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HNPCC, molecular and clinical dilemmas

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References

1. Statement of the American Society of Clinical Oncology: genetic testing for cancer susceptibility, Adopted on February 20, 1996. *J Clin Oncol* 1996;14:1730-6; discussion 1737-40.
2. American Society of Clinical Oncology policy statement update: genetic testing for cancer susceptibility. *J Clin Oncol* 2003;21:2397-406.
3. Aaltonen LA, Peltomaki P, Mecklin JP, Jarvinen H, Jass JR, Green JS, Lynch HT, Watson P, Tallqvist G, Juhola M, et al. Replication errors in benign and malignant tumors from hereditary nonpolyposis colorectal cancer patients. *Cancer Res* 1994;54:1645-8.
4. Aaltonen LA, Peltomaki P, Leach FS, Sistonen P, Pylkkanen L, Mecklin JP, Jarvinen H, Powell SM, Jen J, Hamilton SR, et al. Clues to the pathogenesis of familial colorectal cancer. *Science* 1993;260:812-6.
5. Aarnio M, Sankila R, Pukkala E, Salovaara R, Aaltonen LA, de la Chapelle A, Peltomaki P, Mecklin JP, Jarvinen HJ. Cancer risk in mutation carriers of DNA-mismatch-repair genes. *Int J Cancer* 1999;81:214-8.
6. Aarnio M, Salovaara R, Aaltonen LA, Mecklin JP, Jarvinen HJ. Features of gastric cancer in hereditary non-polyposis colorectal cancer syndrome. *Int J Cancer* 1997;74:551-5.
7. Acharya S, Wilson T, Gradia S, Kane MF, Guerrette S, Marsischky GT, Kolodner R, Fishel R. hMSH2 forms specific mispair-binding complexes with hMSH3 and hMSH6. *Proc Natl Acad Sci U S A* 1996;93:13629-34.
8. Agell N, Bachs O, Rocamora N, Villalonga P. Modulation of the Ras/Raf/MEK/ERK pathway by Ca(2+), and calmodulin. *Cell Signal* 2002;14:649-54.
9. Ahlquist DA, Skoletsky JE, Boynton KA, Harrington JJ, Mahoney DW, Pierceall WE, Thibodeau SN, Shuber AP. Colorectal cancer screening by detection of altered human DNA in stool: feasibility of a multitarget assay panel. *Gastroenterology* 2000;119:1219-27.
10. Akiyama Y, Sato H, Yamada T, Nagasaki H, Tsuchiya A, Abe R, Yuasa Y. Germ-line mutation of the hMSH6/GTBP gene in an atypical hereditary nonpolyposis colorectal cancer kindred. *Cancer Res* 1997;57:3920-3.
11. Akiyama Y, Nagasaki H, Yagi KO, Nomizu T, Yuasa Y. Beta-catenin and adenomatous polyposis coli (APC) mutations in adenomas from hereditary non-polyposis colorectal cancer patients. *Cancer Lett* 2000;157:185-91.
12. Aktan-Collan K, Mecklin JP, Jarvinen H, Nystrom-Lahti M, Peltomaki P, Soderling I, Uutela A, de la Chapelle A, Kaariainen H. Predictive genetic testing for hereditary non-polyposis colorectal cancer: uptake and long-term satisfaction. *Int J Cancer* 2000;89:44-50.
13. Aktan-Collan K, Mecklin JP, de la Chapelle A, Peltomaki P, Uutela A, Kaariainen H. Evaluation of a counselling protocol for predictive genetic testing for hereditary non-polyposis colorectal cancer. *J Med Genet* 2000;37:108-13.
14. Aktan-Collan K, Haukkala A, Mecklin JP, Uutela A, Kaariainen H. Psychological consequences of predictive genetic testing for hereditary non-polyposis colorectal cancer (HNPCC): a prospective follow-up study. *Int J Cancer* 2001;93:608-11.
15. Al-Tassan N, Chmiel NH, Maynard J, Fleming N, Livingston AL, Williams GT, Hodges AK, Davies DR, David SS, Sampson JR, Cheadle JP. Inherited variants of MYH associated with somatic G:C-->T:A mutations in colorectal tumors. *Nat Genet* 2002;30:227-32.
16. Bailey-Wilson JE, Elston RC, Schuelke GS, Kimberling W, Albano W, Lynch JF, Lynch HT. Segregation analysis of hereditary nonpolyposis colorectal cancer. *Genet Epidemiol* 1986;3:27-38.
17. Baker SM, Plug AW, Prolla TA, Bronner CE, Harris AC, Yao X, Christie DM, Monell C, Arnheim N, Bradley A, Ashley T, Liskay RM. Involvement of mouse Mlh1 in DNA mismatch repair and meiotic crossing over. *Nat Genet* 1996;13:336-42.
18. Bapat BV, Madlensky L, Temple LK, Hiruki T, Redston M, Baron DL, Xia L, Marcus VA, Soravia C, Mitri A, Shen W, Gryfe R, Berk T, Chodirker BN, Cohen Z, Gallinger S. Family history characteristics, tumor microsatellite instability and germline MSH2 and MLH1 mutations in hereditary colorectal cancer. *Hum Genet* 1999;104:167-76.
19. Bellacosa A. Functional interactions and signaling properties of mammalian DNA mismatch repair proteins. *Cell Death Differ* 2001;8:1076-92.
20. Berends MJW. Towards optimal identification of germline mutations involved in mismatch repair. Thesis 2003;University Groningen, The Netherlands.
21. Blaszyk H, Wang L, Dietmaier W, Hofstadter F, Burgart LJ, Cheville JC, Hartmann A. Upper tract urothelial carcinoma: a clinicopathologic study including microsatellite instability analysis. *Mod Pathol* 2002;15:790-7.
22. Blobel GC, Schieman WP, Lodish HF. Role of transforming growth factor beta in human disease. *N Engl J Med* 2000;342:1350-8.

23. Boks DE, Trujillo AP, Voogd AC, Morreau H, Kenter GG, Vasen HF. Survival analysis of endometrial carcinoma associated with hereditary nonpolyposis colorectal cancer. *Int J Cancer* 2002;102:198-200.
24. Boland CR, Thibodeau SN, Hamilton SR, Sidransky D, Eshleman JR, Burt RW, Meltzer SJ, Rodriguez-Bigas MA, Fodde R, Ranzani GN, Srivastava S. A National Cancer Institute Workshop on Microsatellite Instability for cancer detection and familial predisposition: development of international criteria for the determination of microsatellite instability in colorectal cancer. *Cancer Res* 1998;58:5248-57.
25. Brieger A, Trojan J, Raedle J, Plotz G, Zeuzem S. Transient mismatch repair gene transfection for functional analysis of genetic hMLH1 and hMSH2 variants. *Gut* 2002;51:677-84.
26. Bronner CE, Baker SM, Morrison PT, Warren G, Smith LG, Lescoe MK, Kane M, Earabino C, Lipford J, Lindblom A, et al. Mutation in the DNA mismatch repair gene homologue hMLH1 is associated with hereditary non-polyposis colon cancer. *Nature* 1994;368:258-61.
27. Burke W, Petersen G, Lynch P, Botkin J, Daly M, Garber J, Kahn MJ, McTiernan A, Offit K, Thomson E, Varricchio C. Recommendations for follow-up care of individuals with an inherited predisposition to cancer. I. Hereditary nonpolyposis colon cancer. *Cancer Genetics Studies Consortium. Jama* 1997;277:915-9.
28. Burn J CP, Bishop DT, Mathers J. Diet and cancer prevention: the Concerted Action Polyp Prevention. *Proc Nutr Soc* 1998;57:183-186.
29. Burt RW. Colon cancer screening. *Gastroenterology* 2000;119:837-53.
30. Cairns S, Scholefield JH. Guidelines for colorectal cancer screening in high risk groups. *Gut* 2002;51 Suppl 5:V1-2.
31. Caldas C, Carneiro F, Lynch HT, Yokota J, Wiesner GL, Powell SM, Lewis FR, Huntsman DG, Pharoah PD, Jankowski JA, MacLeod P, Vogelsang H, Keller G, Park KG, Richards FM, Maher ER, Gayther SA, Oliveira C, Grehan N, Wight D, Seruca R, Roviello F, Ponder BA, Jackson CE. Familial gastric cancer: overview and guidelines for management. *J Med Genet* 1999;36:873-80.
32. Cao Y, Pieretti M, Marshall J, Khattar NH, Chen B, Kam-Morgan L, Lynch H. Challenge in the differentiation between attenuated familial adenomatous polyposis and hereditary nonpolyposis colorectal cancer: case report with review of the literature. *Am J Gastroenterol* 2002;97:1822-7.
33. Chan TL, Wai Chan Y, Ho JW, Chan C, Chan AS, Chan E, Lam PW, Wah Tse C, Cheong Lee K, Wai Lau C, Gwi E, Yi Leung S, Yuen ST. MSH2 c.1452-1455delAATG is a founder mutation and an important cause of hereditary nonpolyposis colorectal cancer in the southern Chinese population. *Am J Hum Genet* 2004;74:1035-42.
34. Chang DK, Goel A, Ricciardiello L, Lee DH, Chang CL, Carethers JM, Boland CR. Effect of H(2)O(2) on cell cycle and survival in DNA mismatch repair-deficient and -proficient cell lines. *Cancer Lett* 2003;195:243-51.
35. Charbonnier F, Olschwang S, Wang Q, Boisson C, Martin C, Buisine MP, Puisieux A, Frebourg T. MSH2 in contrast to MLH1 and MSH6 is frequently inactivated by exonic and promoter rearrangements in hereditary nonpolyposis colorectal cancer. *Cancer Res* 2002;62:848-53.
36. Charbonnier F, Raux G, Wang Q, Drouot N, Cordier F, Limacher JM, Saurin JC, Puisieux A, Olschwang S, Frebourg T. Detection of exon deletions and duplications of the mismatch repair genes in hereditary nonpolyposis colorectal cancer families using multiplex polymerase chain reaction of short fluorescent fragments. *Cancer Res* 2000;60:2760-3.
37. Chiang PW, Schneider A, Borgnat S, Gaub MP, Oudet P, Kurnit DM, Jacqmin D. Molecular analysis of urine sediment for follow-up of urinary tract cancers. *J Natl Cancer Inst* 2000;92:1779-80.
38. Chiaravalli AM, Furlan D, Facco C, Tibiletti MG, Dionigi A, Casati B, Albarello L, Riva C, Capella C. Immunohistochemical pattern of hMSH2/hMLH1 in familial and sporadic colorectal, gastric, endometrial and ovarian carcinomas with instability in microsatellite sequences. *Virchows Arch* 2001;438:39-48.
39. Christensen M, Katballe N, Wikman F, Primdahl H, Sorensen FB, Laurberg S, Orntoft TF. Antibody-based screening for hereditary nonpolyposis colorectal carcinoma compared with microsatellite analysis and sequencing. *Cancer* 2002;95:2422-30.
40. Chung DC. The genetic basis of colorectal cancer: insights into critical pathways of tumorigenesis. *Gastroenterology* 2000;119:854-65.
41. Cruz-Correa M, Hyland LM, Romans KE, Booker SV, Giardiello FM. Long-term treatment with sulindac in familial adenomatous polyposis: a prospective cohort study. *Gastroenterology* 2002;122:641-5.
42. de Jong AE, van Puijenbroek M, Hendriks Y, Tops C, Wijnen J, Ausems MG, Meijers-Heijboer H, Wagner A, van Os TA, Brocker-Vriends AH, Vasen HF, Morreau H. Microsatellite instability, immunohistochemistry, and additional PMS2 staining in suspected hereditary nonpolyposis colorectal cancer. *Clin Cancer Res* 2004;10:972-80.
43. de Leeuw WJ, Dierssen J, Vasen HF, Wijnen JT, Kenter GG, Meijers-Heijboer H, Brocker-Vriends A, Stormorken A, Moller P, Menko F, Cornelisse CJ, Morreau H. Prediction of a mismatch repair gene defect by microsatellite instability and immunohistochemical analysis in endometrial tumours from HNPCC patients [In Process Citation]. *J Pathol* 2000;192:328-35.

44. de Leeuw WJ, van Puijenbroek M, Tollenaar RA, Cornelisse CJ, Vasen HF, Morreau H. Correspondence re: A. Muller et al., Exclusion of breast cancer as an integral tumor of hereditary nonpolyposis colorectal cancer. *Cancer Res.*, 62: 1014-1019, 2002. *Cancer Res* 2003;63:1148-9.
45. De Rosa M, Fasano C, Panariello L, Scarano MI, Belli G, Iannelli A, Ciciliano F, Izzo P. Evidence for a recessive inheritance of Turcot's syndrome caused by compound heterozygous mutations within the PMS2 gene. *Oncogene* 2000;19:1719-23.
46. De Vos M, Hayward BE, Picton S, Sheridan E, Bonthron DT. Novel PMS2 pseudogenes can conceal recessive mutations causing a distinctive childhood cancer syndrome. *Am J Hum Genet* 2004;74:954-64.
47. Debnik T, Kurzawski G, Gorski B, Kladny J, Domagala W, Lubinski J. Value of pedigree/clinical data, immunohistochemistry and microsatellite instability analyses in reducing the cost of determining hMLH1 and hMSH2 gene mutations in patients with colorectal cancer. *Eur J Cancer* 2000;36:49-54.
48. Deng G, Bell I, Crawley S, Gum J, Terdiman JP, Allen BA, Truta B, Sleisenger MH, Kim YS. BRAF mutation is frequently present in sporadic colorectal cancer with methylated hMLH1, but not in hereditary nonpolyposis colorectal cancer. *Clin Cancer Res* 2004;10:191-5.
49. Desai DC, Lockman JC, Chadwick RB, Gao X, Percesepe A, Evans DG, Miyaki M, Yuen ST, Radice P, Maher ER, Wright FA, de La Chapelle A. Recurrent germline mutation in MSH2 arises frequently de novo. *J Med Genet* 2000;37:646-52.
50. Dong SM, Traverso G, Johnson C, Geng L, Favis R, Boynton K, Hibi K, Goodman SN, D'Allesio M, Paty P, Hamilton SR, Sidransky D, Barany F, Levin B, Shuber A, Kinzler KW, Vogelstein B, Jen J. Detecting colorectal cancer in stool with the use of multiple genetic targets. *J Natl Cancer Inst* 2001;93:858-65.
51. dos Santos NR, Seruca R, Constancia M, Seixas M, Sobrinho-Simoes M. Microsatellite instability at multiple loci in gastric carcinoma: clinicopathologic implications and prognosis. *Gastroenterology* 1996;110:38-44.
52. Dove-Edwin I, Boks D, Goff S, Kenter GG, Carpenter R, Vasen HF, Thomas HJ. The outcome of endometrial carcinoma surveillance by ultrasound scan in women at risk of hereditary nonpolyposis colorectal carcinoma and familial colorectal carcinoma. *Cancer* 2002;94:1708-12.
53. Drummond JT, Li GM, Longley MJ, Modrich P. Isolation of an hMSH2-p160 heterodimer that restores DNA mismatch repair to tumor cells. *Science* 1995;268:1909-12.
54. Dunlop MG, Farrington SM, Carothers AD, Wyllie AH, Sharp L, Burn J, Liu B, Kinzler KW, Vogelstein B. Cancer risk associated with germline DNA mismatch repair gene mutations. *Hum Mol Genet* 1997;6:105-10.
55. Ellison AR, Lofing J, Bitter GA. Functional analysis of human MLH1 and MSH2 missense variants and hybrid human-yeast MLH1 proteins in *Saccharomyces cerevisiae*. *Hum Mol Genet* 2001;10:1889-900.
56. Entius MM, Keller JJ, Drilenburg P, Kuypers KC, Giardiello FM, Offerhaus GJ. Microsatellite instability and expression of hMLH-1 and hMSH-2 in sebaceous gland carcinomas as markers for Muir-Torres syndrome. *Clin Cancer Res* 2000;6:1784-9.
57. Falk MJ, Dugan RB, O'Riordan MA, Matthews AL, Robin NH. Medical Geneticists' duty to warn at-risk relatives for genetic disease. *Am J Med Genet* 2003;120A:374-80.
58. Fishel R, Lescoe MK, Rao MR, Copeland NG, Jenkins NA, Garber J, Kane M, Kolodner R. The human mutator gene homolog MSH2 and its association with hereditary nonpolyposis colon cancer. *Cell* 1993;75:1027-38.
59. Fishel R. The selection for mismatch repair defects in hereditary nonpolyposis colorectal cancer: revising the mutator hypothesis. *Cancer Res* 2001;61:7369-74.
60. Fodde R, Smits R. Cancer biology. A matter of dosage. *Science* 2002;298:761-3.
61. Fodde R. The APC gene in colorectal cancer. *Eur J Cancer* 2002;38:867-71.
62. Fodde R, Losekoot M. Mutation detection by denaturing gradient gel electrophoresis (DGGE). *Hum Mutat* 1994;3:83-94.
63. Fodde R, Khan PM. Genotype-phenotype correlations at the adenomatous polyposis coli (APC) gene. *Crit Rev Oncog* 1995;6:291-303.
64. Foulkes WD, Thiffault I, Gruber SB, Horwitz M, Hamel N, Lee C, Shia J, Markowitz A, Figer A, Friedman E, Farber D, Greenwood CM, Bonner JD, Nafa K, Walsh T, Marcus V, Tomsho L, Gebert J, Macrae FA, Gaff CL, Paillerets BB, Gregersen PK, Weitzel JN, Gordon PH, MacNamara E, King MC, Hampel H, De La Chapelle A, Boyd J, Offit K, Rennert G, Chong G, Ellis NA. The founder mutation MSH2*1906G-->C is an important cause of hereditary nonpolyposis colorectal cancer in the Ashkenazi Jewish population. *Am J Hum Genet* 2002;71:1395-412.
65. Froggatt NJ, Green J, Brassett C, Evans DG, Bishop DT, Kolodner R, Maher ER. A common MSH2 mutation in English and North American HNPCC families: origin, phenotypic expression, and sex specific differences in colorectal cancer. *J Med Genet* 1999;36:97-102.
66. Fujita M, Enomoto T, Yoshino K, Nomura T, Buzard GS, Inoue M, Okudaira Y. Microsatellite instability and alterations in the hMSH2 gene in human ovarian cancer. *Int J Cancer* 1995;64:361-6.

67. Fujiwara T, Stolker JM, Watanabe T, Rashid A, Longo P, Eshleman JR, Booker S, Lynch HT, Jass JR, Green JS, Kim H, Jen J, Vogelstein B, Hamilton SR. Accumulated clonal genetic alterations in familial and sporadic colorectal carcinomas with widespread instability in microsatellite sequences. *Am J Pathol* 1998;153:1063-78.
68. Fukushima T, Takenoshita S. Colorectal carcinogenesis. *Fukushima J Med Sci* 2001;47:1-11.
69. Fusaro RM, Lynch HT, Pester J, Lynch PM. Torre's syndrome as phenotypic expression of cancer family syndrome. *Arch Dermatol* 1980;116:986-7.
70. Futreal PA, Coin L, Marshall M, Down T, Hubbard T, Wooster R, Rahman N, Stratton MR. A census of human cancer genes. *Nat Rev Cancer* 2004;4:177-83.
71. Gallinger S, Aronson M, Shayan K, Ratcliffe EM, Gerstle JT, Parkin PC, Rothenmund H, Croitoru M, Baumann E, Durie PR, Weksberg R, Pollett A, Riddell RH, Ngan BY, Cutz E, Lagarde AE, Chan HS. Gastrointestinal cancers and neurofibromatosis type 1 features in children with a germline homozygous MLH1 mutation. *Gastroenterology* 2004;126:576-85.
72. Gazzoli I, Loda M, Garber J, Syngal S, Kolodner RD. A hereditary nonpolyposis colorectal carcinoma case associated with hypermethylation of the MLH1 gene in normal tissue and loss of heterozygosity of the unmethylated allele in the resulting microsatellite instability-high tumor. *Cancer Res* 2002;62:3925-8.
73. Giardiello FM, Brensinger JD, Petersen GM. AGA technical review on hereditary colorectal cancer and genetic testing. *Gastroenterology* 2001;121:198-213.
74. Giardiello FM, Hamilton SR, Krush AJ, Piantadosi S, Hyland LM, Celano P, Booker SV, Robinson CR, Offerhaus GJ. Treatment of colonic and rectal adenomas with sulindac in familial adenomatous polyposis. *N Engl J Med* 1993;328:1313-6.
75. Giardiello FM, Yang VW, Hyland LM, Krush AJ, Petersen GM, Trimpath JD, Piantadosi S, Garrett E, Geiman DE, Hubbard W, Offerhaus GJ, Hamilton SR. Primary chemoprevention of familial adenomatous polyposis with sulindac. *N Engl J Med* 2002;346:1054-9.
76. Giardiello FM, Brensinger JD, Tersmette AC, Goodman SN, Petersen GM, Booker SV, Cruz-Correa M, Offerhaus JA. Very high risk of cancer in familial Peutz-Jeghers syndrome. *Gastroenterology* 2000;119:1447-53.
77. Gille JJ, Hogervorst FB, Pals G, Wijnen JT, van Schooten RJ, Dommering CJ, Meijer GA, Craanen ME, Nederlof PM, de Jong D, McElgunn CJ, Schouten JP, Menko FH. Genomic deletions of MSH2 and MLH1 in colorectal cancer families detected by a novel mutation detection approach. *Br J Cancer* 2002;87:892-7.
78. Goel A, Arnold CN, Boland CR. Multistep progression of colorectal cancer in the setting of microsatellite instability: new details and novel insights. *Gastroenterology* 2001;121:1497-502.
79. Gollub MJ. Virtual colonoscopy. *Lancet* 2002;360:964.
80. Grady WM, Rajput A, Lutterbaugh JD, Markowitz SD. Detection of aberrantly methylated hMLH1 promoter DNA in the serum of patients with microsatellite unstable colon cancer. *Cancer Res* 2001;61:900-2.
81. Green RC, Green AG, Simms M, Pater A, Robb JD, Green JS. Germline hMLH1 promoter mutation in a Newfoundland HNPCC kindred. *Clin Genet* 2003;64:220-7.
82. Gruber SB, Ellis NA, Scott KK, Almog R, Kolachana P, Bonner JD, Kirchhoff T, Tomsho LP, Nafa K, Pierce H, Low M, Satagopan J, Rennert H, Huang H, Greenson JK, Groden J, Rapaport B, Shia J, Johnson S, Gregersen PK, Harris CC, Boyd J, Rennert G, Offit K. BLM heterozygosity and the risk of colorectal cancer. *Science* 2002;297:2013.
83. Guerrette S, Wilson T, Gradia S, Fishel R. Interactions of human hMSH2 with hMSH3 and hMSH2 with hMSH6: examination of mutations found in hereditary nonpolyposis colorectal cancer. *Mol Cell Biol* 1998;18:6616-23.
84. Guilford P, Hopkins J, Harraway J, McLeod M, McLeod N, Harawira P, Taite H, Scoular R, Miller A, Reeve AE. E-cadherin germline mutations in familial gastric cancer. *Nature* 1998;392:402-5.
85. Hadley DW, Jenkins J, Dimond E, Nakahara K, Grogan L, Liewehr DJ, Steinberg SM, Kirsch I. Genetic counseling and testing in families with hereditary nonpolyposis colorectal cancer. *Arch Intern Med* 2003;163:573-82.
86. Hamilton SR, Liu B, Parsons RE, Papadopoulos N, Jen J, Powell SM, Krush AJ, Berk T, Cohen Z, Tetu B, et al. The molecular basis of Turcot's syndrome. *N Engl J Med* 1995;332:839-47.
87. Hampel H, Peltomaki P. Hereditary colorectal cancer: risk assessment and management. *Clin Genet* 2000;58:89-97.
88. Han HJ, Maruyama M, Baba S, Park JG, Nakamura Y. Genomic structure of human mismatch repair gene, hMLH1, and its mutation analysis in patients with hereditary non-polyposis colorectal cancer (HNPCC). *Hum Mol Genet* 1995;4:237-42.
89. Hanahan D, Weinberg RA. The hallmarks of cancer. *Cell* 2000;100:57-70.

90. Hartmann A, Zanardo L, Bocker-Edmonston T, Blaszyk H, Dietmaier W, Stoehr R, Cheville JC, Junker K, Wieland W, Knuechel R, Rueschoff J, Hofstaedter F, Fishel R. Frequent microsatellite instability in sporadic tumors of the upper urinary tract. *Cancer Res* 2002;62:6796-802.
91. Hawk E, Lubet R, Limburg P. Chemoprevention in hereditary colorectal cancer syndromes. *Cancer* 1999;86:2551-63.
92. Hawk ET, Umar A, Viner JL. Colorectal cancer chemoprevention—an overview of the science. *Gastroenterology* 2004;126:1423-47.
93. Hawkins NJ, Gorman P, Tomlinson IP, Bullpitt P, Ward RL. Colorectal carcinomas arising in the hyperplastic polyposis syndrome progress through the chromosomal instability pathway. *Am J Pathol* 2000;157:385-92.
94. He TC, Sparks AB, Rago C, Hermeking H, Zawel L, da Costa LT, Morin PJ, Vogelstein B, Kinzler KW. Identification of c-MYC as a target of the APC pathway. *Science* 1998;281:1509-12.
95. Heinen CD, Wilson T, Mazurek A, Berardini M, Butz C, Fishel R. HNPCC mutations in hMSH2 result in reduced hMSH2-hMSH6 molecular switch functions. *Cancer Cell* 2002;1:469-78.
96. Heinimann K, Thompson A, Locher A, Furlanetto T, Bader E, Wolf A, Meier R, Walter K, Bauerfeind P, Marra G, Muller H, Foernzler D, Dobbie Z. Nontruncating APC germ-line mutations and mismatch repair deficiency play a minor role in APC mutation-negative polyposis. *Cancer Res* 2001;61:7616-22.
97. Helland A, Borresen-Dale AL, Peltomaki P, Hektoen M, Kristensen GB, Nesland JM, de la Chapelle A, Lothe RA. Microsatellite instability in cervical and endometrial carcinomas. *Int J Cancer* 1997;70:499-501.
98. Hemminki A, Peltomaki P, Mecklin JP, Jarvinen H, Salovaara R, Nystrom-Lahti M, de la Chapelle A, Aaltonen LA. Loss of the wild type MLH1 gene is a feature of hereditary nonpolyposis colorectal cancer. *Nat Genet* 1994;8:405-10.
99. Hemminki A, Mecklin JP, Jarvinen H, Aaltonen LA, Joensuu H. Microsatellite instability is a favorable prognostic indicator in patients with colorectal cancer receiving chemotherapy. *Gastroenterology* 2000;119:921-8.
100. Hendriks Y, Franken P, Dierksen JW, De Leeuw W, Wijnen J, Dreef E, Tops C, Breuning M, Brocker-Vriends A, Vasen H, Fodde R, Morreau H. Conventional and tissue microarray immunohistochemical expression analysis of mismatch repair in hereditary colorectal tumors. *Am J Pathol* 2003;162:469-77.
101. Hendriks YM, Wagner A, Morreau H, Menko F, Stormorken A, Quehenberger F, Sandkuijl L, Moller P, Genuardi M, Van Houwelingen H, Tops C, Van Puijbroek M, Verkuijlen P, Kenter G, Van Mil A, Meijers-Heijboer H, Tan GB, Breuning MH, Fodde R, Wijnen JT, Brocker-Vriends AH, Vasen H. Cancer risk in hereditary nonpolyposis colorectal cancer due to MSH6 mutations: impact on counseling and surveillance. *Gastroenterology* 2004;127:17-25.
102. Herfarth KK, Kodner IJ, Whelan AJ, Ivanovich JL, Bracamontes JR, Wells SA, Jr., Goodfellow PJ. Mutations in MLH1 are more frequent than in MSH2 in sporadic colorectal cancers with microsatellite instability. *Genes Chromosomes Cancer* 1997;18:42-9.
103. Herman JG, Umar A, Polyak K, Graff JR, Ahuja N, Issa JP, Markowitz S, Willson JK, Hamilton SR, Kinzler KW, Kane MF, Kolodner RD, Vogelstein B, Kunkel TA, Baylin SB. Incidence and functional consequences of hMLH1 promoter hypermethylation in colorectal carcinoma. *Proc Natl Acad Sci U S A* 1998;95:6870-5.
104. Hienonen T, Laiho P, Salovaara R, Mecklin JP, Jarvinen H, Sistonen P, Peltomaki P, Lehtonen R, Nupponen NN, Launonen V, Karhu A, Aaltonen LA. Little evidence for involvement of MLH3 in colorectal cancer predisposition. *Int J Cancer* 2003;106:292-6.
105. Huang J, Papadopoulos N, McKinley AJ, Farrington SM, Curtis LJ, Wyllie AH, Zheng S, Willson JK, Markowitz SD, Morin P, Kinzler KW, Vogelstein B, Dunlop MG. APC mutations in colorectal tumors with mismatch repair deficiency. *Proc Natl Acad Sci U S A* 1996;93:9049-54.
106. Huang J, Zheng S, Jin SH, Zhang SZ. Somatic mutations of APC gene in carcinomas from hereditary non-polyposis colorectal cancer patients. *World J Gastroenterol* 2004;10:834-6.
107. Huang J, Kuismanen SA, Liu T, Chadwick RB, Johnson CK, Stevens MW, Richards SK, Meek JE, Gao X, Wright FA, Mecklin JP, Jarvinen HJ, Gronberg H, Bisgaard ML, Lindblom A, Peltomaki P. MSH6 and MSH3 are rarely involved in genetic predisposition to nonpolyposis colon cancer. *Cancer Res* 2001;61:1619-23.
108. Husain SS, Szabo IL, Tamawski AS. NSAID inhibition of GI cancer growth: clinical implications and molecular mechanisms of action. *Am J Gastroenterol* 2002;97:542-53.
109. Hutter P, Couturier A, Scott RJ, Alday P, Delozier-Blanchet C, Cachat F, Antonarakis SE, Joris F, Gaudin M, D'Amato L, Buerstedde JM. Complex genetic predisposition to cancer in an extended HNPCC family with an ancestral hMLH1 mutation. *J Med Genet* 1996;33:636-40.
110. Iaccharino I, Palombo F, Drummond J, Totty NF, Hsuan JJ, Modrich P, Jiricny J. MSH6, a Saccharomyces cerevisiae protein that binds to mismatches as a heterodimer with MSH2. *Curr Biol* 1996;6:484-6.

111. Ichikawa Y, Lemon SJ, Wang S, Franklin B, Watson P, Knezetic JA, Bewtra C, Lynch HT. Microsatellite instability and expression of MLH1 and MSH2 in normal and malignant endometrial and ovarian epithelium in hereditary nonpolyposis colorectal cancer family members. *Cancer Genet Cytogenet* 1999;112:2-8.
112. Iino H, Simms L, Young J, Arnold J, Winship IM, Webb SI, Furlong KL, Leggett B, Jass JR. DNA microsatellite instability and mismatch repair protein loss in adenomas presenting in hereditary non-polyposis colorectal cancer. *Gut* 2000;47:37-42.
113. Imperiale TF, Wagner DR, Lin CY, Larkin GN, Rogge JD, Ransohoff DF. Results of screening colonoscopy among persons 40 to 49 years of age. *N Engl J Med* 2002;346:1781-5.
114. Ionov Y, Peinado MA, Malkhosyan S, Shibata D, Perucho M. Ubiquitous somatic mutations in simple repeated sequences reveal a new mechanism for colonic carcinogenesis. *Nature* 1993;363:558-61.
115. Jacob S, Aguado M, Fallik D, Praz F. The role of the DNA mismatch repair system in the cytotoxicity of the topoisomerase inhibitors camptothecin and etoposide to human colorectal cancer cells. *Cancer Res* 2001;61:6555-62.
116. Jagmohan-Changur S, Poikonen T, Vilkkii S, Launonen V, Wikman F, Orntoft TF, Moller P, Vasen H, Tops C, Kolodner RD, Mecklin JP, Jarvinen H, Bevan S, Houlston RS, Aaltonen LA, Fodde R, Wijnen J, Karhu A. EXO1 variants occur commonly in normal population: evidence against a role in hereditary nonpolyposis colorectal cancer. *Cancer Res* 2003;63:154-8.
117. Jarvinen HJ, Aarnio M, Mustonen H, Aktan-Collan K, Aaltonen LA, Peltomaki P, De La Chapelle A, Mecklin JP. Controlled 15-year trial on screening for colorectal cancer in families with hereditary nonpolyposis colorectal cancer. *Gastroenterology* 2000;118:829-34.
118. Jarvinen HJ, Mecklin JP, Sistonen P. Screening reduces colorectal cancer rate in families with hereditary nonpolyposis colorectal cancer. *Gastroenterology* 1995;108:1405-11.
119. Jass JR, Stewart SM. Evolution of hereditary non-polyposis colorectal cancer. *Gut* 1992;33:783-6.
120. Jass JR, Young J, Leggett BA. Hyperplastic polyps and DNA microsatellite unstable cancers of the colorectum. *Histopathology* 2000;37:295-301.
121. Jiricny J, Nystrom-Lahti M. Mismatch repair defects in cancer. *Curr Opin Genet Dev* 2000;10:157-61.
122. Jones S, Emmerson P, Maynard J, Best JM, Jordan S, Williams GT, Sampson JR, Cheadle JP. Biallelic germline mutations in MYH predispose to multiple colorectal adenoma and somatic G:C-->T:A mutations. *Hum Mol Genet* 2002;11:2961-7.
123. Kallioniemi OP, Wagner U, Kononen J, Sauter G. Tissue microarray technology for high-throughput molecular profiling of cancer. *Hum Mol Genet* 2001;10:657-62.
124. Kanamori M, Kon H, Nobukuni T, Nomura S, Sugano K, Mashiyama S, Kumabe T, Yoshimoto T, Meuth M, Sekiya T, Murakami Y. Microsatellite instability and the PTEN1 gene mutation in a subset of early onset gliomas carrying germline mutation or promoter methylation of the hMLH1 gene. *Oncogene* 2000;19:1564-71.
125. Kariola R, Raevaara TE, Lonnqvist KE, Nystrom-Lahti M. Functional analysis of MSH6 mutations linked to kindreds with putative hereditary non-polyposis colorectal cancer syndrome. *Hum Mol Genet* 2002;11:1303-10.
126. Karran P. Appropriate partners make good matches. *Science* 1995;268:1857-8.
127. Karran P, Marinus MG. Mismatch correction at O6-methylguanine residues in *E. coli* DNA. *Nature* 1982;296:868-9.
128. Karran P. Microsatellite instability and DNA mismatch repair in human cancer. *Semin Cancer Biol* 1996;7:15-24.
129. Kat A, Thilly WG, Fang WH, Longley MJ, Li GM, Modrich P. An alkylation-tolerant, mutator human cell line is deficient in strand-specific mismatch repair. *Proc Natl Acad Sci U S A* 1993;90:6424-8.
130. Katballe N, Bentzen SM, Christensen M, Wikman FP, Orntoft T, Laurberg S. Role of chance in familial aggregation of colorectal cancer. *Br J Cancer* 2001;84:1084-6.
131. Key TJ, Allen NE, Spencer EA, Travis RC. The effect of diet on risk of cancer. *Lancet* 2002;360:861-8.
132. Kielman MF, Rindapaa M, Gaspar C, van Poppel N, Breukel C, van Leeuwen S, Taketo MM, Roberts S, Smits R, Fodde R. Apc modulates embryonic stem-cell differentiation by controlling the dosage of beta-catenin signaling. *Nat Genet* 2002;32:594-605.
133. Kinzler KW, Vogelstein B. Landscaping the cancer terrain. *Science* 1998;280:1036-7.
134. Knudson AG, Jr. Mutation and cancer: statistical study of retinoblastoma. *Proc Natl Acad Sci U S A* 1971;68:820-3.
135. Knudson AG, Jr. Hereditary cancer, oncogenes, and antioncogenes. *Cancer Res* 1985;45:1437-43.
136. Koide N, Saito Y, Fujii T, Kondo H, Saito D, Shimoda T. A case of hyperplastic polyposis of the colon with adenocarcinomas in hyperplastic polyps after long-term follow-up. *Endoscopy* 2002;34:499-502.
137. Koliopoulos A, Wirtz M, Buchler MW, Friess H. The role of surgery in the prevention of familial cancer syndromes of the gastrointestinal tract. *Dig Dis* 2002;20:91-101.
138. Kolodner R. Biochemistry and genetics of eukaryotic mismatch repair. *Genes Dev* 1996;10:1433-42.

139. Kolodner RD, Marsischky GT. Eukaryotic DNA mismatch repair. *Curr Opin Genet Dev* 1999;9:89-96.
140. Kolodner RD, Hall NR, Lipford J, Kane MF, Rao MR, Morrison P, Wirth L, Finan PJ, Burn J, Chapman P. Structure of the human MSH2 locus and analysis of two Muir-Torre kindreds for msh2 mutations. *Genomics* 1994;24:516-26.
141. Konishi K, Kaneko K, Kurahashi T, Yamamoto T, Kushima M, Kanda A, Tajiri H, Mitamura K. A comparison of magnifying and nonmagnifying colonoscopy for diagnosis of colorectal polyps: A prospective study. *Gastrointest Endosc* 2003;57:48-53.
142. Konishi M, Kikuchi-Yanoshita R, Tanaka K, Muraoka M, Onda A, Okumura Y, Kishi N, Iwama T, Mori T, Koike M, Ushio K, Chiba M, Nomizu S, Konishi F, Utsunomiya J, Miyaki M. Molecular nature of colon tumors in hereditary nonpolyposis colon cancer, familial polyposis, and sporadic colon cancer. *Gastroenterology* 1996;111:307-17.
143. Kraus C, Kastl S, Gunther K, Klessinger S, Hohenberger W, Ballhausen WG. A proven de novo germline mutation in HNPCC. *J Med Genet* 1999;36:919-21.
144. Kruse R, Rutten A, Lamberti C, Hosseiny-Malayeri HR, Wang Y, Ruelfs C, Jungck M, Mathiak M, Ruzicka T, Hartschuh W, Bisceglia M, Friedl W, Propping P. Muir-Torre phenotype has a frequency of DNA mismatch-repair-gene mutations similar to that in hereditary nonpolyposis colorectal cancer families defined by the Amsterdam criteria. *Am J Hum Genet* 1998;63:63-70.
145. Kuusmanen SA, Moisio AL, Schweizer P, Truninger K, Salovaara R, Arola J, Butzow R, Jiricny J, Nystrom-Lahti M, Peltomaki P. Endometrial and colorectal tumors from patients with hereditary nonpolyposis colon cancer display different patterns of microsatellite instability. *Am J Pathol* 2002;160:1953-8.
146. Laiho P, Launonen V, Lahermo P, Esteller M, Guo M, Herman JG, Mecklin JP, Jarvinen H, Sistonen P, Kim KM, Shibata D, Houlston RS, Aaltonen LA. Low-level microsatellite instability in most colorectal carcinomas. *Cancer Res* 2002;62:1166-70.
147. Laken SJ, Papadopoulos N, Petersen GM, Gruber SB, Hamilton SR, Giardiello FM, Brensinger JD, Vogelstein B, Kinzler KW. Analysis of masked mutations in familial adenomatous polyposis. *Proc Natl Acad Sci U S A* 1999;96:2322-6.
148. Lamberti C, Kruse R, Ruelfs C, Caspari R, Wang Y, Jungck M, Mathiak M, Malayeri HR, Friedl W, Sauerbruch T, Propping P. Microsatellite instability-a useful diagnostic tool to select patients at high risk for hereditary non-polyposis colorectal cancer: a study in different groups of patients with colorectal cancer. *Gut* 1999;44:839-43.
149. Lamers MH, Perrakis A, Enzlin JH, Winterwerp HH, de Wind N, Sixma TK. The crystal structure of DNA mismatch repair protein MutS binding to a G x T mismatch. *Nature* 2000;407:711-7.
150. Lammi L, Arte S, Somer M, Jarvinen H, Lahermo P, Thesleff I, Pirinen S, Nieminen P. Mutations in AXIN2 cause familial tooth agenesis and predispose to colorectal cancer. *Am J Hum Genet* 2004;74:1043-50.
151. Laurent-Puig P, Blons H, Cugnenc PH. Sequence of molecular genetic events in colorectal tumorigenesis. *Eur J Cancer Prev* 1999;8 Suppl 1:S39-47.
152. Leach FS, Nicolaides NC, Papadopoulos N, Liu B, Jen J, Parsons R, Peltomaki P, Sistonen P, Aaltonen LA, Nystrom-Lahti M, et al. Mutations of a mutS homolog in hereditary nonpolyposis colorectal cancer. *Cell* 1993;75:1215-25.
153. Leggett BA, Devereaux B, Biden K, Searle J, Young J, Jass J. Hyperplastic polyposis: association with colorectal cancer. *Am J Surg Pathol* 2001;25:177-84.
154. Lerman C, Hughes C, Trock BJ, Myers RE, Main D, Bonney A, Abbaszadegan MR, Harty AE, Franklin BA, Lynch JF, Lynch HT. Genetic testing in families with hereditary nonpolyposis colon cancer. *Jama* 1999;281:1618-22.
155. Leung SY, Chan TL, Chung LP, Chan AS, Fan YW, Hung KN, Kwong WK, Ho JW, Yuen ST. Microsatellite instability and mutation of DNA mismatch repair genes in gliomas. *Am J Pathol* 1998;153:1181-8.
156. Leung WK, Kim JJ, Wu L, Sepulveda JL, Sepulveda AR. Identification of a second MutL DNA mismatch repair complex (hPMS1 and hMLH1) in human epithelial cells. *J Biol Chem* 2000;275:15728-32.
157. Lieberman DA, Weiss DG. One-time screening for colorectal cancer with combined fecal occult-blood testing and examination of the distal colon. *N Engl J Med* 2001;345:555-60.
158. Lin KM, Shashidharan M, Thorson AG, Tement CA, Blatchford GJ, Christensen MA, Watson P, Lemon SJ, Franklin B, Karr B, Lynch J, Lynch HT. Cumulative incidence of colorectal and extracolonic cancers in MLH1 and MSH2 mutation carriers of hereditary nonpolyposis colorectal cancer. *J Gastrointest Surg* 1998;2:67-71.
159. Lin KM, Shashidharan M, Tement CA, Thorson AG, Blatchford GJ, Christensen MA, Lanspa SJ, Lemon SJ, Watson P, Lynch HT. Colorectal and extracolonic cancer variations in MLH1/MSH2 hereditary nonpolyposis colorectal cancer kindreds and the general population. *Dis Colon Rectum* 1998;41:428-33.

160. Lindor NM, Burgart LJ, Leontovich O, Goldberg RM, Cunningham JM, Sargent DJ, Walsh-Vockley C, Petersen GM, Walsh MD, Leggett BA, Young JP, Barker MA, Jass JR, Hopper J, Gallinger S, Bapat B, Redston M, Thibodeau SN. Immunohistochemistry versus microsatellite instability testing in phenotyping colorectal tumors. *J Clin Oncol* 2002;20:1043-8.
161. Lipkin SM, Wang V, Jacoby R, Banerjee-Basu S, Baxevanis AD, Lynch HT, Elliott RM, Collins FS. MLH3: a DNA mismatch repair gene associated with mammalian microsatellite instability. *Nat Genet* 2000;24:27-35.
162. Lipkin SM, Moens PB, Wang V, Lenzi M, Shanmugarajah D, Gilgeous A, Thomas J, Cheng J, Touchman JW, Green ED, Schwartzberg P, Collins FS, Cohen PE. Meiotic arrest and aneuploidy in MLH3-deficient mice. *Nat Genet* 2002;31:385-90.
163. Lipkin SM, Wang V, Stoler DL, Anderson GR, Kirsch I, Hadley D, Lynch HT, Collins FS. Germline and somatic mutation analyses in the DNA mismatch repair gene MLH3: Evidence for somatic mutation in colorectal cancers. *Hum Mutat* 2001;17:389-96.
164. Lipkin SM, Rozek LS, Rennert G, Yang W, Chen PC, Hacia J, Hunt N, Shin B, Fodor S, Kokoris M, Greenon JK, Fearon E, Lynch H, Collins F, Gruber SB. The MLH1 D132H variant is associated with susceptibility to sporadic colorectal cancer. *Nat Genet* 2004;36:694-9.
165. Liu B, Parsons R, Papadopoulos N, Nicolaides NC, Lynch HT, Watson P, Jass JR, Dunlop M, Wyllie A, Peltomaki P, de la Chapelle A, Hamilton SR, Vogelstein B, Kinzler KW. Analysis of mismatch repair genes in hereditary non-polyposis colorectal cancer patients. *Nat Med* 1996;2:169-74.
166. Liu HX, Zhou XL, Liu T, Werelius B, Lindmark G, Dahl N, Lindblom A. The role of hMLH3 in familial colorectal cancer. *Cancer Res* 2003;63:1894-9.
167. Liu HX, Cartegni L, Zhang MQ, Krainer AR. A mechanism for exon skipping caused by nonsense or missense mutations in BRCA1 and other genes. *Nat Genet* 2001;27:55-8.
168. Liu T, Wahlberg S, Burek E, Lindblom P, Rubio C, Lindblom A. Microsatellite instability as a predictor of a mutation in a DNA mismatch repair gene in familial colorectal cancer. *Genes Chromosomes Cancer* 2000;27:17-25.
169. Liu T, Yan H, Kuismanen S, Percesepe A, Bisgaard ML, Pedroni M, Benatti P, Kinzler KW, Vogelstein B, Ponz de Leon M, Peltomaki P, Lindblom A. The role of hPMS1 and hPMS2 in predisposing to colorectal cancer. *Cancer Res* 2001;61:7798-802.
170. Liu W, Dong X, Mai M, Seelan RS, Taniguchi K, Krishnadath KK, Halling KC, Cunningham JM, Boardman LA, Qian C, Christensen E, Schmidt SS, Roche PC, Smith DJ, Thibodeau SN. Mutations in AXIN2 cause colorectal cancer with defective mismatch repair by activating beta-catenin/TCF signalling. *Nat Genet* 2000;26:146-7.
171. Lodder L, Frets PG, Trijsburg RW, Meijers-Heijboer EJ, Klijn JG, Duivenvoorden HJ, Tibben A, Wagner A, van der Meer CA, van den Ouweland AM, Niermeijer MF. Psychological impact of receiving a BRCA1/BRCA2 test result. *Am J Med Genet* 2001;98:15-24.
172. Lodder LN, Frets PG, Trijsburg RW, Meijers-Heijboer EJ, Klijn JG, Seynaeve C, van Geel AN, Tilanus MM, Bartels CC, Verhoog LC, Brekelmans CT, Burger CW, Niermeijer MF. One year follow-up of women opting for presymptomatic testing for BRCA1 and BRCA2: emotional impact of the test outcome and decisions on risk management (surveillance or prophylactic surgery). *Breast Cancer Res Treat* 2002;73:97-112.
173. Lodder LN. Dealing with the risk for hereditary breast and ovarian cancer; a prospective study on psychological consequences of choices on genetic testing, surveillance and prophylactic surgery. Thesis 2001;erasmus University Rotterdam, The Netherlands.
174. Loeb LA. A mutator phenotype in cancer. *Cancer Res* 2001;61:3230-9.
175. Loukola A, de la Chapelle A, Aaltonen LA. Strategies for screening for hereditary non-polyposis colorectal cancer. *J Med Genet* 1999;36:819-22.
176. Loukola A, Vilkki S, Singh J, Launonen V, Aaltonen LA. Germline and somatic mutation analysis of MLH3 in MSI-positive colorectal cancer. *Am J Pathol* 2000;157:347-52.
177. Lu SL, Kawabata M, Imamura T, Akiyama Y, Nomizu T, Miyazono K, Yuasa Y. HNPCC associated with germline mutation in the TGF-beta type II receptor gene. *Nat Genet* 1998;19:17-8.
178. Lynch HT, Watson P, Shaw TG, Lynch JF, Harty AE, Franklin BA, Kapler CR, Tinley ST, Liu B, Lerman C. Clinical impact of molecular genetic diagnosis, genetic counseling, and management of hereditary cancer: part II: hereditary nonpolyposis colorectal carcinoma as a model. *Cancer* 1999;86:1637-43.
179. Lynch HT, Smyrk T, Lynch J. An update of HNPCC (Lynch syndrome). *Cancer Genet Cytogenet* 1997;93:84-99.
180. Lynch HT, Smyrk TC, Watson P, Lanspa SJ, Lynch JF, Lynch PM, Cavalieri RJ, Boland CR. Genetics, natural history, tumor spectrum, and pathology of hereditary nonpolyposis colorectal cancer: an updated review. *Gastroenterology* 1993;104:1535-49.

181. Lynch HT, Lanspa S, Smyrk T, Boman B, Watson P, Lynch J. Hereditary nonpolyposis colorectal cancer (Lynch syndromes I & II). Genetics, pathology, natural history, and cancer control, Part I. *Cancer Genet Cytogenet* 1991;53:143-60.
182. Lynch HT, Boman B, Fitzgibbons RJ, Jr., Lanspa SJ, Smyrk TC. Hereditary nonpolyposis colon cancer: (Lynch syndrome I and II). A challenge for the clinician. *Nebr Med J* 1989;74:2-7.
183. Lynch HT, Kriegler M, Christiansen TA, Smyrk T, Lynch JF, Watson P. Laryngeal carcinoma in a Lynch syndrome II kindred. *Cancer* 1988;62:1007-13.
184. Lynch HT, Kimberling W, Albano WA, Lynch JF, Biscione K, Schuelke GS, Sandberg AA, Lipkin M, Deschner EE, Mikol YB, et al. Hereditary nonpolyposis colorectal cancer (Lynch syndromes I and II). I. Clinical description of resource. *Cancer* 1985;56:934-8.
185. Lynch HT, Shaw MW, Magnuson CW, Larsen AL, Krush AJ. Hereditary factors in cancer. Study of two large midwestern kindreds. *Arch Intern Med* 1966;117:206-12.
186. Lynch HT, Krush AJ. Cancer family "G" revisited: 1895-1970. *Cancer* 1971;27:1505-11.
187. Lynch HT. Is there a role for prophylactic subtotal colectomy among hereditary nonpolyposis colorectal cancer germline mutation carriers? *Dis Colon Rectum* 1996;39:109-10.
188. Lynch HT, Fusaro RM, Roberts L, Voorhees GJ, Lynch JF. Muir-Torre syndrome in several members of a family with a variant of the Cancer Family Syndrome. *Br J Dermatol* 1985;113:295-301.
189. Lynch HT, Taylor RJ, Lynch JF, Knezetic JA, Barrows A, Fodde R, Wijnen J, Wagner A. Multiple primary cancer, including transitional cell carcinoma of the upper uroepithelial tract in a multigeneration HNPCC family: molecular genetic, diagnostic, and management implications. *Am J Gastroenterol* 2003;98:664-70.
190. Lynch HT, Lynch PM, Pester J, Fusaro RM. The cancer family syndrome. Rare cutaneous phenotypic linkage of Torre's syndrome. *Arch Intern Med* 1981;141:607-11.
191. Lynch HT, Riley BD, Weissman SM, Coronel SM, Kinarsky Y, Lynch JF, Shaw TG, Rubinstein WS, Weismann S. Hereditary nonpolyposis colorectal carcinoma (HNPCC) and HNPCC-like families: Problems in diagnosis, surveillance, and management. *Cancer* 2004;100:53-64.
192. Lynch HT, Coronel SM, Okimoto R, Hampel H, Sweet K, Lynch JF, Barrows A, Wijnen J, van der Klift H, Franken P, Wagner A, Fodde R, de la Chapelle A. A founder mutation of the MSH2 gene and hereditary nonpolyposis colorectal cancer in the United States. *Jama* 2004;291:718-24.
193. Marsischky GT, Filosi N, Kane MF, Kolodner R. Redundancy of *Saccharomyces cerevisiae* MSH3 and MSH6 in MSH2-dependent mismatch repair. *Genes Dev* 1996;10:407-20.
194. Marten K, Bremer C, Khazaie K, Sameni M, Sloane B, Tung CH, Weissleder R. Detection of dysplastic intestinal adenomas using enzyme-sensing molecular beacons in mice. *Gastroenterology* 2002;122:406-14.
195. Martin RH, Green J, Ko E, Barclay L, Rademaker AW. Analysis of Aneuploidy Frequencies in Sperm from Patients with Hereditary Nonpolyposis Colon Cancer and an hMSH2 Mutation. *Am J Hum Genet* 2000;66:1149-1152.
196. McAllister M. Personal theories of inheritance, coping strategies, risk perception and engagement in hereditary non-polyposis colon cancer families offered genetic testing. *Clin Genet* 2003;64:179-89.
197. McGivern A, Wynter CV, Whitehall VL, Kambara T, Spring KJ, Walsh MD, Barker MA, Arnold S, Simms LA, Leggett BA, Young J, Jass JR. Promoter hypermethylation frequency and BRAF mutations distinguish hereditary non-polyposis colon cancer from sporadic MSI-H colon cancer. *Fam Cancer* 2004;3:101-7.
198. Mecklin JP, Jarvinen HJ. Clinical features of colorectal carcinoma in cancer family syndrome. *Dis Colon Rectum* 1986;29:160-4.
199. Mecklin JP, Jarvinen HJ. Tumor spectrum in cancer family syndrome (hereditary nonpolyposis colorectal cancer). *Cancer* 1991;68:1109-12.
200. Menko FH, Kaspers GL, Meijer GA, Claes K, van Hagen JM, Gille JJ. A homozygous MSH6 mutation in a child with cafe-au-lait spots, oligodendroglioma and rectal cancer. *Fam Cancer* 2004;3:123-7.
201. Menko FH, Sijmons RH. Erfelijk Darmkanker, richtlijnen voor diagnostiek, voorlichting en preventie. Werkgroep Klinische Oncogenetica/Vereniging Klinische Genetica Nederland 2001.
202. Miki Y, Swensen J, Shattuck-Eidens D, Futreal PA, Harshman K, Tavtigian S, Liu Q, Cochran C, Bennett LM, Ding W, et al. A strong candidate for the breast and ovarian cancer susceptibility gene BRCA1. *Science* 1994;266:66-71.
203. Mitchell RJ, Brewster D, Campbell H, Porteous ME, Wyllie AH, Bird CC, Dunlop MG. Accuracy of reporting of family history of colorectal cancer. *Gut* 2004;53:291-5.
204. Miyaki M, Iijima T, Kimura J, Yasuno M, Mori T, Hayashi Y, Koike M, Shitara N, Iwama T, Kuroki T. Frequent mutation of beta-catenin and APC genes in primary colorectal tumors from patients with hereditary nonpolyposis colorectal cancer. *Cancer Res* 1999;59:4506-9.
205. Miyaki M, Nishio J, Konishi M, Kikuchi-Yanoshita R, Tanaka K, Muraoka M, Nagato M, Chong JM, Koike M, Terada T, Kawahara Y, Fukutome A, Tomiyama J, Chuganji Y, Momoi M, Utsunomiya J. Drastic genetic instability of tumors and normal tissues in Turcot syndrome. *Oncogene* 1997;15:2877-81.

206. Miyaki M, Konishi M, Tanaka K, Kikuchi-Yanoshita R, Muraoka M, Yasuno M, Igari T, Koike M, Chiba M, Mori T. Germline mutation of MSH6 as the cause of hereditary nonpolyposis colorectal cancer. *Nat Genet* 1997;17:271-2.
207. Miyaki M, Iijima T, Ohue M, Kita Y, Hishima T, Kuroki T, Iwama T, Mori T. A novel case with germline p53 gene mutation having concurrent multiple primary colon tumours. *Gut* 2003;52:304-6.
208. Mizuguchi T, Collod-Beroud G, Akiyama T, Abifadel M, Harada N, Morisaki T, Allard D, Varret M, Claustres M, Morisaki H, Ihara M, Kinoshita A, Yoshiura K, Junien C, Kajii T, Jondeau G, Ohta T, Kishino T, Furukawa Y, Nakamura Y, Niikawa N, Boileau C, Matsumoto N. Heterozygous TGFBR2 mutations in Marfan syndrome. *Nat Genet* 2004;36:855-60.
209. Modrich P. Mismatch repair, genetic stability, and cancer. *Science* 1994;266:1959-60.
210. Moiso AL, Sistonen P, Weissenbach J, de la Chapelle A, Peltomaki P. Age and origin of two common MLH1 mutations predisposing to hereditary colon cancer. *Am J Hum Genet* 1996;59:1243-51.
211. Morin PJ, Sparks AB, Korinek V, Barker N, Clevers H, Vogelstein B, Kinzler KW. Activation of beta-catenin-Tcf signaling in colon cancer by mutations in beta-catenin or APC. *Science* 1997;275:1787-90.
212. Muir EG, Bell AJ, Barlow KA. Multiple primary carcinomata of the colon, duodenum, and larynx associated with kerato-acanthomata of the face. *Br J Surg* 1967;54:191-5.
213. Mukherjee D, Nissen SE, Topol EJ. Risk of cardiovascular events associated with selective COX-2 inhibitors. *Jama* 2001;286:954-9.
214. Muller A, Edmonston TB, Corao DA, Rose DG, Palazzo JP, Becker H, Fry RD, Rueschoff J, Fishel R. Exclusion of breast cancer as an integral tumor of hereditary nonpolyposis colorectal cancer. *Cancer Res* 2002;62:1014-9.
215. Nagase H, Nakamura Y. Mutations of the APC (adenomatous polyposis coli) gene. *Hum Mutat* 1993;2:425-34.
216. Nakagawa H, Yan H, Lockman J, Hampel H, Kinzler KW, Vogelstein B, De La Chapelle A. Allele separation facilitates interpretation of potential splicing alterations and genomic rearrangements. *Cancer Res* 2002;62:4579-82.
217. Nicolaides NC, Littman SJ, Modrich P, Kinzler KW, Vogelstein B. A naturally occurring hPMS2 mutation can confer a dominant negative mutator phenotype. *Mol Cell Biol* 1998;18:1635-41.
218. Nicolaides NC, Papadopoulos N, Liu B, Wei YF, Carter KC, Ruben SM, Rosen CA, Haseltine WA, Fleischmann RD, Fraser CM, et al. Mutations of two PMS homologues in hereditary nonpolyposis colon cancer. *Nature* 1994;371:75-80.
219. Nystrom-Lahti M, Perra C, Raschle M, Panyushkina-Seiler E, Marra G, Curci A, Quaresima B, Costanzo F, D'Urso M, Venuta S, Jiricny J. Functional analysis of MLH1 mutations linked to hereditary nonpolyposis colon cancer. *Genes Chromosomes Cancer* 2002;33:160-7.
220. Obmolova G, Ban C, Hsieh P, Yang W. Crystal structures of mismatch repair protein MutS and its complex with a substrate DNA. *Nature* 2000;407:703-10.
221. Ogura Y, Bonen DK, Inohara N, Nicolae DL, Chen FF, Ramos R, Britton H, Moran T, Karaliuskas R, Duerr RH, Achkar JP, Brant SR, Bayless TM, Kirschner BS, Hanauer SB, Nunez G, Cho JH. A frameshift mutation in NOD2 associated with susceptibility to Crohn's disease. *Nature* 2001;411:603-6.
222. Palombo F, Gallinari P, Iaccarino I, Lettieri T, Hughes M, D'Arrigo A, Truong O, Hsuan JJ, Jiricny J. GTBP, a 160-kilodalton protein essential for mismatch-binding activity in human cells. *Science* 1995;268:1912-4.
223. Pang Q, Prolla TA, Liskay RM. Functional domains of the *Saccharomyces cerevisiae* Mlh1p and Pms1p DNA mismatch repair proteins and their relevance to human hereditary nonpolyposis colorectal cancer-associated mutations. *Mol Cell Biol* 1997;17:4465-73.
224. Papadopoulos N, Leach FS, Kinzler KW, Vogelstein B. Monoallelic mutation analysis (MAMA) for identifying germline mutations. *Nat Genet* 1995;11:99-102.
225. Papadopoulos N, Nicolaides NC, Wei YF, Ruben SM, Carter KC, Rosen CA, Haseltine WA, Fleischmann RD, Fraser CM, Adams MD, et al. Mutation of a mutL homolog in hereditary colon cancer [see comments]. *Science* 1994;263:1625-9.
226. Park JG, Park YJ, Wijnen JT, Vasen HF. Gene-environment interaction in hereditary nonpolyposis colorectal cancer with implications for diagnosis and genetic testing. *Int J Cancer* 1999;82:516-9.
227. Peltomaki P, Vasen HF. Mutations predisposing to hereditary nonpolyposis colorectal cancer: database and results of a collaborative study. The International Collaborative Group on Hereditary Nonpolyposis Colorectal Cancer. *Gastroenterology* 1997;113:1146-58.
228. Peltomaki P. Deficient DNA mismatch repair: a common etiologic factor for colon cancer. *Hum Mol Genet* 2001;10:735-40.
229. Peterson SK, Watts BG, Koehly LM, Vernon SW, Baile WF, Kohlmann WK, Gritz ER. How families communicate about HNPCC genetic testing: findings from a qualitative study. *Am J Med Genet* 2003;119C:78-86.

230. Pharoah PD, Guilford P, Caldas C. Incidence of gastric cancer and breast cancer in CDH1 (E-cadherin) mutation carriers from hereditary diffuse gastric cancer families. *Gastroenterology* 2001;121:1348-53.
231. Phillips RK, Wallace MH, Lynch PM, Hawk E, Gordon GB, Saunders BP, Wakabayashi N, Shen Y, Zimmerman S, Godio L, Rodrigues-Bigas M, Su LK, Sherman J, Kelloff G, Levin B, Steinbach G. A randomised, double blind, placebo controlled study of celecoxib, a selective cyclooxygenase 2 inhibitor, on duodenal polyposis in familial adenomatous polyposis. *Gut* 2002;50:857-60.
232. Plaschke J, Ruschoff J, Schackert HK. Genomic rearrangements of hMSH6 contribute to the genetic predisposition in suspected hereditary non-polyposis colorectal cancer syndrome. *J Med Genet* 2003;40:597-600.
233. Plaschke J, Engel C, Kruger S, Holinski-Feder E, Pagenstecher C, Mangold E, Moeslein G, Schulmann K, Gebert J, von Knebel Doeberitz M, Ruschoff J, Loeffler M, Schackert HK. Lower Incidence of Colorectal Cancer and Later Age of Disease Onset in 27 Families With Pathogenic MSH6 Germline Mutations Compared With Families With MLH1 or MSH2 Mutations: The German Hereditary Nonpolyposis Colorectal Cancer Consortium. *J Clin Oncol* 2004;22:4486-94.
234. Polaczek P, Putzke AP, Leong K, Bitter GA. Functional genetic tests of DNA mismatch repair protein activity in *Saccharomyces cerevisiae*. *Gene* 1998;213:159-67.
235. Ponz de Leon M, Benatti P, Di Gregorio C, Pedroni M, Losi L, Genuardi M, Viel A, Fornasari M, Lucci-Cordisco E, Anti M, Ponti G, Borghi F, Lamberti I, Roncucci L. Genetic testing among high-risk individuals in families with hereditary nonpolyposis colorectal cancer. *Br J Cancer* 2004;90:882-7.
236. Potter JD. Colorectal cancer: molecules and populations. *J Natl Cancer Inst* 1999;91:916-32.
237. Rashid A, Houlihan PS, Booker S, Petersen GM, Giardiello FM, Hamilton SR. Phenotypic and molecular characteristics of hyperplastic polyposis. *Gastroenterology* 2000;119:323-32.
238. Renkonen-Sinisalo L, Aarnio M, Mecklin JP, Jarvinen HJ. Surveillance improves survival of colorectal cancer in patients with hereditary nonpolyposis colorectal cancer. *Cancer Detect Prev* 2000;24:137-42.
239. Renkonen-Sinisalo L, Sipponen P, Aarnio M, Julkunen R, Aaltonen LA, Sarna S, Jarvinen HJ, Mecklin JP. No support for endoscopic surveillance for gastric cancer in hereditary non-polyposis colorectal cancer. *Scand J Gastroenterol* 2002;37:574-7.
240. Reyes CM, Allen BA, Terdiman JP, Wilson LS. Comparison of selection strategies for genetic testing of patients with hereditary nonpolyposis colorectal carcinoma: effectiveness and cost-effectiveness. *Cancer* 2002;95:1848-56.
241. Rhyu MS. Molecular mechanisms underlying hereditary nonpolyposis colorectal carcinoma. *J Natl Cancer Inst* 1996;88:240-51.
242. Ribic CM, Sargent DJ, Moore MJ, Thibodeau SN, French AJ, Goldberg RM, Hamilton SR, Laurent-Puig P, Gryfe R, Shepherd LE, Tu D, Redston M, Gallinger S. Tumor microsatellite-instability status as a predictor of benefit from fluorouracil-based adjuvant chemotherapy for colon cancer. *N Engl J Med* 2003;349:247-57.
243. Ricciardone MD, Ozcelik T, Cevher B, Ozdag H, Tuncer M, Gurgey A, Uzunalimoglu O, Cetinkaya H, Tanyeli A, Erken E, Ozturk M. Human MLH1 deficiency predisposes to hematological malignancy and neurofibromatosis type 1. *Cancer Res* 1999;59:290-3.
244. Rijcken FE, Mourits MJ, Kleibeuker JH, Hollema H, van der Zee AG. Gynecologic screening in hereditary nonpolyposis colorectal cancer. *Gynecol Oncol* 2003;91:74-80.
245. Risinger JI, Barrett JC, Watson P, Lynch HT, Boyd J. Molecular genetic evidence of the occurrence of breast cancer as an integral tumor in patients with the hereditary nonpolyposis colorectal carcinoma syndrome. *Cancer* 1996;77:1836-43.
246. Risinger JI, Berchuck A, Kohler MF, Watson P, Lynch HT, Boyd J. Genetic instability of microsatellites in endometrial carcinoma. *Cancer Res* 1993;53:5100-3.
247. Rodriguez-Bigas MA, Vasen HF, Lynch HT, Watson P, Myrhoj T, Jarvinen HJ, Mecklin JP, Macrae F, St. John DJ, Bertario L, Fidalgo P, Madlensky L, Rozen P. Characteristics of small bowel carcinoma in hereditary nonpolyposis colorectal carcinoma. International Collaborative Group on HNPCC. *Cancer* 1998;83:240-4.
248. Rodriguez-Bigas MA, Boland CR, Hamilton SR, Henson DE, Jass JR, Khan PM, Lynch H, Perucho M, Smyrk T, Sobin L, Srivastava S. A National Cancer Institute Workshop on Hereditary Nonpolyposis Colorectal Cancer Syndrome: meeting highlights and Bethesda guidelines. *J Natl Cancer Inst* 1997;89:1758-62.
249. Roth S, Johansson M, Loukola A, Peltomaki P, Jarvinen H, Mecklin JP, Aaltonen LA. Mutation analysis of SMAD2, SMAD3, and SMAD4 genes in hereditary non-polyposis colorectal. *J Med Genet* 2000;37:298-300.
250. Saeterdal I, Bjorheim J, Lislerud K, Gjertsen MK, Bukholm IK, Olsen OC, Nesland JM, Eriksen JA, Moller M, Lindblom A, Gaudernack G. Frameshift-mutation-derived peptides as tumor-specific antigens in inherited and spontaneous colorectal cancer. *Proc Natl Acad Sci U S A* 2001;98:13255-60.

251. Saeterdal I, Gjertsen MK, Straten P, Eriksen JA, Gaudernack G. A TGF betaRII frameshift-mutation-derived CTL epitope recognised by HLA-A2-restricted CD8+ T cells. *Cancer Immunol Immunother* 2001;50:469-76.
252. Salahshor S, Kressner U, Pahlman L, Glimelius B, Lindmark G, Lindblom A. Colorectal cancer with and without microsatellite instability involves different genes. *Genes Chromosomes Cancer* 1999;26:247-52.
253. Sambrook J, Fritsch FE, Maniatis T. *A Laboratory Manual*. Cold Spring Harbor Laboratory Press, NY 1989.
254. Sankila R, Aaltonen LA, Jarvinen HJ, Mecklin JP. Better survival rates in patients with MLH1-associated hereditary colorectal cancer. *Gastroenterology* 1996;110:682-7.
255. Santucci-Darmanin S, Neyton S, Lespinasse F, Saunieres A, Gaudray P, Paquis-Flucklinger V. The DNA mismatch-repair MLH3 protein interacts with MSH4 in meiotic cells, supporting a role for this MutL homolog in mammalian meiotic recombination. *Hum Mol Genet* 2002;11:1697-706.
256. Sarles JC, Consentino B, Leandri R, Dor AM, Navarro PH. Mixed familial polyposis syndromes. *Int J Colorectal Dis* 1987;2:96-9.
257. Sawyer EJ, Cerar A, Hanby AM, Gorman P, Arends M, Talbot IC, Tomlinson IP. Molecular characteristics of serrated adenomas of the colorectum. *Gut* 2002;51:200-6.
258. Schmutte C, Marinescu RC, Sadoff MM, Guerrette S, Overhauser J, Fishel R. Human exonuclease I interacts with the mismatch repair protein hMSH2. *Cancer Res* 1998;58:4537-42.
259. Sepulveda AR, Santos AC, Yamaoka Y, Wu L, Gutierrez O, Kim JG, Graham DY. Marked differences in the frequency of microsatellite instability in gastric cancer from different countries. *Am J Gastroenterol* 1999;94:3034-8.
260. Shimizu Y, Ikeda S, Fujimori M, Kodama S, Nakahara M, Okajima M, Asahara T. Frequent alterations in the Wnt signaling pathway in colorectal cancer with microsatellite instability. *Genes Chromosomes Cancer* 2002;33:73-81.
261. Shimodaira H, Filosi N, Shibata H, Suzuki T, Radice P, Kanamaru R, Friend SH, Kolodner RD, Ishioka C. Functional analysis of human MLH1 mutations in *Saccharomyces cerevisiae*. *Nat Genet* 1998;19:384-9.
262. Shin KH, Shin JH, Kim JH, Park JG. Mutational analysis of promoters of mismatch repair genes hMSH2 and hMLH1 in hereditary nonpolyposis colorectal cancer and early onset colorectal cancer patients: identification of three novel germ-line mutations in promoter of the hMSH2 gene. *Cancer Res* 2002;62:38-42.
263. Shinmura K, Tani M, Isogaki J, Wang Y, Sugimura H, Yokota J. RER phenotype and its associated mutations in familial gastric cancer. *Carcinogenesis* 1998;19:247-51.
264. Sijmons R, Hofstra R, Hollema H, Mensink R, van der Hout A, Hoekstra H, Kleibeuker J, Molenaar W, Wijnen J, Fodde R, Vasen H, Buys C. Inclusion of malignant fibrous histiocytoma in the tumour spectrum associated with hereditary non-polyposis colorectal cancer. *Genes Chromosomes Cancer* 2000;29:353-5.
265. Sijmons RH, Kiemeneij LA, Witjes JA, Vasen HF. Urinary tract cancer and hereditary nonpolyposis colorectal cancer: risks and screening options. *J Urol* 1998;160:466-70.
266. Simms LA, Radford-Smith G, Biden KG, Buttenshaw R, Cummings M, Jass JR, Young J, Meltzer SJ, Leggett BA. Reciprocal relationship between the tumor suppressors p53 and BAX in primary colorectal cancers. *Oncogene* 1998;17:2003-8.
267. Smith KJ, Johnson KA, Bryan TM, Hill DE, Markowitz S, Willson JK, Paraskeva C, Petersen GM, Hamilton SR, Vogelstein B, et al. The APC gene product in normal and tumor cells. *Proc Natl Acad Sci U S A* 1993;90:2846-50.
268. Song K, Fendrick AM, Ladabaum U. Fecal DNA testing compared with conventional colorectal cancer screening methods: a decision analysis. *Gastroenterology* 2004;126:1270-9.
269. Soravia C, van der Klift H, Brundler MA, Blouin JL, Wijnen J, Hutter P, Fodde R, Delozier-Blanchet C. Prostate cancer is part of the hereditary non-polyposis colorectal cancer (HNPCC) tumor spectrum. *Am J Med Genet* 2003;121A:159-62.
270. Sparks AB, Morin PJ, Vogelstein B, Kinzler KW. Mutational analysis of the APC/beta-catenin/Tcf pathway in colorectal cancer. *Cancer Res* 1998;58:1130-4.
271. Srivastava S, Zou ZQ, Pirolo K, Blattner W, Chang EH. Germ-line transmission of a mutated p53 gene in a cancer-prone family with Li-Fraumeni syndrome. *Nature* 1990;348:747-9.
272. Stanley AJ, Gaff CL, Aittomaki AK, Fabre LC, Macrae FA, St John J. Value of predictive genetic testing in management of hereditary non-polyposis colorectal cancer (HNPCC). *Med J Aust* 2000;172:313-6.
273. Stella A, Wagner A, Shito K, Lipkin SM, Watson P, Guanti G, Lynch HT, Fodde R, Liu B. A nonsense mutation in MLH1 causes exon skipping in three unrelated HNPCC families. *Cancer Res* 2001;61:7020-4.
274. Stoeber K, Halsall I, Freeman A, Swinn R, Doble A, Morris L, Coleman N, Bullock N, Laskey RA, Hales CN, Williams GH. Immunoassay for urothelial cancers that detects DNA replication protein Mcm5 in urine. *Lancet* 1999;354:1524-5.
275. Sun X, Zheng L, Shen B. Functional alterations of human exonuclease 1 mutants identified in atypical hereditary nonpolyposis colorectal cancer syndrome. *Cancer Res* 2002;62:6026-30.

276. Suter CM, Martin DI, Ward RL. Germline epimutation of MLH1 in individuals with multiple cancers. *Nat Genet* 2004;36:497-501.
277. Syngal S, Fox EA, Eng C, Kolodner RD, Garber JE. Sensitivity and specificity of clinical criteria for hereditary non-polyposis colorectal cancer associated mutations in MSH2 and MLH1. *J Med Genet* 2000;37:641-5.
278. Tamura G, Sakata K, Maesawa C, Suzuki Y, Terashima M, Satoh K, Sekiyama S, Suzuki A, Eda Y, Satodate R. Microsatellite alterations in adenoma and differentiated adenocarcinoma of the stomach. *Cancer Res* 1995;55:1933-6.
279. Taylor CF, Charlton RS, Burn J, Sheridan E, Taylor GR. Genomic deletions in MSH2 or MLH1 are a frequent cause of hereditary non-polyposis colorectal cancer: identification of novel and recurrent deletions by MLPA. *Hum Mutat* 2003;22:428-33.
280. Taylor GRe. Laboratory methods for the detection of mutations and polymorphisms in DNA. CRC Press 1997.
281. te Riele H, Maandag ER, Berns A. Highly efficient gene targeting in embryonic stem cells through homologous recombination with isogenic DNA constructs. *Proc Natl Acad Sci U S A* 1992;89:5128-32.
282. Terdiman JP, Gum JR, Jr., Conrad PG, Miller GA, Weinberg V, Crawley SC, Levin TR, Reeves C, Schmitt A, Hepburn M, Sleisenger MH, Kim YS. Efficient detection of hereditary nonpolyposis colorectal cancer gene carriers by screening for tumor microsatellite instability before germline genetic testing. *Gastroenterology* 2001;120:21-30.
283. Tetsu O, McCormick F. Beta-catenin regulates expression of cyclin D1 in colon carcinoma cells. *Nature* 1999;398:422-6.
284. Thibodeau SN, French AJ, Roche PC, Cunningham JM, Tester DJ, Lindor NM, Moslein G, Baker SM, Liskay RM, Burgart LJ, Honchel R, Halling KC. Altered expression of hMSH2 and hMLH1 in tumors with microsatellite instability and genetic alterations in mismatch repair genes. *Cancer Res* 1996;56:4836-40.
285. Thibodeau SN, Bren G, Schaid D. Microsatellite instability in cancer of the proximal colon. *Science* 1993;260:816-9.
286. Thomas HJ, Whitelaw SC, Cottrell SE, Murday VA, Tomlinson IP, Markie D, Jones T, Bishop DT, Hodgson SV, Sheer D, Northover JM, Talbot IC, Solomon E, Bodmer WF. Genetic mapping of hereditary mixed polyposis syndrome to chromosome 6q. *Am J Hum Genet* 1996;58:770-6.
287. Thorstensen L, Diep CB, Meling GI, Aagesen TH, Ahrens CH, Rognum TO, Lothe RA. WNT1 inducible signaling pathway protein 3, WISP-3, a novel target gene in colorectal carcinomas with microsatellite instability. *Gastroenterology* 2001;121:1275-80.
288. Thun MJ, Henley SJ, Patrono C. Nonsteroidal anti-inflammatory drugs as anticancer agents: mechanistic, pharmacologic, and clinical issues. *J Natl Cancer Inst* 2002;94:252-66.
289. Tibben A, Vegter-van der Vlis M, Skraastad MI, Frets PG, van der Kamp JJ, Niermeijer MF, van Ommen GJ, Roos RA, Rooijmans HG, Stronks D, et al. DNA-testing for Huntington's disease in The Netherlands: a retrospective study on psychosocial effects. *Am J Med Genet* 1992;44:94-9.
290. Tishkoff DX, Amin NS, Viars CS, Arden KC, Kolodner RD. Identification of a human gene encoding a homologue of *Saccharomyces cerevisiae* EXO1, an exonuclease implicated in mismatch repair and recombination. *Cancer Res* 1998;58:5027-31.
291. Torre D. Multiple sebaceous tumors. *Arch Dermatol* 1968;98:549-51.
292. Traverso G, Shuber A, Olsson L, Levin B, Johnson C, Hamilton SR, Boynton K, Kinzler KW, Vogelstein B. Detection of proximal colorectal cancers through analysis of faecal DNA. *Lancet* 2002;359:403-4.
293. Traverso G, Shuber A, Levin B, Johnson C, Olsson L, Schoetz DJ, Jr., Hamilton SR, Boynton K, Kinzler KW, Vogelstein B. Detection of APC mutations in fecal DNA from patients with colorectal tumors. *N Engl J Med* 2002;346:311-20.
294. Trojan J, Zeuzem S, Randolph A, Hemmerle C, Brieger A, Raedle J, Plotz G, Jiricny J, Marra G. Functional analysis of hMLH1 variants and HNPCC-related mutations using a human expression system. *Gastroenterology* 2002;122:211-9.
295. Turcot J, Despres JP, St Pierre F. Malignant tumors of the central nervous system associated with familial polyposis of the colon: report of two cases. *Dis Colon Rectum* 1959;2:465-8.
296. Umar A, Boland CR, Terdiman JP, Syngal S, de la Chapelle A, Ruschoff J, Fishel R, Lindor NM, Burgart LJ, Hamelin R, Hamilton SR, Hiatt RA, Jass J, Lindblom A, Lynch HT, Peltomaki P, Ramsey SD, Rodriguez-Bigas MA, Vasen HF, Hawk ET, Barrett JC, Freedman AN, Srivastava S. Revised Bethesda Guidelines for hereditary nonpolyposis colorectal cancer (Lynch syndrome) and microsatellite instability. *J Natl Cancer Inst* 2004;96:261-8.
297. van der Klift H, Wijnen J, Wagner A, Verkuijlen P, Tops C, Otway R, Kohonen-Corish M, Vasem H, Oliani C, Barana D, Muller P, Hutter P, Delozier-Blanchet C, Foulkes W, Lynch HT, Burn J, Moslein G, Fodde R. Molecular characterization of the spectrum of genomic deletions at the mismatch repair genes

- MSH2, MLH1, MSH6 and PMS2, responsible for hereditary non-polyposis colorectal cancer (HNPCC). submitted.
298. van Nagell JR, Jr., DePriest PD, Reedy MB, Gallion HH, Ueland FR, Pavlik EJ, Kryscio RJ. The efficacy of transvaginal sonographic screening in asymptomatic women at risk for ovarian cancer. *Gynecol Oncol* 2000;77:350-6.
 299. Vasen HF, Watson P, Mecklin JP, Lynch HT. New clinical criteria for hereditary nonpolyposis colorectal cancer (HNPCC, Lynch syndrome) proposed by the International Collaborative group on HNPCC. *Gastroenterology* 1999;116:1453-6.
 300. Vasen HF, Sanders EA, Taal BG, Nagengast FM, Griffioen G, Menko FH, Kleibeuker JH, Houwing-Duistermaat JJ, Meera Khan P. The risk of brain tumours in hereditary non-polyposis colorectal cancer (HNPCC). *Int J Cancer* 1996;65:422-5.
 301. Vasen HF, Mecklin JP, Khan PM, Lynch HT. The International Collaborative Group on Hereditary Non-Polyposis Colorectal Cancer (ICG-HNPCC). *Dis Colon Rectum* 1991;34:424-5.
 302. Vasen HF, Wijnen JT, Menko FH, Kleibeuker JH, Taal BG, Griffioen G, Nagengast FM, Meijers-Heijboer EH, Bertario L, Varesco L, Bisgaard ML, Mohr J, Fodde R, Khan PM. Cancer risk in families with hereditary nonpolyposis colorectal cancer diagnosed by mutation analysis. *Gastroenterology* 1996;110:1020-7.
 303. Vasen HF, Stormorken A, Menko FH, Nagengast FM, Kleibeuker JH, Griffioen G, Taal BG, Moller P, Wijnen JT. MSH2 mutation carriers are at higher risk of cancer than MLH1 mutation carriers: a study of hereditary nonpolyposis colorectal cancer families. *J Clin Oncol* 2001;19:4074-80.
 304. Vasen HF, Morreau H, Nortier JW. Is breast cancer part of the tumor spectrum of hereditary nonpolyposis colorectal cancer? *Am J Hum Genet* 2001;68:1533-5.
 305. Verma L, Porter TR, Richards FM, Rajpar MH, Evans DG, Macdonald F, Maher ER. Germline mutation analysis of the transforming growth factor beta receptor type II (TGFBR2) and E-cadherin (CDH1) genes in early onset and familial colorectal cancer. *J Med Genet* 2001;38:E7.
 306. Viel A, Novella E, Genuardi M, Capozzi E, Fornasari M, Pedroni M, Santarosa M, De Leon MP, Della Puppa L, Anti M, Boiocchi M. Lack of PMS2 gene-truncating mutations in patients with hereditary colorectal cancer. *Int J Oncol* 1998;13:565-9.
 307. Viel A, Petronzelli F, Della Puppa L, Lucci-Cordisco E, Fornasari M, Pucciarelli S, Rovella V, Quaia M, Ponz de Leon M, Boiocchi M, Genuardi M. Different molecular mechanisms underlie genomic deletions in the MLH1 Gene. *Hum Mutat* 2002;20:368-74.
 308. Villemure JF, Abaji C, Cousineau I, Belmaaza A. MSH2-deficient human cells exhibit a defect in the accurate termination of homology-directed repair of DNA double-strand breaks. *Cancer Res* 2003;63:3334-9.
 309. Viner JL, Umar A, Hawk ET. Chemoprevention of colorectal cancer: problems, progress, and prospects. *Gastroenterol Clin North Am* 2002;31:971-99.
 310. Vogelstein B, Fearon ER, Hamilton SR, Kern SE, Preisinger AC, Leppert M, Nakamura Y, White R, Smits AM, Bos JL. Genetic alterations during colorectal-tumor development. *N Engl J Med* 1988;319:525-32.
 311. Vogelstein B, Lane D, Levine AJ. Surfing the p53 network. *Nature* 2000;408:307-10.
 312. Vogelstein B, Kinzler KW. Cancer genes and the pathways they control. *Nat Med* 2004;10:789-99.
 313. Voskuil DW, Kampman E, Grubben MJ, Kok FJ, Nagengast FM, Vasen HF, van 't Veer P. Meat consumption and meat preparation in relation to colorectal adenomas among sporadic and HNPCC family patients in The Netherlands. *Eur J Cancer* 2002;38:2300-8.
 314. Wagner A, Hendriks Y, Meijers-Heijboer EJ, de Leeuw WJ, Morreau H, Hofstra R, Tops C, Bik E, Brocker-Vriends AH, van Der Meer C, Lindhout D, Vasen HF, Breuning MH, Cornelisse CJ, van Krimpen C, Niermeijer MF, Zwinderman AH, Wijnen J, Fodde R. Atypical HNPCC owing to MSH6 germline mutations: analysis of a large Dutch pedigree. *J Med Genet* 2001;38:318-22.
 315. Wagner A, Barrows A, Wijnen JT, van der Klift H, Franken PF, Verkuijlen P, Nakagawa H, Geugien M, Jaghmohan-Changur S, Breukel C, Meijers-Heijboer H, Morreau H, van Puijenbroek M, Burn J, Coronel S, Kinarski Y, Okimoto R, Watson P, Lynch JF, de la Chapelle A, Lynch HT, Fodde R. Molecular analysis of hereditary nonpolyposis colorectal cancer in the United States: high mutation detection rate among clinically selected families and characterization of an American founder genomic deletion of the MSH2 gene. *Am J Hum Genet* 2003;72:1088-100.
 316. Wagner A, Tops C, Wijnen JT, Zwinderman K, van der Meer C, Kets M, Niermeijer MF, Klijn JG, Tibben A, Vasen HF, Meijers-Heijboer H. Genetic testing in hereditary non-polyposis colorectal cancer families with a MSH2, MLH1, or MSH6 mutation. *J Med Genet* 2002;39:833-7.
 317. Wahlberg SS, Schmeits J, Thomas G, Loda M, Garber J, Syngal S, Kolodner RD, Fox E. Evaluation of microsatellite instability and immunohistochemistry for the prediction of germ-line MSH2 and MLH1 mutations in hereditary nonpolyposis colon cancer families. *Cancer Res* 2002;62:3485-92.

318. Wang L, Baudhuin LM, Boardman LA, Steenblock KJ, Petersen GM, Halling KC, French AJ, Johnson RA, Burgart LJ, Rabe K, Lindor NM, Thibodeau SN. MYH mutations in patients with attenuated and classic polyposis and with young-onset colorectal cancer without polyps. *Gastroenterology* 2004;127:9-16.
319. Wang Q, Lasset C, Desseigne F, Saurin JC, Maugard C, Navarro C, Ruano E, Descos L, Trillet-Lenoir V, Bosset JF, Puisieux A. Prevalence of germline mutations of hMLH1, hMSH2, hPMS1, hPMS2, and hMSH6 genes in 75 French kindreds with nonpolyposis colorectal cancer. *Hum Genet* 1999;105:79-85.
320. Wang Q, Lasset C, Desseigne F, Frappaz D, Bergeron C, Navarro C, Ruano E, Puisieux A. Neurofibromatosis and early onset of cancers in hMLH1-deficient children. *Cancer Res* 1999;59:294-7.
321. Wang Q, Montmain G, Ruano E, Upadhyaya M, Dudley S, Liskay RM, Thibodeau SN, Puisieux A. Neurofibromatosis type 1 gene as a mutational target in a mismatch repair-deficient cell type. *Hum Genet* 2003;112:117-23.
322. Wang Y, Cortez D, Yazdi P, Neff N, Elledge SJ, Qin J. BASC, a super complex of BRCA1-associated proteins involved in the recognition and repair of aberrant DNA structures. *Genes Dev* 2000;14:927-39.
323. Ward R, Meldrum C, Williams R, Mokany E, Scott R, Turner J, Hawkins N, Burgess B, Groombridge C, Spigelman A. Impact of microsatellite testing and mismatch repair protein expression on the clinical interpretation of genetic testing in hereditary non-polyposis colorectal cancer. *J Cancer Res Clin Oncol* 2002;128:403-11.
324. Warthin AS. Heredity with reference to carcinoma; as shown by the study of cases examined in the pathological laboratory of the University of Michigan 1895-1913. *Arch Intern Med* 1913;12:546-555.
325. Watanabe A, Ikejima M, Suzuki N, Shimada T. Genomic organization and expression of the human MSH3 gene. *Genomics* 1996;31:311-8.
326. Watanabe T, Muto T, Sawada T, Miyaki M. Flat adenoma as a precursor of colorectal carcinoma in hereditary nonpolyposis colorectal carcinoma. *Cancer* 1996;77:627-34.
327. Watson P, Lin KM, Rodriguez-Bigas MA, Smyrk T, Lemon S, Shashidharan M, Franklin B, Karr B, Thorson A, Lynch HT. Colorectal carcinoma survival among hereditary nonpolyposis colorectal carcinoma family members. *Cancer* 1998;83:259-66.
328. Watson P, Lynch HT. Extracolonic cancer in hereditary nonpolyposis colorectal cancer. *Cancer* 1993;71:677-85.
329. Watson P, Narod SA, Fodde R, Wagner A, Lynch JF, Tinley ST, Snyder CL, Coronel SA, Riley B, Kinarsky Y, Lynch HT. Carrier risk status changes resulting from mutation testing in hereditary non-polyposis colorectal cancer and hereditary breast-ovarian cancer. *J Med Genet* 2003;40:591-6.
330. Whitelaw SC, Murday VA, Tomlinson IP, Thomas HJ, Cottrell S, Ginsberg A, Bukofzer S, Hodgson SV, Skudowitz RB, Jass JR, Talbot IC, Northover JM, Bodmer WF, Solomon E. Clinical and molecular features of the hereditary mixed polyposis syndrome. *Gastroenterology* 1997;112:327-34.
331. Whiteside D, McLeod R, Graham G, Steckley JL, Booth K, Somerville MJ, Andrew SE. A homozygous germ-line mutation in the human MSH2 gene predisposes to hematological malignancy and multiple cafe-au-lait spots. *Cancer Res* 2002;62:359-62.
332. WHO. Proposed international guidelines on ethical issues in medical genetics and genetic services. *Human Genetic Programme* 1998.
333. Wijnen J, Khan PM, Vasen H, van der Klift H, Mulder A, van Leeuwen-Cornelisse I, Bakker B, Losekoot M, Moller P, Fodde R. Hereditary nonpolyposis colorectal cancer families not complying with the Amsterdam criteria show extremely low frequency of mismatch-repair- gene mutations. *Am J Hum Genet* 1997;61:329-35.
334. Wijnen J, van der Klift H, Vasen H, Khan PM, Menko F, Tops C, Meijers Heijboer H, Lindhout D, Moller P, Fodde R. MSH2 genomic deletions are a frequent cause of HNPCC. *Nat Genet* 1998;20:326-8.
335. Wijnen J, de Leeuw W, Vasen H, van der Klift H, Moller P, Stormorken A, Meijers-Heijboer H, Lindhout D, Menko F, Vossen S, Moslein G, Tops C, Brocker-Vriends A, Wu Y, Hofstra R, Sijmons R, Cornelisse C, Morreau H, Fodde R. Familial endometrial cancer in female carriers of MSH6 germline mutations [letter]. *Nat Genet* 1999;23:142-4.
336. Wijnen JT, Vasen HF, Khan PM, Zwiderman AH, van der Klift H, Mulder A, Tops C, Moller P, Fodde R. Clinical findings with implications for genetic testing in families with clustering of colorectal cancer. *N Engl J Med* 1998;339:511-8.
337. Winawer S, Fletcher R, Rex D, Bond J, Burt R, Ferrucci J, Ganiats T, Levin T, Woolf S, Johnson D, Kirk L, Litin S, Simmang C. Colorectal cancer screening and surveillance: clinical guidelines and rationale-Update based on new evidence. *Gastroenterology* 2003;124:544-60.
338. Wirtzfeld DA, Petrelli NJ, Rodriguez-Bigas MA. Hamartomatous polyposis syndromes: molecular genetics, neoplastic risk, and surveillance recommendations. *Ann Surg Oncol* 2001;8:319-27.
339. Wong YF, Ip TY, Chung TK, Cheung TH, Hampton GM, Wang VW, Chang AM. Clinical and pathologic significance of microsatellite instability in endometrial cancer. *Int J Gynecol Cancer* 1999;9:406-410.

340. Wooster R, Neuhausen SL, Mangion J, Quirk Y, Ford D, Collins N, Nguyen K, Seal S, Tran T, Averill D, et al. Localization of a breast cancer susceptibility gene, BRCA2, to chromosome 13q12-13. *Science* 1994;265:2088-90.
341. Wu Y, Berends MJ, Sijmons RH, Mensink RG, Verlind E, Kooi KA, van der Sluis T, Kempinga C, van dDer Zee AG, Hollema H, Buys CH, Kleibeuker JH, Hofstra RM. A role for MLH3 in hereditary nonpolyposis colorectal cancer. *Nat Genet* 2001;29:137-8.
342. Wu Y, Berends MJ, Post JG, Mensink RG, Verlind E, Van Der Sluis T, Kempinga C, Sijmons RH, van der Zee AG, Hollema H, Kleibeuker JH, Buys CH, Hofstra RM. Germline mutations of EXO1 gene in patients with hereditary nonpolyposis colorectal cancer (HNPCC) and atypical HNPCC forms. *Gastroenterology* 2001;120:1580-7.
343. Yamamoto H, Itoh F, Nakamura H, Fukushima H, Sasaki S, Perucho M, Imai K. Genetic and clinical features of human pancreatic ductal adenocarcinomas with widespread microsatellite instability. *Cancer Res* 2001;61:3139-44.
344. Yan H, Papadopoulos N, Marra G, Perrera C, Jiricny J, Boland CR, Lynch HT, Chadwick RB, de la Chapelle A, Berg K, Eshleman JR, Yuan W, Markowitz S, Laken SJ, Lengauer C, Kinzler KW, Vogelstein B. Conversion of diploidy to haploidy. *Nature* 2000;403:723-4.
345. Yin J, Kong D, Wang S, Zou TT, Souza RF, Smolinski KN, Lynch PM, Hamilton SR, Sugimura H, Powell SM, Young J, Abraham JM, Meltzer SJ. Mutation of hMSH3 and hMSH6 mismatch repair genes in genetically unstable human colorectal and gastric carcinomas. *Hum Mutat* 1997;10:474-8.
346. Young J, Simms LA, Biden KG, Wynter C, Whitehall V, Karamatic R, George J, Goldblatt J, Walpole I, Robin SA, Borten MM, Stitz R, Searle J, McKeone D, Fraser L, Purdie DR, Podger K, Price R, Buttenshaw R, Walsh MD, Barker M, Leggett BA, Jass JR. Features of colorectal cancers with high-level microsatellite instability occurring in familial and sporadic settings: parallel pathways of tumorigenesis. *Am J Pathol* 2001;159:2107-16.

