Current Approaches in Hereditary Nonpolyposis Colorectal Cancer

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Abstract
This article emphasizes the central role of tumor-based testing for microsatellite instability followed by performance of genetic counselor–driven germline mutation testing in hereditary nonpolyposis colorectal cancer (HNPCC). Suitably aggressive colorectal neoplasm surveillance is shown to be critical. Limitations of the evidentiary base for extracolonic screening are conceded, with some cautious suggestions for possible strategies notwithstanding the lack of data. Advances in chemoprevention have been made in both familial adenomatous polyposis (clinical trial data favoring eicosapentaenoic acid) and HNPCC (controversial aspirin data). For various reasons, however, no agent or combination of agents has yet come into routine use in either condition, with further trials underway or being designed for both conditions. (JNCCN 2012;10:961–967)

Background
This update of a similarly titled paper appearing in JNCCN in 20061 emphasizes clinical trends in the diagnosis and management of inherited colorectal cancer (CRC) susceptibility that have since emerged, been reinforced, or been reversed. In most respects it reflects the position of the NCCN Colorectal Cancer Screening Panel, of which I am a member. However, this article discusses some emerging trends that may yet not be well established. As a formulator of clinical practice guidelines, the NCCN panel seeks to be in the forefront while trying to embody best practices that are currently clinically feasible and achievable.

This article emphasizes the central role of tumor-based testing for microsatellite instability (MSI), followed by performance of genetic counselor–driven germline mutation testing, in patients with hereditary nonpolyposis colorectal cancer (HNPCC)–related tumors, also known as Lynch syndrome. Suitably aggressive colorectal neoplasm surveillance is shown to be critical. Limitations of the evidentiary base for extracolonic screening are conceded, with some cautious suggestions for possible strategies notwithstanding this lack of data.

Advances in chemoprevention have been made in both familial adenomatous polyposis (FAP; clinical trial data favoring eicosapentaenoic acid) and HNPCC (controversial aspirin data). For various reasons, however, no agent or combination of agents has yet come into routine use in either condition, with further trials underway or being designed for both conditions.

Background
At the time of writing a “current approaches” summary of clinical practice for inherited CRC predisposition in 2006, the notion of identifying high-risk patients from among the mix of patients presenting with CRC or for average-risk screening seemed more a promise than a reality. In the intervening years, I have become somewhat more optimistic that clinical practices are beginning to embrace the approaches outlined herein.

The story surrounding patients with multiple adenomas, those suspected of having FAP, has not been as dramatic as the HNPCC controversies. Recent interest has focused on developing an appropriate threshold for genetic testing of patients with adenoma counts falling short of the classic FAP burden, such as 10 to 15 adenomas over a lifetime. Clinical decisions, of course, must be
made for those with or without adenomatous polyposis coli (APC) or mutY homolog (MYH) gene mutations. Polyp burdens short of those indicating surgical intervention may be found in the course of screening otherwise “average-risk” patients. In these cases, roles for enhanced imaging (chromocolonoscopy) and chemoprevention must at least be considered.

The newest phenomena, serrated polyps and serrated polyp-“osis,” are only starting to be given serious attention by the NCCN panel, partly because 1) familial occurrence of serrated polyposis is exceedingly rare; 2) no responsible gene has been identified that would account for these cases (much less for nonfamilial serrated polyposis, which is the more typical); and 3) clinical management of solitary serrated polyps and serrated polyposis is on a very uncertain footing. This last point reflects the very tentative embrace of serrated polyps as cancer-associated lesions, given their historical treatment as a variant of hyperplastic, and therefore clinically unimportant, polyps. Because no definite genetic basis for serrated polyposis has been identified, it is not discussed further, but it has been addressed recently elsewhere.²,³

Key Research Since 2006
Clinical practice appropriately lags at least a few years behind the research that provides a foundation for paradigm shifts. NCCN has reacted to key research publications only when evidence shows that they 1) support a change in current practice; 2) have been validated, when appropriate; and 3) seem to be cost-effective and thus feasible in markets with increasingly limited resources. I have chosen to highlight a handful of papers that have truly broken new ground, provided critical proof of principle, or otherwise given a needed validation to suspected but unproven approaches. This list is somewhat personal and necessarily selective. Although I do not wish to imply that nothing really new has occurred in FAP, most of the important new work has been in the HNPCC arena.

Chemoprevention
Some interesting new developments have occurred in the field of FAP and HNPCC chemoprevention. One recently published trial used eicosapentaenoic acid (EPA) as a free fatty acid derivative (EPA-FFA) in subjects with FAP.⁴ A reduction in adenoma burden of approximately 30% was seen, a magnitude of effect similar to that observed with the various nonsteroidal anti-inflammatory drugs (NSAIDs), such as sulindac, celecoxib, and rofecoxib. The trial is significant because EPA seemed to be less toxic than NSAIDs, and therefore the opportunity seems to exist to use EPA as one component of a potential combination.

What is also notable about this study is that despite a good safety profile and efficacy akin to that of NSAIDs, EPA-FFA was not granted accelerated approval by the FDA. This did not seem to have much to do with the merits or demerits of EPA-FFA but rather seemed to reflect a new perspective on the part of the FDA regarding the standard for new drug approval. Several anticancer (including chemopreventive) agents had failed in follow-up studies to achieve anticipated measures of clinical benefit after receiving accelerated approval.² In other cases, their makers had not shown due diligence in the conduct of these confirmatory trials. The FDA has indicated that it will no longer offer an accelerated approval pathway for new drugs in the same manner that it had previously. What this means, not just for EPA-FFA but also for any other promising chemopreventive agent, is that any clinical trial that hopes to lead to FDA approval will need to meet the much more stringent test of “clinical benefit” up front.

In response to the tougher FDA standard for regular new-drug approval, some in the field of FAP clinical chemoprevention have undertaken to formulate FAP disease end points that would meet the emerging FDA guidelines. No more will a specified percent reduction in adenoma burden in short-term trials be sufficient for approval. One personal anecdote may help illustrate this seemingly subtle but important point. Shortly after accelerated FDA approval had been given for use of celecoxib as an adjunct to surgery/endoscopy in FAP, I was giving a presentation to a clinical audience about the trial that led to this approval. On commenting on the 30% short-term reduction in adenoma burden shown by the trial, a surgeon pointed out that a patient with 1000 adenomas would still need surgery if the tumor burden were reduced to 700. I never did have a fully satisfactory answer to this challenge. It seems that a reduction in cancer risk and/or mortality is preferred. In the case of FAP, these are virtually unachievable. Therefore, the question, not yet formally posed, is:
what measures of FAP disease severity would, if impacted in a sufficiently favorable fashion, constitute a real clinical benefit? Therefore the stage is set for development of a staging system for colorectal polyposis, somewhat akin to the so-called Spigelman stage for duodenal adenomatosis.6

Regression from one stage to a lower stage, or delay in time to progression from one stage to another, might be regarded as appropriate measures of clinical benefit. Reduction in need for polypectomy could be another potential measure. Because there has been remarkably little public commentary about the impact of the FDA actions on clinical trial development, the comments here must be considered tentative. Other perspectives are invited in the interest of properly framing an overdue, yet critical, debate on the appropriate standards for determining chemoprevention benefit.

Meanwhile, some important, though controversial, work has been done in the chemoprevention of HNPCC. A trial that was initially negative and disappointing “turned positive” on longer-term examination.7 Over the past decade, a predominantly European group of clinical investigators, led by Sir John Burn, completed the Concerted Action Polyp Prevention II (CAPP II) trial.8 A factorial design was used to investigate the effects of aspirin (at the relatively high dose of 600 mg/d), resistant starch, both, and neither in more than 1000 patients with HNPCC, most with a genetic diagnosis. The trial end point was adenoma incidence over an interval of 3 or more years. Drop-out rate was approximately 20%. Initial results were entirely disappointing, showing no difference in adenoma incidence in the aspirin, starch, and starch-plus-aspirin arms, and in the pooled data.

However, these investigators continued to observe the study subjects for several more years, involving follow-up colonoscopy and recording of historical and current aspirin use. Over a longer time frame of 5 or more years, it became apparent that there was a clear and significant separation in risk of not only CRC but also some extracolonic cancers.7

Based on the more promising long-term data, the CAPP II investigators are undertaking a CAPP III trial, with the goal of finding the optimal dose of aspirin for adenoma/cancer prevention in HNPCC. The large-scale and long time frame of the study should lend itself to various nested and drop-in investigations, perhaps including the addition of agents that may complement aspirin.

HNPCC Diagnosis

Controversy remains over the best approach for evaluating patients with CRC for possible HNPCC. A clear consensus exists among clinical experts that newly diagnosed CRCs should be tested for evidence of MSI, whether using a PCR-based assay or, more commonly and conveniently, immunohistochemistry (IHC). Clinical practice guidelines, such as those from NCCN9 and the Evaluation of Genomic Applications in Practice and Prevention (EGAPP) working group,10,11 take this position. The controversy surrounds the threshold for testing. Most agree that a liberal application of the revised Bethesda Guidelines12,13 should be a standard of clinical practice. But even such a low threshold for testing (any diagnosis < 50 years of age or any CRC if multiple or associated with any family history of HNPCC-spectrum tumors) may still miss some HNPCC. Thus, some would argue for truly universal MSI testing of all new CRCs, reckoning that even the large proportion of non-HNPCC MSI-positive cases (sporadic, MSI-high CRC from epigenetic hypermethylation of the hMLH1 promoter, and also typically showing BRAF mutation) are worth detecting because of differences in prognosis and response to adjuvant therapies that include 5-FU.14 This is the position of the EGAPP.15

The various possible approaches have been determined through cost-effectiveness analysis, modeling various workup strategies according to assumptions about yield and cost that are clearly stated, if otherwise debatable. Mvundura et al.16 concluded that the most cost-effective strategy is testing all new CRCs using IHC, with BRAF mutation used to exclude false-positives (from loss of staining for MLH1), followed by germline testing of MMR gene implicated by the IHC testing. Ladabaum et al.17 reached virtually the same conclusion using a similar analytic strategy.

It is further generally agreed that any practice or program that undertakes to perform MSI/IHC tumor testing must be prepared to routinely offer genetic counseling to patients with informative tumor testing. Strictly speaking, use of a genetic counselor is not required for either tumor testing or germline mutation testing. That said, the clinician performing tumor and germline testing without the benefit of a genetic counselor must be held to high standards of familiarity with clinical testing laboratories and their practices, and have an adequate knowledge-base regarding intricacies of testing and its limitations. Anyone arrang-
ing mutational testing must be willing to address the key points included on informed consent checklists,\textsuperscript{18} even though written consent is generally not required for either tumor or germline testing. These issues are emphasized to underscore my personal preference that a genetic counselor experienced in HNPCC counseling be involved from start to finish if possible. This is for the sake of having the most well-informed patient and to allow busy practitioners to make the best use of limited time in patient encounters.

Most population studies have relied on tumor-based HNPCC workup strategies, with endorsement by cost-effectiveness analyses. However, one study concluded that a priori risk-modeling, not requiring any MSI/IHC of tumor tissue, can also prove cost-effective. Relying on the PREMM(1,2,6) model developed at Dana-Farber Cancer Center,\textsuperscript{19,20} Dinh et al.\textsuperscript{21} performed a modeling analysis in which a priori risk-based testing fared well, with comprehensive mutational testing considered cost-effective at a 5% level of probability for mutation detection. Although performed by an independent organization and supervised by a panel of well-known experts, the analysis was sponsored by a commercial entity (Myriad Genetics, Salt Lake City, UT) that is engaged in comprehensive genetic testing.

Most of the efforts to improve HNPCC detection have focused on MSI testing or IHC as a surrogate for MSI as the key first step in screening patients most likely to carry mismatch repair mutations. Improvement in the detection of germline mutations in patients found to have MSI has not been dramatic. Probably the most clinically relevant recent advancement has been the discovery and evaluation of the clinical role of mutations in the epithelial cell adhesion molecule (EPCAM) gene.\textsuperscript{22,23} EPCAM is located just upstream from the hMSH2 gene. Germline mutations in EPCAM cause downstream silencing of hMSH2. This becomes relevant in patients with clinically suspected HNPCC (or who otherwise have loss of hMSH2 expression on IHC), but in whom no germline mutation in hMSH2 is detected. As many as 25% of these cases have been found to be caused by germline mutations in EPCAM.\textsuperscript{24} Clinical testing for EPCAM is now available as a reflex response to nondiagnostic hMSH2 testing. Interestingly, families with EPCAM mutations seem to have a phenotype that is mainly limited to CRC, with extracolonic HNPCC tumors being relatively uncommon.\textsuperscript{25,26}

HNPCC Screening

Screening recommendation for colorectal and other neoplasms associated with HNPCC have not changed much in recent years, and there are few new data brought to bear on the matter. Recent studies have shown a worrisome rate of interval cancers despite frequent colonoscopy, whereas others have suggested that risk of these interval lesions may be reduced through the use of enhanced mucosal imaging. A German consortium found, in 1126 individuals undergoing 3474 colonoscopies, that although only 5% of 43 tumors detected on follow-up examination were stage III or worse, 19 of these were detected at intervals of less than 1 year.\textsuperscript{27} This reinforces the conventional wisdom favoring intervals of 1 to 2 years between colonoscopies, even when no adenomas are detected.

Recognizing that colonoscopy surveillance in HNPCC commonly results in the detection of flat adenomas, measures to detect these adenomas at the earliest possible endoscopically manageable stage must be considered an appropriate goal. In the interest of evaluating measures for enhanced detection of flat adenomas, several trials have compared standard white light with use of indigo carmine dye spray. The one trial showing no particular advantage to the use of dye spray\textsuperscript{28} involved a protocol that required at least a 20-minute withdrawal of the colonoscope from the cecum in the standard white light arm, which is 3 times as long as the currently recommended minimum for screening of the colon.

One study in the United Kingdom focused on the potential advantages of narrow band imaging (NBI) compared with white light colonoscopy.\textsuperscript{29} In this trial, 62 patients with genetic or clinical HNPCC diagnosis were examined with high-definition white light followed by a second examination with NBI. One or more adenomas were found in 17 patients (27%) on initial white light pass, and NBI yielded additional adenomas in 17 (27%). Overall, one or more adenomas were found in 26 patients (42%) in the course of both white light and NBI examination. With respect to flat adenomas only, the proportion detected during NBI (9 of 21; 45%) was significantly greater than that found with white light (3 of 25; 12%).

In a French series, Lecomte et al.\textsuperscript{30} evaluated 36 patients with genetic diagnosis of HNPCC. Conventional white light colonoscopy was performed.
followed by an indigo carmine chromoendoscopy. White light identified 25 lesions in 13 patients. Chromoendoscopy identified an additional 45 polyps in 20 patients; mostly flat and hyperplastic. However, 11 additional adenomas were detected in the right colon of 8 patients, and 8 of these lesions were flat. Thus, chromoendoscopy significantly increased detection of adenomas in the proximal colon.

In one series, 114 German patients who were MMR mutation carriers or from an Amsterdam Criteria–positive family (90% with prior colonoscopy), back-to-back white light colonoscopy was followed by indigo carmine chromoscopy (n = 47), whereas in a second phase, NBI was followed by chromoscopy (n = 62). In the first series, 13 adenomas, mainly flat, were detected on repeat NBI colonoscopy after 7 had been detected with white light. In the second series, 39 additional adenomas were found with chromoscopy after initial detection of only 11 polyps with NBI. Incidentally, a high number of hyperplastic (presumably including sessile serrated) polyps were also detected only with indigo carmine dye spray.

As with screening in average-risk populations, colonoscopy is not the only CRC screening to have been considered. Tremendous recent interest has been devoted to CT colonography (CTC). Although enthusiasm for CTC in HNPCC would be reduced by the subtle, flat nature of the adenomas that commonly occur and by the cumulative radiation exposure in patients requiring frequent examination, some data are available. Renkonen-Sinisalo et al. performed both colonoscopy and CTC on 78 mutation-positive subjects. A total of 37 polyps or malignancies were found in 28 subjects. Most polyps were diminutive. Per-patient sensitivity of CTC for any lesion was 0.25 to 0.29, with specificities of 0.82 to 0.76. CTC sensitivities of 0.6 to 1.0 and a specificity of 0.96 were found for more clinically significant polyps larger than 1 cm. Based on these limited numbers, CTC was regarded as having an acceptable accuracy for significant lesions, but detection of small polyps was less satisfactory.

**Extracolonic Surveillance in HNPCC**

Very few hard data show any benefit from extracolonic screening in HNPCC. Largely because of the relative infrequency of extracolonic tumors, prospective yield from screening would require a large, long-term, and reasonably well-organized program. To these limitations one must add the lack of validated measures for screening in other increased-risk settings. Therefore, for example, in thinking about the notion of ovarian cancer screening in women with HNPCC, one would look to screening yield in other settings. In hereditary breast-ovarian cancer, some data exist and are disappointing.

In a series comparing yield of transvaginal ultrasound and endometrial biopsy, Gerritzen et al. evaluated 100 women with a clinical diagnosis of HNPCC (colorectal or other HNPCC-spectrum tumor in the setting of typical family history). In all, 285 surveillance visits were the source of data. In the course of 64 visits, endometrial samplings were performed and yielded 3 atypical hyperplasias and 1 endometrial carcinoma. This yield compared favorably with the 1 atypical hyperplasia and 2 endometrial carcinomas detected in 28 patients sampled for abnormal surveillance results (pelvic exam, transvaginal ultrasound, CA 125) in 221 visits. No interval carcinomas were detected on follow-up. Ovarian cancer detection through transvaginal ultrasound was limited to 1 stage IIIC case.

Recommendations by the NCCN CRC Screening Panel are conservative for any surveillance of at-risk organs beyond the colorectum and endometrium (including, arguably, transvaginal ultrasound for ovarian cancer notwithstanding known poor yield). The panel could find no trial data to actively support upper gastrointestinal evaluation.

**Conclusions**

In 2007, a survey by Wideroff et al. indicated that a large proportion of specialists in relevant fields, such as medical oncology, gastroenterology, and surgery, were not aware of the clinical availability of mutational testing for HNPCC. Although this has hopefully improved in recent years, no more recent data exist. My concern, based anecdotally on conversations with clinicians in academia and the community, is that there is a persistent inability to routinely use the simple tool of IHC for the proteins associated with the MMR genes. In some cases this is because the tumor material is at another institution, in the case of previously operated patients. In these cases one would have to address the logistics of retrieving these tumor blocks, but this is a routine undertaking.
In other cases, the issue is that the local pathology department has not yet embraced IHC for HNPCC detection. Here, too, the issue is simply that of making a decision to add such a service or, in the case of low-volume laboratories, send out slides to a reference laboratory. But penetration of MSI testing, typically with IHC, is likely increasing significantly as a result of the studies noted earlier.

Mutation testing in HNPCC is still performed far less often than it is in familial breast cancer, in which the frequency of the disease and informativeness of testing are roughly equivalent. The reasons are not entirely clear, but likely relate to differences in patient awareness and advocacy, and lack of a programmatic approach on the part of providers. Because the process for selecting subjects for MSI testing is nuanced, setting the threshold for testing very low (ie, testing all patients with CRCs, or at least all those < 50–55 years) would eliminate many of the challenges surrounding decision-making. Once MSI testing is performed, the results readily drive the performance of germline mutation testing, at least when one is familiar with the algorithm for doing so. Here, early reliance on qualified genetic counselors, or similarly qualified professionals, obviates the need for personal familiarity with the details and pitfalls of the workup strategy.

Gastroenterologists in particular must be more aggressive at the level of both screening and diagnosis. Requesting MSI testing at initial tumor biopsy remains an uncommon practice, but has the best potential to exploit the entire window of opportunity for diagnosing HNPCC preoperatively, even if the performance of or findings from germline mutation testing are not readily available. When the diagnosis is made and genetic testing is informative, the endoscopist should really be a more active player in designing a suitably aggressive surveillance program for at-risk relatives, including more widespread routine clinical use of chromogens in the course of colonoscopy.

References


