CLINICAL UTILITY

26. What is the natural history of the disorder?

The natural history of HNPCC is also described in Question 2.

The probability of survival after the diagnosis of colorectal cancer in patients with HNPCC appears to be higher than in patients with sporadic colorectal cancer. The death rate is about two-thirds that documented for sporadic colorectal patients (Watson *et al*., 1998). One explanation is that HNPCC cases have a lower stage of disease at diagnosis, because distant metastases are less often present. It is speculated that the peritumoral lymphocytic infiltration characteristic of HNPCC tumors represents an immune response that may slow tumor progression (Lynch and Lynch, 2002).

27. What is the impact of a positive (or negative) test result on patient care, and does the individual understand the meaning of his or her test result?

One of the first reports of the experience of cancer patients actually undergoing genetic testing for HNPCC was that of Vernon *et al*. (1997). Twenty-four percent of those tested reported symptoms of depression. Greater depression was associated with female sex, less formal education, fewer sources of social contact, and less satisfaction with these sources. Anxiety was associated with a younger age, less formal education, minority status, and a more advanced stage of disease.

In a second study by Vernon *et al*. (1999) of 269 colorectal cancer patients who had already given blood for genetic testing for research purposes, 90 percent requested to learn their own test result. Acceptors had a higher income and thought being tested would help their relatives. Although they worried about having a mutation, they expected to be able to cope with it.

Lynch and Watson, *et al*. (1999) provided testing and counseling to 199 relatives of seven probands with a mismatch repair gene mutation. The most common reason (66 percent) for accepting testing was to inform other relatives of their potential risk. A majority of these relatives expressed concern about discrimination. Pretest education sessions, provided for the family as a group, revealed pressure by some on others to be tested. Some found not have the family mutation experienced survivor guilt.

Preventing untoward effects of learning test results requires adequate pretest counseling and avoidance of any pressure to consent. In Finland, a one-hour counseling session is followed by a two-week period for reflection before patients are contacted to determine their decision about being tested (Aktan-Collan *et al*., 2000a). Nevertheless 53 percent of tested subjects stated that they might have used professional psychological support, if it had been offered to them when they were making their decision about whether to be tested or when learning their test result. Women reported more adverse emotional reactions and found counseling more helpful than did men.

In a study of individuals who were the first in their family to undergo DNA testing for HNPCC, Esplen *et al*. (2001) determined to whom the patient revealed his/her test result. Eighty percent told their parents, 75 percent told extended family members, 68 percent told their family physician, 65 percent told their spouse, and 27 percent told their children. Fifty percent who told their

spouse or their parents indicated a "positive" effect on the relationship. Ten percent expressed regret at having disclosed their result, but the reasons for regret were not stated.

When individuals are offered DNA testing for an inherited susceptibility to colorectal cancer, those who accept have generally been more educated, have experienced more instances of cancer in the family, and have manifested less depression. The most common reason for declining is fear of discrimination. The most important motivation to be tested is to inform family members.

28. If applicable, are diagnostic tests available?

For colon cancer, as for most cancers, biopsy and microscopic examination are diagnostic and available. In diagnosing a predisposition to cancer, the finding of a mutation is, in a sense, diagnostic of disease because of the high penetrance.

29. Is there an effective remedy, acceptable action, or other measurable benefit?

Trimbath and Giardello (2002) have summarized potential benefits from HNPCC testing (Table 8).

Table 8. Potential benefits of testing for hereditary colorectal cancer

If a disease-causing mutation is detected:

- Removal of uncertainty
- Early detection of polyps and prevention of cancer
- Provision of information for family and career planning
- Increased compliance with colonic screening/surveillance
- Greater choice of surgical and medical management

If result is negative for a gene mutation identified in the family:

- Removal of uncertainty
- Assurance that offspring are not at risk
- Avoidance of intensive surveillance and attendant effort and costs
- Removal of threat to insurability

Finnish studies have demonstrated that colonoscopic surveillance can reduce mortality from HNPCC. Ninety individuals who had an HNPCC mutation were followed for 15 years. Among the 46 without such surveillance, 41 percent developed colorectal cancer. Among the 44 who had colonoscopy and removal of polyps every 3-5 years, the rate of colorectal cancer diagnosis was 18 percent. Deaths due to colorectal cancer were 12 in the unscreened group, but only four in the screened group.

A decision analysis of colonoscopic surveillance and prophylactic colectomy in patients with HNPCC mutations was conducted by Syngal *et al*. (1998). If instituted at 25 years of age, the gain in life expectancy was 13.5 years for colonoscopic surveillance and 15.6 years for prophylactic colectomy, compared to no intervention. The benefits of colectomy compared with surveillance decreased with increasing age and were minimal if colectomy was delayed until the time

of colorectal cancer diagnosis. If quality of life was considered, colonoscopic surveillance led to a greater quality of life-adjusted benefit (3.1 years) than did colectomy (0.3 year).

In 1996, the Cancer Genetic Studies Consortium, a temporary NIH-appointed body, made recommendations for follow-up care of individuals diagnosed with HNPCC-associated mutations (Burke *et al*., 1997). Recommendations consisted of having colonoscopy beginning at age 20-25 and repeated every 1-3 years, and transvaginal pelvic ultrasound or endometrial aspiration annually beginning at age 25-35. If colorectal cancer is diagnosed, a subtotal colectomy with ileorectal anastomosis should be considered. Those not willing or able to undergo periodic colonoscopic surveillance should consider prophylactic colectomy on the basis of carrier status alone. The group felt that there was insufficient evidence to recommend for or against prophylactic colectomy, hysterectomy, or oophorectomy.

Lynch recommends a more aggressive policy that involves offering prophylactic subtotal colectomy as soon as the diagnosis of HNPCC is made (Lynch, 1996). He further recommends prophylactic oophorectomy and hysterectomy for a woman operated on for a colorectal carcinoma, if her childbearing has been completed.

Nonsteroidal anti-inflammatory agents reduce the risk of colorectal adenomas in patients with a history of sporadic colorectal adenomas or carcinomas by as much as 50 percent (Arber, 2000; Baron *et al*., 2003; Sandler *et al*., 2003) and hence may reduce the risk of colorectal cancer in HNPCC, also. The most recent studies found that daily low-dose aspirin produced a 35 percent reduction of adenomas in patients who had had a colorectal cancer (Sandler *et al*., 2003) and a smaller reduction (up to 19 percent) in adenomas in patients who had had a previous adenoma (Baron *et al*., 2003).

Supportive measures include a low-fat, high-fiber diet, adequate intake of vegetables and fruit, regular exercise, and avoidance of carcinogens such as cigarettes.

30. Is there general access to that remedy or action?

There is not yet consensus as to whether systematic identification of HNPCC mutations in index cases and other family members is feasible and worthwhile. Taking that into account, lack of general access to remedies can be nearly totally attributed to the absence of a process for identifying and counseling those for whom these remedies are appropriate.

The primary group being considered in this question is family members with an HNPCC mutation who do not have cancer. Access to the remedies described in Question 29 are directed at preventing cancer and would best be gained systematically, through centrally managed programs aimed at implementing recommendations of an authoritative group, such as the Cancer Genetic Studies Consortium. The remedies recommended by that group are presently limited mostly to surveillance measures (colonoscopy, transvaginal ultrasound, endometrial aspiration). Prophylactic surgical procedures, such as colectomy, hysterectomy, and oophorectomy are considered to not yet be of proven value (although some individuals with HNPCC are likely to choose one or more of the surgical options, in spite of this). The types of surveillance and surgical procedures being discussed in this section are all widely available and commonly done, and so access to these procedures would be determined in large part by economic considerations, such as insurance, once a family member has been identified as having an HNPCC mutation.

If, in the future, it is determined that the programs should be developed for this purpose, it will be important to assess adequacy of existing resources for accommodating the influx of additional cases and, as well, the additional resources that need to be put in place for orderly management. The resource implications that this type of program development carry can be more explicitly demonstrated by examining the hypothetical protocol shown in Question 18.

Physicians' unfamiliarity with the syndromes in question is one of the obstacles to detection of affected families. Even family practice physicians take a family history in new patient visits only half the time and record it only 36 percent of the time (Yoon *et al*., 2002). A survey of gastroenterologists revealed that only 34 percent were aware of genetic tests for HNPCC (Batra *et al*., 2002.) Any program being designed for systematic identification and treatment of family members with HNPCC mutations would need to include education initiatives.

31. Is the test being offered to a socially vulnerable population?

Testing for HNPCC, like testing for other genetic conditions for which there is no intervention indicated in childhood, should be delayed until adulthood (American Society of Human Genetics, 1995). Initially, the evaluative process for identifying HNPCC focuses on individuals with colorectal cancer, as a means for selectively gaining access to other family members. This is not considered a socially vulnerable group. If genetic testing is offered at the time of diagnosis or of surgical treatment, anxiety about the patient's own fate may cloud his or her consideration of genetic testing for the benefit of relatives. Conversely, delaying the offer may endanger completeness of coverage of the target population.

Racial differences in rates for HNPCC specifically are not available. Minorities may be socially vulnerable populations. For example, African Americans are more likely to be fatalistic about cancer if they are less educated or less affluent (Powe *et al*., 1994). African American women are less likely than white women to participate in colorectal cancer screening, even after controlling for the cost of screening, access to services, and educational level (Powe *et al*., 1994).

Hispanics are at a significant risk of death from colorectal cancer, although at a lower risk than whites or African Americans (Healthy People, 2010). Hispanics are less knowledgeable about the warning signs of cancer, less aware of available screening tests for cancer, and less convinced about the effectiveness of cancer treatments (Villejo, 1989). Hispanics may be less familiar with genetic screening than other U.S. population groups. Language barriers may complicate genetic counseling with this group.

32. What quality assurance measures are in place?

For the laboratory component, please see Questions 11-17. Regarding the counseling component, DNA testing done in genetic centers generally involves an informed consent process with written documentation. Myriad Genetic Laboratories and the larger DNA testing companies require certification that genetic counseling has occurred.

33. What are the results of pilot trials?

Trials involving offering counseling and DNA testing to clinically suspect individuals, including relatives of individuals with known mutations and their utilization of the test result information, are summarized under Question 27. Most reports deal with index family members only. Some of the Finnish studies report extensive investigation of family members, but most U.S. studies do not report the response of relatives to learning about the detection of a mutation in the index family member.

34. What health risks can be identified for follow-up testing and/or intervention?
The Finnish group studying HNPCC evaluated comprehension of DNA test results among families (Aktan-Collan *et al*., 2001). Despite thorough counseling, they found in follow-up surveys that 56 percent of those detected to have a mutation thought that their risk of developing colorectal cancer was only about 50 percent rather than the actual 80 percent. The authors were concerned that this misunderstanding might result in neglecting surveillance. The only predictor of this misunderstanding was a low perceived risk before testing.

35. What are the financial costs associated with testing?

a. Cost of individual tests. The costs of commercially available genetic tests for hereditary colorectal cancer are summarized in **Table 3**.

Of the eight U.S. laboratories responding to our survey, the charge for complete DNA sequencing of MLH1 and MSH2 averaged $1467 (range $1200 to $1950) and the cost for single site analysis averaged $300 (range $200 to $460).

The cost of MSI testing ranged from $350 to $850, depending on whether or not it included a charge for a pathologist to separate tumor cells from contiguous nontumor cells. Two of the reporting laboratories attempt to identify the abnormal mismatch repair gene before sequencing by detecting a deficiency in the gene product by immunohistochemical staining of tumor sections. If a deficiency of one gene product is found, then the effort and cost of sequencing both genes may be averted. However this procedure involves the laboratory having tumor material, which is not always available, and the cost saving is modest.

b. Costs of systematic HNPCC case-finding. What costs are associated with a program that would test all new colorectal cancer patients meeting the Bethesda criteria for MSI, perform DNA sequencing for those with high MSI, and, for those found to have mutations, offer subtotal colectomy or provide colonoscopy every three years life-long?.

Ramsey et al. (2001) conducted such an analysis using the protocol illustrated in Figure 2**.** This analysis assumed that a clinician would assess evaluate whether each patient newly diagnosed with colorectal cancer met the Bethesda criteria. It assumed that only some patients offered a Bethesda assessment would agree to it (50–100%), that, of those who met the criteria, only some would agree to MSI testing (75–100%), that, of those who were MSI-positive, only some would accept gene testing (30-60%), and that, of those found to have mutations, only some would accept prophylactic colectomy (50-75%). In a program starting with 100,000 colorectal cancer cases, the estimated yield was 16,104 (16.1%) meeting the Bethesda guidelines, 2304 (14.3%) with high MSI, 665 (28.9%) carriers detected among the index cases, and 225 cases detected among first-degree relatives. The average cost per carrier detected was estimated at $12,815. For siblings and children of detected carriers, the cost was, as expected, much lower, $1047 per carrier detected.

36. What are the economic benefits associated with actions resulting from testing?

a. A cost-effectiveness analysis of HNPCC detection. In the Ramsey analysis presented above, the estimated cost-effectiveness, compared with no screening, was $42,210 per index case life-year gained. If screening of siblings and children were included, cost-effectiveness improved to $7,556 per life-year gained. Thus this analysis appears to show that such a screening program is cost-effective, since measures costing less than $100,000 per life-year saved are generally regarded as cost-effective (Laupacis et al., 1992).

Obviously this analysis is based on many assumptions. A sensitivity analysis was conducted and showed that the three most influential variables were the relative mortality risk associated with increased surveillance of HNPCC-positive siblings and children, the overall prevalence of HNPCC mutation carriers among patients with new diagnoses of colorectal cancer, and the discount rate for future costs and benefits.

The authors point out barriers to implementing such a program, e.g. that incidence figures are not well established for African-American and Hispanic populations, that a limited number of laboratories perform MSI, that legal restrictions complicate the release of confidential patient information to third parties, that genetic counselors do not customarily contact relatives, that costs would be borne by private and public health insurance plans that now do not always cover genetic testing, especially for relatives without cancer, and that the benefits are delayed and do not accrue directly to the payers.

The main criticism of this study is the low cost assumed for MSI testing. A cost of $80 – 120 is assumed, but our survey showed an average cost of $400. This would increase the cost per index carrier detected by 60%, from $12,815 to $20,566. It should be noted the entire Ramsey study is based on 1999 dollars.

In another U.S. study, Reyes et al. (2002) compared the cost-effectiveness of four different testing strategies to detect HNPCC gene carriers in consecutive patients with colorectal cancer. These were (1) directly sequencing MSH2 and MLH1 in all individuals meeting the Amsterdam criteria (the "Amsterdam strategy"), (2) performing MSI analysis on tumors of individuals meeting the Salovaara criteria and sequencing those with high MSI (the "modified strategy"), (3) MSI analysis of all individuals and sequencing those with high MSI (test-all strategy), and (4) direct sequencing of those meeting the Amsterdam criteria, while testing those who meet the Salovaara criteria (but not the Amsterdam criteria) only if they are MSI high ("mixed strategy"). The Amsterdam strategy cost the least ($277 per CRC patient) but detected the fewest carriers (only 9.7% of all those detectable if all CRC patients were sequenced). In contrast, the test-all strategy detected the most carriers (67%), but cost the most ($998 per CRC patient). The most cost-effective was the mixed strategy, which had an intermediate cost ($611 per CRC patient), but detected many more carriers (60%). The modified strategy ranked as a close second. (The Salovaara criteria identify any individual with CRC who is diagnosed before 50 years of age or who has a personal or family history of another CRC or endometrial cancer (Salovaara et al., 2000)).

Vasen et al. (1998) performed a decision analysis in Denmark showing that, given a diagnosis of HNPCC, colonoscopy every 2-3 years beginning at age 25 would not only extend life by 6.9 years, but also save money by avoiding the expense of treatment of advanced colon cancer. However the cost assumed for colonoscopy ($285) is far lower than the cost in the U.S. (~$1000).

Stanley et al. (2000) illustrated the projected cost-savings resulting from testing members of a single large family with an HNPCC mutation in Australia. Following testing, the need for regular colonoscopic screening among 76 family members, who had undergone 70 colonoscopies in the preceding five years, was cut in half by the demonstration that the majority tested negative for the family mutation.

None of these studies considered the cost or benefit of screening HNPCC patients for cancers other than colorectal.

b. Insurance coverage. Myriad Genetics offers to contact a patient's insurer to seek coverage for testing. Myriad claims that 97% of such requests are granted and that coverage averages 94% of the test cost. The most common reason for denial is that the patient does not meet the insurance company's guidelines, although the American College of Medical Genetics guidelines (ACMG/ASHG Policy Statement, 2000) are gaining wide acceptance. Insurers generally prefer to test an affected family member first, but some do not insist on it if doing so is impractical. In order to provide information for an unaffected client, one insurance company is even willing to pay for testing of an affected relative who is not a client.

37. What facilities/personnel are available or easily put in place?

A program involving contacting all individuals newly diagnosed with colorectal cancer, obtaining informed consent, testing for MSI, and performing DNA sequencing on individuals with high MSI, informing the patient of the results, and, if a mutation is found, offering counseling and testing would strain current capabilities. Following establishing a successful program of this nature in Finland, de la Chapelle has conducted a similar program in the Columbus, Ohio, region and encountered a number of barriers. First, comprehensive coverage of the target population required approaching the patient at the time of hospital entry for tumor resection. However, hospitals were reluctant to release the name and diagnosis of cancer patients to outside parties before the Health Insurance Protection and Accountability Act (HIPAA) regulations were instituted and may be forbidden to do so now. Second, time for interacting with the patient is short because patients are frequently admitted the day before surgery. Third, the setting is suboptimal for education of and consideration by the patient since the patient is primarily concerned about the imminent surgery. Fourth, a skilled genetic counselor or nurse is needed to take a cancer family history, explain what HNPCC is, the nature of the proposed testing, its benefits, burdens, and limitations, and to obtain informed consent in this time-limited setting.

Before recommendations are made for systematic testing, there should be assurance of an accepted effective treatment for those diagnosed, adequate facilities for diagnosis and treatment, a reasonable cost of case-finding, and acceptance of the test by the target population (Wilson and Jungner, 1968). In the case of HNPCC, there is an accepted treatment for those diagnosed, but the other three criteria listed may not be met. Facilities for diagnosis and treatment are not adequate if one considers the lack of knowledge of these disorders by practicing physicians and the fact that the U.S. has 40,000,000 uninsured persons. The cost of index case-finding is high. The target population generally does not appreciate the role played by genetic susceptibility in colon cancer and many are uncertain about the value of genetic testing.

For HNPCC, MSI testing is currently offered by few laboratories. Of the eight laboratories responding to our survey, only five offer MSI testing.

Practical difficulties in implementing a population-based molecular HNPCC testing and management program include noncompliance of patients (Lerman, *et al*., 1999), inability to provide accurate first-degree relative family histories of cancer (Andrykowski *et al*., 1997), lack of interest on the part of physicians (Batra *et al*., 2002), fear of discrimination (Geller *et al*., 1997), and cost.

Other practical difficulties are the uncertain interpretation of missense mutations (which account for some 30 percent of *MLH1* and *MSH2* mutations) (de la Chapelle, 2003a), the aversiveness of screening colonoscopy, and the risk of cancer in organs not easily monitored, such as the ovaries.

A survey of U.S. gastroenterologists conducted by Batra *et al*. (2002) revealed that, although 99 percent claimed to obtain a family history from patients, only 34 percent were aware of genetic testing for HNPCC, and only 51 percent would routinely refer patients for genetic counseling before providing cancer predisposition testing. Presented with a family history consistent with HNPCC, 79 percent could identify the syndrome, but only 26 percent recommended genetic counseling for the patient, and only 16 percent advised surveillance consistent with current guidelines.

38. What is the availability of validated educational materials and have they been shown to be effective in achieving understanding?

Myriad Genetic Laboratories has developed written and video educational materials for physicians and patients. The Familial Gastrointestinal Cancer Registry in Toronto has an internet site with patient educational materials (www.mtsinai.on.ca/familialgicancer). The materials from neither of these sources have been validated, but the Toronto materials have been evaluated informally by focus groups.

A variety of educational resources are available for physicians. The AMA has an online continuing medical education program entitled "Identifying and Managing Risk for Hereditary Colorectal Cancer Syndromes (www.ama-assn.org/cmeselec/hnpcc/target/index.htm). The American Society of Clinical Oncology has a curriculum entitled "Cancer Genetics and Cancer Predisposition Testing" containing 323 slides with commentary (www.kendallhunt.com). Especially for oncologists are ONCOSEP: Genetics, an individual learning program in book or CD form (www.kendallhung.com). and Genetics for Oncologists (2002) (www.weatherhill.com). No validation was found for these.

39. Are there informed consent requirements and is there evidence that those offered the test make informed choices?

The American Society of Clinical Oncology has developed a list of 11 elements of informed consent for cancer genetic testing. They are 1) information about the specific test being performed, 2) implications of a positive and negative result, 3) the possibility that the test will not be informative, 4) options for risk estimation without genetic testing, 5) the risk of passing a mutation to children, 6) technical accuracy of the test, 7) fees involved in testing and counseling, 8) risks of psychological distress, 9) risks of insurer or employment discrimination, 10) confidentiality issues, and 11) options and limitations of medical surveillance and screening following testing (ASCO 1996). It is recommended that all testing utilize a comprehensive informed consent document.

For research studies, institutional review boards serve as patient advocates and try to ensure that patients' rights are respected through full disclosure and voluntary participation and insist on measures to insure confidentiality. Increasingly informed consent documents have also included statements about disposition of samples. Certificates of confidentiality can be obtained by investigators to provide a guarantee that records cannot be subpoenaed.

In the non-research setting, some testing laboratories supply their own informed consent documents and frequently provide a genetic counselor by telephone to providers or self-referred patients.

Genetic centers conducting research spend considerable time educating patients before testing. The adequacy of pretest education provided in the primary care setting is less certain. A study of the use of commercial DNA testing for familial polyposis, for example, revealed serious defi-

ciencies in the use of such testing by physicians (Giardiello *et al*., 1997b). Of 177 patients from whom samples were submitted, only 19 percent received genetic counseling before the test and only 17 percent provided written informed consent. In 32 percent of cases, the physician did not know that a negative result could be a false negative in a patient in whose family an APC gene mutation had not been identified.

40. What methods exist for long-term monitoring?

The National Cancer Institute has funded a multicenter project to enroll patients found to have a mutation in order to collect data on natural history and the effectiveness of intervention.

41. What guidelines have been developed for evaluating program performance?

No guidelines have been located for evaluating program performance.