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HNPCC, molecular and clinical dilemmas

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Genetic testing in hereditary non-polyposis colorectal cancer families with a *MSH2*, *MLH1* or *MSH6* mutation

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LETTERTOJMG

Genetictestinginhereditarynon-polyposiscolorectal cancerfamilieswitha *MSH2*, *MLH1*,or *MSH6* mutation

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About5%ofcolorectalcancersareassociatedwiththe autosomaldominantlyinheritedcancersusceptibility syndromehereditarynon-polyposiscolorectalcancer (HNPCC).[12] HNPCCischaracterisedbyahighriskofdevelop-ingcolorectalcancerandendometrialcanceratayoungage (cumulativelifetimerisk80-90%and30-40%,respectively), andbyanincreasedriskofdevelopingvariousothertumour types,suchasovarian,uroepithelial,smallintestine,biliary tract,stomach,brain,andskincancers.[2–5] Germlinemutations inoneofthreemismatchrepairgenes(*MSH2*, *MLH1*,and *MSH6*)werefoundtoberesponsibleforamajorityofHNPCC families.[6–9]

Knowledgeofthecausativemutationinaparticular HNPCC familyenablestheidentificationofatriskfamilymembersby geneticstesting.Clearly,theabsenceorpresenceofamutation isofconsiderablemedicalandpsychologicalsignificance. Subjectsnotcarryingthemutationarerelievedfroma continuousanxietyandcanbedismissedfrommedical surveillance,savingthemtroubleandreducinghealthcare costs.[10] Importantly,subjectswiththemutationcanbenefit fromamedicalsurveillanceprogramme.ForHNPCC,colon-oscopyhasbeenshowntobeapotenttoolforthedetection andtreatmentofpremalignantadenomasorearlycolorectal carcinomasinatrisksubjects,reducingtheriskofdeveloping colorectalcanceranddecreasingtheoverallmortalitybyabout 65%.[11,12] Thepossibilityofearlydetectionofcolorectalcancer bystoolanalysisusingthegeneticmarkersTP53,BAT26,and K-RASraisesexpectationsforthedevelopmentoflessinvasive surveillanceprocedures.[13] Furthermore,interventiontrials withnon-steroidalanti-inflammatorydrugs(NSAID)insub-jectsatriskfordevelopingcolorectalcancerarein progress.[14,15]

Sofar,studiesontheuseofgenetictestinginHNPCC familieshaveusedfamiliesorsubjectswhohadbeen registeredforresearchpurposes.[10,16,17] Itisconceivable, however,thattheseresearchfamiliesrepresentaselected groupofHNPCCfamilieswheredecisionmakingprocesses aredifferentfromthoseinfamiliesinaclinicalsetting.Here, wereporttheuseofgenetictestingin18clinically ascertainedHNPCCfamilieswithaknownmutationin *MSH2*,*MLH1* ,or *MSH6*.

MATERIALANDMETHODS

Patients

EligibleHNPCCfamilieshavebeenreferredtotheDepartment ofClinicalGeneticsoftheErasmusUniversityMedicalCentre Rotterdamforoncogeneticcounsellingbygeneralpractition-ersandmedicalspecialistssince1992.DNAanalysisofthe *MSH2*, *MLH1*,and *MSH6* geneswasperformedatthe DepartmentofHumanandClinicalGenetics,LeidenUniver-sityMedicalCentre,asdescribedpreviously.[18–20] Familieswere includedinthestudywhenamutationineitherofthesethree mismatchrepairgeneswasidentifiedbefore2000.Subjectsof thesefamilieswereincludedwhentheywereaged18years andoveratthetimeofmoleculardiagnosisinthefamilyand whentheyhadapre-testgeneticriskforcarryingthe mutationof100%,50%,or25%(seeresults).

Keypoints

- Inaclinicalsetting,considerableinterestwasobserved forgenetictestinginHNPCCfamilieswithaknown germlinemutation.
- Testingwasusedmorefrequentlybysubjectswitha higherpre-testgeneticriskforthemutation,bywomen, andbysubjectswithchildren.
- Genetictestinghasearnedaplaceinthestandard medicalcareforsubjectsatriskforHNPCC.

Table1 Mutationsinthe *MLH1*, *MSH2*,and *MSH6* genesintheHNPCCfamiliesstudied

Gene	Natureofthemutation(nucleotidechange)	Families (n=18)
MSH2	Genomicdeletionexon3	1
	Spliceacceptorsiteintron9(IVS9_2A>G)1	
	Frameshiftmutationexon2(229_230delAG)1	
	Nonsensemutationexon13(2038C>T)1	
	Genomicdeletionexon1	1
	Nonsensemutationexon8(1285C>T)	2
	Frameshiftmutationexon2(1705_1706delGA)1	
	Frameshiftmutationexon14(2347delC)1	
MLH1	Splicedonorsiteintron8(IVS8+1delG)1	
	Inframedeletionexon16(1852_1854delAAG)5	
	Splicedonorsiteexon16(1896G>A)	1
	Spliceacceptorsiteintron9(IVS9-1G>C)1	
MSH6	Frameshiftmutationexon4(1784delT)	1

Procedure

Ingeneral,theinitialsearchforthecausativemutationhad beenperformedonbloodDNAoftheyoungestcolorectal cancerpatientinthefamily(theindexsubject).Identified mutationswereconfirmedinallrelativesaffectedwithan HNPCCrelatedtumourfromwhichDNAsampleswereavail-able.Theinitialcounselleeandindexsubjectswereaskedto informalltheadultfirstandseconddegreerelativesof patientswithanHNPCCrelatedtumouraboutthegenetic predispositiontocancerintheirfamily.Writteninformation todistributeamongtheirfamilymemberswasmade availabletothem.Thisinformationincludedfactsonthe inheritanceofthecancersusceptibilityintheirfamily,the

Table2 Characteristicsofthefamiliesstudied

Gene	Families (n=18)	Meannumber CRC/family	MeanageCRC (range)	Meannumber EC/family	MeanageEC (range)
MSH2	9	4.8	43.8y(23–75)1		46.4y(30–54)
MLH1	8	5.4	43.7y(27–72)0.5		46.3y(41–82)
MSH6	1	7	60.4y(32–84)5		55y(50–60)

CRC,colorectalcancer.EC,endometrialcancer.

possibilityofgenetictesting,therisksofdevelopingcancer, andtheoptionsforintervention.Relativesoptingforgenetic testingreceivedoneormoreindividualpre-testcounselling sessionsaccordingtotherecommendationsoftheAmerican SocietyofClinicalOncology,[21] includingthediscussion ofmedical,genetic,andpsychosocialaspectsofgenetic testing.Psychologicalsupportwasofferedtoallsubjects throughoutthetestingprocedure.Disclosureofthetest resultsfollowedwithin6-12weeksafterbloodsampling. Mutationcarrierswerereferredtolocalspecialistsforfollow upandsurveillance.InTheNetherlands,thissurveillance comprisescolonoscopyandgynaecologicalexamination everyonetotwoyears.Inthiscountry,prophylactic colectomyiscurrentlynotofferedtounaffectedmutation carriers.

Datacollectionandstatisticalanalysis

Alldatawerecollectedfrommedicalrecords.Descriptivestatisticswereusedtoestablishtestratesofgenetictesting.The influenceofpre-testgeneticrisk,gender,parenthood,andage ontheuseofgenetictestingwasfirstassessedbyunivariate analysis.Subjectswerecategorisedintosubjectsyounger than50yearsandsubjects50yearsandolder.Thesimultaneousinfluenceofgender,parenthood,andagewasalso assessedbymultivariatelogisticregressionanalysisinthe 50%risksubjects.Pre-testgeneticriskhadbeenexcluded fromthemultivariateanalysis,asabouthalfofthedata onparenthoodandageweremissingforthe25%risk subjects.
Toassessthetimedependentrateofgenetictesting, Kaplan-Meiersurvivalprobabilitieswerecalculatedfor50% risksubjectswithafirstdegreerelativewithanHNPCC relatedtumour.Bydoingso,weavoidedincludingthetime 25%risksubjectshadtowaitforthegenetictestresultof theirparent.

RESULTS

AcohortofIsconsecutiveHNPCCfamilieswasselectedthat hadaknownmutationin *MSH2* (n=9), *MLH1* (n=8),or *MSH6* (n=1)(table1).AllfamilieswereofEuropeanorigin.Five apparentlyunrelatedfamilieshadanidentical *MLH1* mutationandtwoapparentlyunrelatedfamilieshadanidentical *MSH2* mutation(table1).AtthetimeofclinicalascertainMent,15ofthe18familiesfulfilledtheAmsterdamII criteria.[22] Oftheotherthreefamilies,twofamiliespresented withasinglepatientwithcolorectalcancerundertheageof40 yearsandonefamilyhadthreepatientswithendometrial cancerandonepatientwithovariancancer,alldiagnosedover theageof50years.[23] Specificdetailsofthenumberof colorectalandendometrialcancersperfamilyandagesof onsetarelistedintable2.

The18selectedfamiliesconsistedof523living subjectswitha100%(n=60),50%(n=308),or25%(n=155) pre-testgeneticriskofcarryingthefamilyspecificmutation (table3).Forpracticalreasons,thesubjectsdiagnosedwith anHNPCCrelatedtumour(n=56)andobligatecarriers (n=4)weredesignatedashavinga100%pre-testgenetic risk.Thesubjectswitha50%riskhadafirstdegree relativewithanHNPCCrelatedtumour(n=267)orafirst degreerelativewhowasamutationcarrier(n=41). Thesubjectswitha25%riskhadalivingunaffectedparent witha50%risk(n=64)oraparentwitha50%riskwho haddiedwithoutevidenceofanHNPCCrelatedtumour (n=91).

Genetictestingwasusedby260of523(50%)eligible subjects(table3).Amutationwasdetectedin133(51%) subjects,ofwhom83wereunaffected.Ofthesubjects withapre-testgeneticriskof100%,50%,and25%for carryingthemutation,87%,57%,and21%respectively usedgenetictesting($p<0.0001$for100% *v* 50%;$p<0.0001$for 50% *v* 25%)(tables3and4).Ofthe25%risksubjectswhohad anunaffected50%riskparentwhodidnotoptfortesting, onlythreeof64(5%)subjectsusedgenetictesting.In contrast,ofthe25%risksubjectswithadeadunaffected50% riskparent,30of91(33%)subjectsusedgenetictesting (table4).Thetestrateamongthe30850%risksubjectswas 62%inwomenversus51%inmen,suggestingasmallbut significantpreferenceforwomentousegenetictesting ($p=0.041$,table4).Thetestratein50%risksubjectswith childrenwas70%versus45%forthosewithoutchildren, indicatingparenthoodasastrongerpositivepredictor towardstesting($p<0.001$,table4).Theageofthesubjectsdid notinfluencetestrates(table4).Multivariateanalysisofthe datawasconsistentwiththeunivariateanalysis,again indicatinggenderandparenthoodassignificantparameters forgenetictestusage(table4).Themeantimeoffollowup afteridentificationofthemutationinthefamilywas42 months(range12-74months).Forty-onepercentof50%risk subjectsdecidedforgenetictestingwithinoneyear.Ata

Table3 Genetictestingandoutcomein100%,50%,and25%riskcarriersinthe 18HNPCCfamilies

			25%		
Pre-testrisk	100%	50%	Parental	Parent dead	Total
Number	60	308	64	91	523
Tested	52(87%)	175(57%)	3(5%)	30(33%)	260(50%)
Mutationcarrier	50(96%)	80(46%)	0	3(10%)	133(51%)

Table 4 Genetic test use in relation to gender, parenthood, age, and pre-test genetic risk

	Tot d Tested (%)	Univariate	Multivariate
Gender*			
Females	15697 (62)	p=0.041	p=0.045
Males	15278 (51)		
Children*			
Yes	182127 (70)	p<0.001	p=0.013
No	10748 (45)		
Age*			
<50 y	191104 (55)	p=0.24	p=0.39
>50 y	11772 (62)		
Pre-test risk			
50%	308175 (57)	p<0.0001	-
25%	15533 (21)		
25% risk carriers			
Parent alive	643 (5)	p<0.0001	-
Parent dead	9130 (33)		

*In subjects with a pre-test genetic risk of 50%.

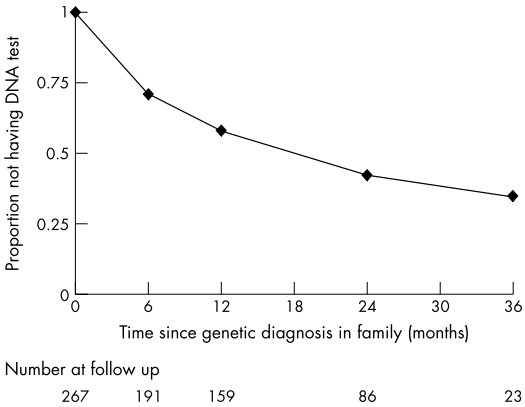

Figure 1 Time dependent rate of genetic testing in subjects with a 50% pre-test genetic risk. The proportion of 50% risk carriers not having the genetic test is shown at 0, 6, 12, 24, and 36 months after the identification of the familial mutation. Only 50% risk carriers with a first degree relative with an HNPCC related tumour are included.

follow up at two years and three years after molecular diagnosis, 58% and 65% respectively of the 50% risk subjects were tested (fig 1).

DISCUSSION

To our knowledge, the present study is the first to evaluate the use of genetic testing for HNPCC in a clinical setting. Importantly, we determined the use of genetic testing in complete pedigrees, including all affected family members and their unaffected first and second degree relatives. This was done in 18 HNPCC families with an identified pathogenic mutation in *MSH2*, *MLH1*, or *MSH6*. These families were quite extensive, with an average of 29 study subjects per family. The use of genetic testing by 50% risk carriers in our families was 57%. This test rate was lower than the 75% test rate in a Finnish cohort of 446 subjects at similar risk for an HNPCC germline mutation.[16] The Finnish subjects, however, had consented to registration and participation in research, which is likely to be positively correlated with interest in genetic testing. Also, the Finnish population is known for its positive attitude towards genetic testing.[24] In a Northern American study only 90 out of 208 subjects (43%) from four extended HNPCC research families were tested.[17] As the pre-test genetic risks of the study subjects were not specified, we cannot compare their data with our s.

We found that the magnitude of pre-test genetic risk for carrying the mutation was strongly correlated with test rates (87%, 57%, and 21% for 100%, 50%, and 25% risk subjects, table 3). This phenomenon has also been observed in other inherited diseases.[25–27] Interestingly, 25% risk subjects with an unaffected 50% risk parent who was alive rarely opted for genetic testing (5%), whereas subjects with the same pre-test genetic risk but with a deceased unaffected 50% risk parent used genetic testing in one-third of the cases (tables 3 and 4). This may be because the identification of the mutation in a child designates the parent as an obligate carrier and children from a living unaffected 50% risk subject may therefore be more likely to refrain from genetic testing in order not to overrule their parents' preference for "not knowing". Also, children may share strategies to cope with genetic risks with their parents. The slightly higher genetic test rates in women than men (62% *v* 51%) was also seen in another late onset inherited disease.[26] In HNPCC, however, the additional risk for endometrial cancer in female mutation carriers probably also influences the use of genetic testing. The significantly higher test rates among subjects with children compared to subjects without children (70% *v* 45%) has also been observed in families with inherited breast and ovarian cancer (HBOC).[25] These findings emphasise that knowledge of the cancer risks for offspring is a major reason for subjects to opt for genetic testing. The high test rate in the affected 100% risk subjects also seems to reflect this phenomenon, since their participation is pivotal especially for the identification and conformation of the pathogenic mutation in the family, but generally has few medical implications for themselves.

A significant proportion of subjects was tested more than one year after the identification of the family specific mutation (65% of the 50% risk carriers at a follow up of three years) (fig 1). Interestingly, at our institute, the time period for deciding for genetic testing was strikingly longer for subjects at risk for HNPCC than for subjects at risk for HBOC (50% at 18 months versus 9 months).[25] The differences in time needed for decision making may perhaps be related to the one to two years interval for colonoscopy in HNPCC families versus the six months interval for breast surveillance in HBOC families.

Genetic testing rates depend on the natural history of the disease concerned, the success of treatment, the efficacy and acceptability of surveillance and prevention, and the costs involved.[28] The use of genetic testing in 50% risk subjects varies from about 20% in Huntington's disease (no interventions available, but relief of uncertainty and relevance for, for example, reproductive choices)[2629] to ~55% in hereditary breast and ovarian cancer (*BRCA1* and *BRCA2* genes, surveillance and prophylactic mastectomy, prophylactic oophorectomy, and chemoprevention available for female carriers),[2630] to ~90% in familial hypercholesterolaemia (lipid lowering treatment available).[31] The 57% HNPCC genetic testing rate in 50% risk carriers reported here is similar to that of women with the same genetic risk for carrying a *BRCA1* or *BRCA2* mutation. This suggests that the total load of factors that influence the choice to opt for genetic testing in HNPCC equals that in HBOC. The efficacy of regular colonoscopy in HNPCC mutation carriers is more favourable compared to regular mammography in young women with a *BRCA1* or *BRCA2* mutation.[1132] This limited efficacy of mammography causes some women with a *BRCA1* or *BRCA2* mutation to opt for prophylactic mastectomy.[2530] Though colonoscopy is not as invasive as the prophylactic mastectomy in HBOC, the burden and violation of physical integrity of this surveillance may be an underestimated factor. Also, the additional risks for other HNPCC related cancers, like brain tumours, for which no

options for surveillance and prevention are available, can cause subjects to refrain from testing. Other reasons not to opt for testing might be fear of financial and social discrimination and inability to cope with a positive test result. Notably, in The Netherlands, cancer predisposition is no reason for exclusion by the health insurance companies, nor for denial of access to employment. It was shown that most tested subjects are able to cope with genetic testing for cancer predisposition in the short term, particularly also for HNPCC. More data on the long term psychosocial impact of genetic testing for HNPCC as well as data on the reasons and psychosocial impact of refraining from genetic testing are needed.

From the data reported here, however, it can be concluded that there is considerable interesting genetic testing in subjects from HNPCC families with a known mutation. Also, in view of the reduction in morbidity and mortality upon surveillance of identified mutation carriers, genetic testing has earned a place in the standard medical care for people at risk for HNPCC.

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REFERENCES

1 **Peel DJ**, Ziogas A, Fox EA, Gildea M, Lahamb, Clements E, Kolodner RD, Anton-Culver H. Characterization of hereditary nonpolyposis colorectal cancer families from a population-based series of cases. *J Natl Cancer Inst* 2000; **92**:1517-22.
2 **Lynch HT**, de La Chapelle A. Genetic susceptibility to non-polyposis colorectal cancer. *J Med Genet* 1999; **36**:801-18.
3 **Hampel H**, Peltomaki P. Hereditary colorectal cancer: risk assessment and management. *Clin Genet* 2000; **58**:89-97.
4 **Vasen HF**, Wijnen JT, Menko FH, Kleibeuker JH, Taal BG, Griffioen G, Nagengast FM, Meijers-Heijboer H, Bertario L, Varescol, Bisgaard M, Mohr J, Fodde R, Khan M. Cancer risk in families with hereditary nonpolyposis colorectal cancer diagnosed by mutation analysis. *Gastroenterology* 1996; **110**:1020-7.
5 **Watson P**, Vasen HF, Mecklin JP, Jarvinen H, Lynch HT. The risk of endometrial cancer in hereditary nonpolyposis colorectal cancer. *Am J Med* 1994; **96**:516-20.
6 **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.
7 **Bronner CE**, Baker SM, Morrison PT, Warren G, Smith LG, Lescoe MK, Kane M, Earabino C, Lipford R, Lindblom A, Tannergård P, Bollag R, Godwin A, Ward D, Nordenskjöld M, Fishel R, Kolodner R, Liskay M. Mutation in the DNA mismatch repair gene homologue hMLH1 is associated with hereditary non-polyposis colon cancer. *Nature* 1994; **368**:258-61.
8 **Akiyama Y**, Sato H, Yamada T, Nagasaki H, Tsuchiya A, Abe R, Yuasa Y. Germ-line mutations of the hMSH6/GTBP gene in an atypical hereditary nonpolyposis colorectal cancer kindred. *Cancer Res* 1997; **57**:3920-3.
9 **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.
10 **Stanley AJ**, Gaff CL, Aittomaki AK, Fabre LC, Macrae FA, John J. Value of predictive genetic testing in management of hereditary non-polyposis colorectal cancer (HNPCC). *Med J Aust* 2000; **172**:313-16.
11 **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.
12 **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.
13 **Dong SM**, Traverso G, Johnson C, Geng L, Favis R, Boynton K, Hibi K, Goodman S, D'Allessio M, Paty P, Hamilton SR, Sidransky D, Baranyf, 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.
14 **Burn JCP**, Bishop DT, Mathers J. Diet and cancer prevention: the Concerted Action Polyp Prevention. *Proc Nutr Soc* 1998; **57**:183-6.
15 **Hawk E**, Lubet R, Limburg P. Chemoprevention in hereditary colorectal cancer syndromes. *Cancer* 1999; **86**:2551-63.
16 **Aktan-Collan K**, Mecklin JP, Jarvinen H, Nystrom-Lahti M, Peltomaki P, Soderling I, Utela A, de La Chapelle A, Kääriäinen H. Predictive genetic testing for hereditary non-polyposis colorectal cancer: uptake and long-term satisfaction. *Int J Cancer* 2000; **89**:44-50.
17 **Lerman C**, Hughes C, Trock BJ, Myers RE, Main D, Bonney A, Abbaszadegan MR, Harty AE, Franklin B, Lynch JF, Lynch HT. Genetic testing in families with hereditary nonpolyposis colon cancer. *JAMA* 1999; **281**:1618-22.
18 **Wijnen J**, Vasen H, Khan PM, Menko FH, van der Kliftt H, van Leeuwen C, van den Broek M, van Leeuwen-Cornelissen I, Nagengast F, Meijers-Heijboer H, Lindhout D, Griffioen G, Cats A, Kleibeuker J, Varescol, Bertario L, Bisgaard ML, Mohr J, Fodde R. Seven new mutations in hMSH2, an HNPCC gene, identified by denaturing gradient-gel electrophoresis. *Am J Hum Genet* 1995; **56**:1060-6.
19 **Wijnen J**, van der Kliftt H, Vasen H, Khan PM, Menko F, Tops C, Meijers-Heijboer H, Lindhout D, Møller P, Fodde R. MSH2 genomic deletions are a frequent cause of HNPCC. *Nat Genet* 1998; **20**: 326-8.
20 **Wijnen J**, Khan PM, Vasen H, Menko F, van der Kliftt H, van den Broek M, van Leeuwen-Cornelissen I, Nagengast F, Meijers-Heijboer H, Lindhout D, Griffioen G, Cats A, Kleibeuker J, Varescol, Bertario L, Bisgaard M-L, Mohr J, Fodde R. Majority of hMLH1 mutations responsible for hereditary nonpolyposis colorectal cancer cluster at the exonic region 15-16. *Am J Hum Genet* 1996; **58**:300-7.
21 **Statement of the American Society of Clinical Oncology**. Genetic testing for cancer susceptibility, adopted on 20 February 1996. *J Clin Oncol* 1996; **14**:1730-6.
22 **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.
23 **Wagner A**, Hendriks Y, Meijers-Heijboer EJ, de Leeuw WJ, Morreau H, Hofstra R, Tops C, Bik E, Bröcker-Vriends A, van der Meer C, Lindhout D, Vasen H, Breuning M, Cornelisse CJ, van Krimpen C, Niermeijer M, 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.
24 **Hietala M**, Hakonen A, Aro AR, Niemela P, Peltonen L, Aula P. Attitudes toward genetic testing among the general population and relatives of patients with a severe genetic disease: a survey from Finland. *Am J Hum Genet* 1995; **56**:1493-500.
25 **Meijers-Heijboer EJ**, Verhoog LC, Brekelmans CT, Seynaeve C, Tilanus-Linthorst MM, Wagner A, Dukel L, Devilee P, van den Ouweland A, van Geel AN, Klijn JGM. Presymptomatic DNA testing and prophylactic surgery in families with a BRCA1 or BRCA2 mutation. *Lancet* 2000; **355**:2015-20.
26 **Maat-Kievit A**, Vegter-van der Vlis M, Zoeteweij M, Losekoot M, van Haeringen A, Roos R. Paradoxo fa bettertest for Huntington's disease. *J Neurol Neurosurg Psychiatry* 2000; **69**:579-83.
27 **van Rijn MA**, de Vries BB, Tibben A, van den Ouweland AM, Halley DJ, Niermeijer MF. DNA testing for fragile X syndrome: implications for parents and family. *J Med Genet* 1997; **34**:907-11.
28 **Evans JP**, Skrzynia C, Burke W. The complexities of predictive genetic testing. *BMJ* 2001; **322**:1052-6.
29 **Craufurd D**, Dodge A, Kerzin-Storrar L, Harris R. Uptake of presymptomatic predictive testing for Huntington's disease. *Lancet* 1989; **ii**:603-5.
30 **Meijers-Heijboer H**, van Geel B, van Putten WL, Henzen-Logmans SC, Seynaeve C, Menke-Pluymers MB, Bartels C, Verhoog L, van den Ouweland A, Niermeijer M, Brekelmans C, Klijn JGM. Breast cancer after prophylactic bilateral mastectomy in women with a BRCA1 or BRCA2 mutation. *N Engl J Med* 2001; **345**:159-64.
31 **Umans-Eckenhausen MA**, Defesche JC, Sijbrands EJ, Scheerder RL, Kastelein JJ. Review of first 5 years of screening for familial hypercholesterolaemia in the Netherlands. *Lancet* 2001; **357**:165-8.

32 **BrekelmansCT** ,SeynaeveC,BartelsCC,Tilanus-LinthorstMM, Meijers-HeijboerEJ,CrepinCM,vanGeelAA,MenkeM,VerhoogLC, vandenOuwelandA,ObdeijnIM,KlijnJGM.Effectivenessofbreast cancersurveillanceinBRCA1/2genemutationcarriersandwomenwith highfamilialrisk. *JClinOncol* 2001;**19**:924-30.
33 **Dudok-deWitAC** ,TibbenA,DuivenvoordenHJ,NiermeijerMF, PasschierJ,TrijsburgRW.DistressinindividualsfacingpredictiveDNA testingforautosomaldominantlate-onsetdisorders:comparing questionnaireresultswithin-depthinterviews.Rotterdam/LeidenGenetics Workgroup. *AmJMedGenet* 1998;**75**:62-74.
34 **LodderL** ,FretsPG,TrijsburgRW,Meijers-HeijboerEJ,KlijnJG, DuivenvoordenHJ,TibbenA,WagnerA,vanderMeerC,vanden OuwelandA,NiermeijerM.Psychologicalimpactofreceivinga BRCA1/BRCA2testresult. *AmJMedGenet* 2001;**98**:15-24.
35 **Aktan-CollanK** ,MecklinJP,delaChapelleA,PeltomäkiP,UutelaA. KääriäinenH.Evaluationofacounsellingprotocolforpredictivetesting forhereditarynon-polyposiscolorectalcancer. *JMedGenet* 2000;**37**:108-13.
36 **Aktan-CollanK** ,HaukkalaA,MecklinJP,UutelaA,KääriäinenH. Psychologicalconsequencesofpredictivetestingforhereditary non-polyposiscolorectalcancer(HNPCC):aprospectivefollow-upstudy. *IntJCancer* 2001;**93**:608-11.

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