EDITORIAL

Screening to detect Lynch syndrome and prevent hereditary cancers in relatives

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There is now an opportunity to consider a new screening initiative to prevent a small, but important, subgroup of inherited colorectal (and endometrial) cancers that occur as a consequence of disease-causing germ line mutations. Extensive interdisciplinary planning and co-operation will be necessary, however, before such screening can become a reality.

In 2009, the Evaluation of Genomic Applications in Practice and Prevention Working Group (EWG), convened by the Office of Public Health Genomics at the US Centers for Disease Control and Prevention, recommended that specific protein tests of the excised tumour be offered to individuals with newly diagnosed colorectal cancer (CRC).[1] This recommendation was subsequently incorporated into the US Department of Health and Human Services Goals for Healthy People 2020.[2] The EWG arrived at its recommendation after reviewing findings from two commissioned structured evidence reviews.[3,4] When offered routinely, screening can identify most cases of Lynch syndrome, best defined as a dominantly inherited predisposition to CRC and endometrial cancer caused by mutations in mismatch repair genes that interfere with normal function.[5] This condition occurs in about 3% of all newly diagnosed CRC cases. When a mutation is identified in an index case, testing for that same mutation can then be offered to relatives for the purpose of identifying Lynch syndrome before cancers occur and taking the steps outlined below.

Immunohistochemical analysis of the tumour measures normal protein products of four mismatch repair genes (*MLH1, MSH2, MSH6* and *PMS2*).[4] Microsatellite instability testing can also serve as the initial screening test but is not as useful, because it does not provide information as to which mismatch repair gene might be involved. Immunohistochemical testing can identify up to 83% of the Lynch syndrome cases among newly diagnosed individuals with CRC. Initially, 11% of all screening test results will be positive, but most of these are due to a single somatic mutation in the *BRAF* gene (V600E), which causes hypermethylation of the normal *MLH1* gene. In such cases, there is no increased risk for CRC in other family members.[4] The BRAF mutation can be immediately identified in the tumour specimen via polymerase chain reaction and pyrosequencing, thereby eliminating the need for further testing. Among the remaining individuals with an abnormal immunohistochemical test, the next step is to obtain a blood sample and perform targeted DNA analysis for definitive diagnosis. Guided by information from the immunohistochemical test, sequencing is necessary in only one, or at most two, mismatch repair genes. When a specific DNA mutation is identified in a CRC patient, targeted sequencing for that same mutation can then be offered to first degree relatives.

The newly diagnosed CRC patient identified with Lynch syndrome (index case) generally does not derive a health benefit from this knowledge. An exception is a woman who might choose hysterectomy to avoid uterine cancer.[6] Among first degree relatives found to carry the MMR mutation (Lynch syndrome), an estimated 45% of men and 35% of women will develop CRC by age 70. In addition, endometrial cancer will occur by that age in more than 30% of female relatives with a mutation.[4] The benefit from screening, therefore, is realized when one or more family members are found to carry the same MMR gene mutation, thereby allowing them to undergo earlier and more frequent colonoscopy (and, for women, to consider hysterectomy after childbearing is done). A marked reduction in endometrial and ovarian cancer has been documented in a 10-year follow-up study of women with mismatch gene mutations who chose risk-reducing surgery.[7] Evidence for a health benefit among family members of both sexes comes from a 15-year controlled trial in Finland in which an intention to treat analysis showed a 62% reduction in CRC incidence among those undergoing surveillance. No deaths occurred in the surveillance group, while there were nine deaths in the control group.[8] More recently, a cohort study from the Netherlands documented a 70% decrease in standardized mortality in Lynch syndrome family members who underwent surveillance colonoscopy.[9] The impact may even be larger if aspirin were given as preventive therapy.[10,11]

Economic modeling and a comprehensive cost-effectiveness analysis support the feasibility of Lynch syndrome screening, with estimated costs of $25,000 per life-year saved relative to no testing.[12]

Several obstacles must be overcome before this screening initiative can be introduced. In the USA, systems for health-care reimbursement are justified by the extent to which a patient's health might be improved, rather than the impact on family members. Such policies might well be modified to accommodate genomic applications, but remain an important barrier for the moment. Even if costs were not a concern, however, new interdisciplinary alliances would need to be formed among existing health disciplines, to assure accurate translation of screening and diagnostic test results to the patient, to assist with contacting, counselling and testing family members, and to co-ordinate longer term follow-up for those for whom regularly scheduled colonoscopy is indicated. Although co-operation from the Clinical Pathology Laboratory is necessary, the partners of such alliances might differ, depending on the region. Surgical staff, for example, might take responsibility for

arranging initial testing in one center, while oncologists might serve in that capacity in another.

Any decision to move forward will not be made lightly. Even though cost-effective, Lynch syndrome screening cost savings come later, and current economic stresses in health-care delivery systems everywhere make front-end investment more difficult. As a counter-balance to all of this, the potential for Lynch syndrome screening to reduce the burden of colorectal cancer is real and offers one of the most solid screening applications of genomic technology. The Lynch syndrome screening initiative deserves serious attention in future health-care planning.

James E Haddow and Glenn E Palomaki

Division of Medical Screening and Special Testing, Department of Pathology and Laboratory Medicine, Women & Infants Hospital/Alpert Medical School of Brown University, Providence, Rhode Island

Correspondence to: James E Haddow
jhaddow@ipmms.org

REFERENCES

1 Recommendations from the EGAPP Working Group: genetic testing strategies in newly diagnosed individuals with colorectal cancer aimed at reducing morbidity and mortality from Lynch syndrome in relatives. *Genet Med* 2009;**11**:35–41
2 Genomics. Healthy People 2020. U.S. Department of Health and Human Services. http://www.healthypeople.gov/2020/topicsobjectives2020/overview.aspx?topicid=15 (last accessed October 21 2011)
3 Bonis PA, Trikalinos TA, Chung M, *et al*. Hereditary nonpolyposis colorectal cancer: accuracy of diagnostic strategies and implications to patients with colorectal cancer and their families. Evidence report/technology assessment No. 07-E008. Agency for Healthcare Research and Quality, Rockville, MD, 2007
4 Palomaki GE, McClain MR, Melillo S, Hampel HL, Thibodeau SN. EGAPP supplementary evidence review: DNA testing strategies aimed at reducing morbidity and mortality from Lynch syndrome. *Genet Med* 2009;**11**:42–65
5 Jass JR. Hereditary non-polyposis colorectal cancer: the rise and fall of a confusing term. *World J Gastroenterol* 2006;**12**:4943–50
6 Johnson N, Barlow D, Lethaby A, Tavender E, Curr L, Garry R. Methods of hysterectomy: systematic review and meta-analysis of randomised controlled trials. *BMJ* 2005;**330**:1478
7 Schmeler KM, Lynch HT, Chen LM, *et al*. Prophylactic surgery to reduce the risk of gynecologic cancers in the Lynch syndrome. *N Engl J Med* 2006;**354**:261–9
8 Jarvinen HJ, Aarnio M, Mustonen H, *et al*. Controlled 15-year trial on screening for colorectal cancer in families with hereditary nonpolyposis colorectal cancer. *Gastroenterology* 2000;**118**:829–34
9 de Jong AE, Hendriks YM, Kleibeuker JH, *et al*. Decrease in mortality in Lynch syndrome families because of surveillance. *Gastroenterology* 2006;**130**:665–71
10 Burn J, Gerdes AM, Macrae F, *et al*. Long-term effect of aspirin on cancer risk in carriers of hereditary colorectal cancer: an analysis from the CAPP2 randomised controlled trial. *Lancet* 2011 [Epub ahead of print]
11 Rothwell PM, Wilson M, Elwin CE, *et al*. Long-term effect of aspirin on colorectal cancer incidence and mortality: 20-year follow-up of five randomised trials. *Lancet* 2010;**376**:1741–50
12 Mvundura M, Grosse SD, Hampel H, Palomaki GE. The cost-effectiveness of genetic testing strategies for Lynch syndrome among newly diagnosed patients with colorectal cancer. *Genet Med* 2010;**12**:93–104