DNA TESTING STRATEGIES AIMED AT REDUCING MORBIDITY AND MORTALITY FROM HEREDITARY NON-POLYPOSIS COLORECTAL CANCER (HNPCC)

An A C C E Mini-review

Sponsored by

Office of Genomics and Disease Prevention

Centers for Disease Control and Prevention

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SUMMARY

The main aim of this Colorectal Cancer ACCE Review is to evaluate the efficacy of identifying hereditary non-polyposis colorectal cancer (HNPCC) mutations among individuals with newly diagnosed colorectal cancer. Testing for the mutation could then be made available to their first degree relatives, so that preventive measures might be offered to those who are found to carry the mutation. There could also be some benefit to the index cases, themselves. In the absence of preventive measures, about 80 percent of male relatives and 40 percent of female relatives with mutations will develop colorectal cancer during their lifetime; the women, however, are also at high risk for endometrial and ovarian malignancies. The death rate from colorectal cancer caused by HNPCC mutations is lower (by about one-third) than sporadic colorectal cancer, but this is more than offset by the high rate of cancer in the presence of one of these mutations. Preventive measures recommended for individuals with HNPCC mutations by the Cancer Genetic Studies Consortium include colonoscopy every 1-3 years, and, for women, transvaginal ultrasound or endometrial aspiration, annually. Other experts recommend more aggressive preventive steps including subtotal colectomy, prophylactic oophorectomy, and hysterectomy.

At present, testing is readily available for identifying mutations in two selected genes (*MLH1*, *MSH2*) and possibly a third, as well (*MSH6*). Collectively, mutations in these three genes account for more than 90 percent of HNPCC cases, but clinically available DNA testing (sequencing) detects only a portion of those mutations, accounting for 64 percent of the HNPCC cases. The cost of such testing (about $2,000), coupled with the relatively low frequency of HNPCC mutations among individuals with colorectal cancer, precludes its use in all individuals with newly diagnosed colorectal cancer. Instead, preliminary evaluations that utilize family history and/or microsatellite instability (MSI) testing of the tumor have been developed for selecting a subgroup of cases for mutation testing. While there are practical reasons to consider both family history and MSI testing for preliminary evaluation, each is associated with a reduction in HNPCC cases detected. For example, about 86 percent of individuals with HNPCC-associated cancer will have a positive family history, and about 90 percent of colorectal cancers caused by HNPCC mutations will display microsatellite instability.

Among the 147,500 new cases of colorectal cancer diagnosed annually in the United States, approximately 5,900 can be attributed to a mutation in one of the HNPCC genes. If tumor tissue from all of these cases was tested for microsatellite instability, 19,500 would be positive, and DNA testing for *MLH1, MSH2*, and *MSH6* could be performed on blood samples from all of the

MSI positive cases - 3,400 HNPCC mutations would be found and family members of these index cases approached. Alternatively, if family history were the initial test applied to the 147,500 new cases, 19,230 would report at least one family member with colorectal cancer. MSI testing would then be performed on tumor samples only from this subset of cases. MSI results would be positive in 5,980 of the tumors; blood samples would then be obtained for DNA analysis from individuals with these tumors, and 2,290 HNPCC mutations would be found. The protocol that starts with family history identifies fewer HNPCC mutations than when microsatellite instability testing is applied as the first test, but the cost per case detected using family history is considerably lower, as the initial step of family history costs much less than MSI testing. If either of these diagnostic approaches were to be introduced into everyday practice, participation at each step of the evaluation would likely be appreciably below 100 percent, meaning that the final number of index cases found would be lower than presently estimated.

The most important information for determining the efficacy of detecting HNPCC mutations involves documenting the willingness of index cases to discuss the implications with other family members, and the receptivity of those notified family members to being tested, themselves. Preliminary data are available indicating that privacy issues (such as created by HIPAA, for example) could also represent an important barrier to sharing information at all levels. For those who are found to carry HNPCC mutations, it will be important to determine the acceptability of the recommended preventive measures, including long-term follow through, and the level of anxiety created. For example, prophylactic removal of the colon (primary prevention) may be less acceptable than frequent colonoscopy and polyp removal (a mix of early detection and primary prevention). For women, oophorectomy and hysterectomy may be more acceptable than colectomy, especially after childbearing is complete. Data on these kinds of decisions and their impact on disease prevention and overall morbidity and mortality are lacking in U.S. populations, especially among minority groups. Pilot trials would be the most appropriate vehicle for gathering the necessary additional data.

Ultimately, decisions pro or con instituting systematic detection of HNPCC mutations in the U.S. must rest on issues of clinical utility, as described above. Mutation testing is highly specific for detecting individuals with HNPCC using protocols described in this document, but assay methods used for clinical purposes currently fail to identify 36% of individuals with a mutation. The overall assay performance appears satisfactory, but data to document day-to-day performance are sparse. If testing were to become more widespread, quality assurance procedures would

need to be extended and formalized, including external proficiency testing. Appropriate follow-up diagnostic and treatment steps are already well established and widely available, but any policy calling for introduction of systematic testing would require assuring that genetic counselors would be available to manage the specialized needs of individuals with mutations, and that reliable, up-to-date information could be distributed to appropriate practitioners throughout the U.S. If a program of this type were to be introduced, it would need to be centrally organized and managed, in order to assure equal access and reliable delivery of services.