial of sulindac or celecoxib in the meantime (see below). In the case of Peutz-Jeghers and juvenile polyposis syndromes, management must be even more individualized, as the polyph burden is much more variable, and the risk of dysplasia and cancer in the hamartoma considerably lower than in FAP. Many such patients can be managed indefinitely with colonoscopic and enteroscopic (due to risk of small bowel polyps) polypectomy.

The issues are even more complicated in HNPCC. If cancer is diagnosed, one controversy is whether a standard segmental resection or subtotal colectomy should be done. Surgical opinion is divided. One view is to favor the smallest resection possible, along with careful endoscopic follow-up. The other view is to favor abdominal colectomy and ileorectal Anastomosis, as the rate of second primaries is high, and colonicoscopic miss rates can reach 10%.

In the case of patients without previous cancer resection, adenomas found in the course of surveillance pose another challenge. The endoscopist’s bias is to aggressively tackle any adenoma that is found. With advances in endoscopic mucosal resection techniques, this could include large, flat, right-sided adenomas that would until recently have required surgical resection (23). It is very important that the patient understand the issues and options in such cases. One approach (mine) is to merely sample large polyps that would otherwise require endoscopic mucosal resection. Once invasive cancer is reasonably excluded, the pros and cons of both surgical and colonoscopic approaches can be presented, with second opinions encouraged. Even if the lesion can be safely and completely removed at colonoscopy, it is important that a surgeon familiar with HNPCC be “on the case.” The patient is reminded that adenomas are commonly very flat and rapidly progress to cancer, leading to the problem of interval cancer (i.e., missed cancers occurring between even frequently schedule colonoscopies).

The issue of “pure prophylaxis” is even more vexing (24). The possibility of missed or interval cancer must be weighed against the risks and long-term adverse effects of colectomy, as well as the fact that as many as 20% to 30% of HNPCC mutation carriers will not develop colorectal cancer, perhaps even without the benefit of screening and polypectomy.

Developing Chemoprevention Strategies, Including New Clinical Trials

Rightly or not, FAP has come to serve as a common proving-ground for the clinical evaluation of agents believed to have promise in the prevention of colorectal adenomas. Virtually every trial whose aim has been the reduction in recurrence of sporadic adenomas had a predecessor trial in FAP. This has been the case with the use of nutritional supplements (fiber, vitamins, calcium), as well as pharmacologic agents, most notably nonsteroidal anti-inflammatory drugs, including aspirin. A nonselective nonsteroidal anti-inflammatory drug (sulindac) and two selective cyclooxygenase-2 inhibitors (celecoxib and rofecoxib) have shown efficacy, with celecoxib receiving U.S. Food and Drug Administration approval for adjunctive use in FAP. An excellent review has been provided by Hawk et al. (25). FAP has been a good model because, despite its rarity, a given patient can be easily and quickly evaluated for quantitative evidence of adenoma regression. A few similar trials have been conducted in HNPCC, but its rarity and the relative infrequency of adenomas (compared with FAP) have required larger samples.

Future studies in FAP can be expected to follow the pattern of previous trials: an agent showing preclinical promise and preliminary safety in phase I or other human experience is offered for use in FAP. A sample of 40 to 80 patients with FAP is chosen, as this is the number of patients generally required to show a ≥20% reduction in adenoma burden, compared with placebo, over an interval of 6 to 12 months, in patients with measurable residual adenoma burden. Trials could involve patients with prior colectomy with ileorectal anastomosis, intact colons, and/or duodenal adenomas. Again, adenoma regression is the usual end point. Trials involving true prevention in FAP would, of necessity, involve children and take much longer to conduct, as the end point (i.e., time to adenoma formation) is quite variable and may take years, even without intervention, in a given patient (26). Trial designs can involve prevention of adenoma “recurrence”, but ablation and “clearance” of polyps in an anatomic segment that has historically shown evidence of high polyp formation are required (27).

Recruitment of eligible patients for clinical chemoprevention trials poses the greatest logistic challenge, due to the infrequency of disease and the need for a requisite adenoma burden. Most early trials were single institution studies, but more

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4 http://www.CGAICC.com  
5 http://www.insight-group.org  
6 http://www.cancer.gov/search/geneticsservices/  
7 http://www.acmg.net/
recently, multicenter trials have been reported. To quickly carry out trials according to the rather generic designs described above, studies will need to be conducted on a multicenter basis and/or marketed directly to patients. A “cooperative group” approach holds the greatest promise.

Conclusion

Numerous sets of practice guidelines focus on the diagnosis and management of inherited cancer susceptibility, and the algorithms that have been developed are quite consistent. The Santa Monica Consensus Development Group on Early-Stage Colorectal Cancer has often broached the issue of whether a given practice guideline is considered a “floor” or a “ceiling.” In other words, in codifying a standard of care, does a particular set of guidelines attempt to summarize a minimal acceptable practice or enunciate the ideal level of practice that is achievable with existing technology? Whether limited to genetic counseling and testing, as dealt with here, or more broadly to staging, surgery, and chemotherapy for early-stage colorectal cancer, the sense seems to be that existing standards are set fairly high, on the one hand, but that practice in both the community and academia fall short of such standards. Our challenge therefore is to identify the key elements of practice that must be upgraded and to develop measures for enabling such standards to be met. Because this is a new field, knowledge of existing practice(s) in genetic counseling for colorectal cancer is lacking, but would be a good place to start. Subsequent attention could then be drawn to measures for educating practitioners and setting benchmarks for performance.

References

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