

Hereditary Non-polyposis Colon Cancer – an Overview

Disease Summary

Hereditary non-polyposis colon cancer (HNPCC, also known as Lynch syndrome) is an autosomal dominant familial cancer syndrome estimated to account for 1-3% of colorectal cancer (CRC) and, in women, 1-2% of endometrial cancer.^{1,2} HNPCC has been associated with mutations in any one of several different genes, and carriers of such HNPCC-associated mutations have a 50-80% lifetime risk of colon cancer and, if female, a 40-60% lifetime risk of endometrial cancer.² In addition, risk of gastric and ovarian cancer, as well as a number of other cancers, is also increased (see Table 1).^{1,2} As is typical for familial cancer syndromes, HNPCC is associated with early age of cancer onset and occurrence of multiple primary cancers.² In mutation carriers, regular screening by colonoscopy and removal of adenomatous polyps has been shown to reduce colon cancer incidence by more than 50%.² Similarly, Lynch syndrome patients who had regular screening colonoscopies had a reduced risk of death from colon cancer (2%) compared to a 12% mortality rate among Lynch syndrome patients who decline screening.²

Genetic testing can confirm a diagnosis of HNPCC and alert patients to their increased risk of HNPCC-associated cancers.^{1,2} Female HNPCC patients may consider prophylactic hysterectomy and ovariectomy after childbearing is completed.^{1,2} Once the specific mutation causing HNPCC in a particular family has been identified, genetic testing can help to detect both carriers and non-carriers among family members with close to 100% accuracy.³ Mutation carriers can then undergo regular colonoscopies beginning at an earlier age.¹⁻³

HNPCC has been linked to mutations in the genes *MLH1*, *MSH2*, *MSH6*, and *PMS2*.¹ These genes are known as mismatch repair

(MMR) genes because they are involved in repair of errors that occur during the normal DNA replication process prior to cell division. If such errors are not repaired, cancer risk is increased. There are two copies of each MMR gene in a cell, and both gene copies must be rendered dysfunctional in the same cell for errors to accumulate. Normally, this is an unlikely event. However, in individuals carrying an HNPCC-associated germline mutation one of the gene copies is already disabled in each cell. Therefore, such germline mutation carriers have an increased risk of cancer. Mutations in *MHL1*, *MSH2*, *MSH6*, and *PMS2* are estimated to account for about 30%, 60%, 7-10%, and less than 5%, respectively, of HNPCC cases.^{1,4} Sequencing of the coding regions for these genes is estimated to detect about 90-95% of HNPCC-associated mutations in *MLH1* and 50-80% of mutations in *MSH2*.¹ Approximately 17-50% of *MSH2* mutations and 5-10% of *MLH1* mutations are large deletions or other chromosomal rearrangements that cannot be detected by currently used sequencing techniques.¹

HNPCC is diagnosed based on clinical criteria and/or genetic testing.^{1-3,5} Several different testing strategies have been proposed:^{1-3,5}

- HNPCC-associated genes can directly be sequenced in germline DNA (derived, eg, from a blood sample) in patients fulfilling the Amsterdam II criteria (see Table 3). These clinical diagnostic criteria detect patients with HNPCC with a sensitivity of up to 78%, but show relatively low specificity of 50% or less - ie, up to 78% of patients with a germline mutation in an MMR gene fulfill the Amsterdam II criteria, but only up to 50% of patients fulfilling these criteria carry a germline mutation in an MMR gene.^{1,5} Specificity can be increased to

88% by testing tumor tissue for microsatellite instability (MSI).⁵ Microsatellites are repeating sequences of 1 to 6 bases, and defects in MMR gene function lead to characteristic variation (or instability) in the number of repeats between individual tumor cells.¹

- (2) The modified Bethesda guidelines (see Table 3) show similar sensitivity (72%)² to the Amsterdam II criteria, but lower specificity (about 20%).¹ Again, specificity can be increased (to about 50%) by MSI testing.¹ This approach is especially useful in individuals who cannot be evaluated by the Amsterdam II criteria because their family history is unknown.⁵

- (3) The highest sensitivity may be achieved by using MSI testing and immunohistochemical (IHC) staining with antibodies against the protein products of the MMR genes on every CRC tumor.^{1,2,5} The results of IHC testing can then guide which gene to sequence. Specificity of this approach is very high for detecting HNPCC-associated mutations in *MSH2* (close to 100%), but much lower for mutations in *MLH1* (about 8%).¹

For additional information, see Tables 1-3 below and references 1-6.

Table 1: Disease Facts (based on references 1 and 2, unless otherwise noted)

Disease Name	HNPCC	CRC
MIM* number	120435	114500
Estimated Incidence	1,426 to 4,277 ⁶ (1-3% of CRC)	142,570 ⁶
Lifetime risk	Individuals with HNPCC	
Colon cancer	50-80%	
Endometrial cancer	40-60%	
Stomach cancer	11-19%	
Ovarian cancer	9-12%	
Hepatobiliary tract cancer	2-7%	
Urinary tract cancer	4-5%	
Small bowel cancer	1-4%	
Brain /CNS cancer	1-3%; common in Turcot syndrome	
Sebaceous skin neoplasias	Common in Muir-Torre syndrome	
Typical Symptoms	high microsatellite instability poorly differentiated, mucinous, signet-ring cell morphology presence of tumor-infiltrating lymphocytes proximal location for colon cancer	
Therapy	Routine colonoscopy beginning between ages 20-25 or 10 years before the earliest diagnosis in the family ³ Full colectomy if colon cancer is detected Prophylactic hysterectomy and/or ovariectomy after childbearing is complete	General Population Routine colonoscopy beginning at age 50 ³

*MIM: Mendelian Inheritance in Man, see <http://www.ncbi.nlm.nih.gov/omim>

Table 2: Molecular Genetics of HNPCC (based on refs 1, 2, and 4)

Gene	Transmission	Mutation type	Proportion of HNPCC attributable to gene	Comments
MLH1	Autosomal dominant	Loss-of-function	30%	Large deletions account for 5-10% of HNPCC-associated mutations Large deletions are estimated to account for 17-50% of HNPCC-associated mutations
MSH2	Autosomal dominant	Loss-of-function	60%	Deletions in the 3' part of the gene (<i>TACSTD1</i> , or <i>Ep-CAM</i>) located upstream of <i>MSH2</i> have been shown to lead to transcriptional read-through, fusion transcripts, and <i>MSH2</i> silencing Mutations in <i>MSH2</i> appear to impart higher risk of extra-colonic cancers than mutations in <i>MLH1</i> and be more often associated with Muir-Torre syndrome
MSH6	Autosomal dominant	Loss-of-function	7-10%	Mutations in <i>MSH6</i> are associated with MSI-low tumors, later age of onset, distally located colon tumors, and higher risk of endometrial cancer
PMS2	Autosomal dominant	Loss-of-function	<5%	Reported in patients with Turcot syndrome

Table 3: Clinical diagnostic criteria for HNPCC (based on refs 1-3 and 5)

Amsterdam II Criteria ¹	Modified Bethesda Guidelines ¹
At least 3 relatives with an HNPCC-associated cancer (colorectal, endometrium, small bowel, ureter or renal-pelvis)	Colorectal cancer diagnosed before age 50 years
One relative is a first degree relative of the other two	Presence of synchronous or metachronous HNPCC-related tumors
Two successive generations are affected	Colorectal cancer showing presence of tumor-infiltrating lymphocytes, Crohn's-like lymphocytic reaction, mucinous/signet-ring differentiation, or medullary growth pattern, diagnosed before age 60 years
One or more of the HNPCC-related cancers were diagnosed before age 50 years	Colorectal cancer in one or more first-degree relatives with HNPCC-related tumors diagnosed before age 50 years
Familial adenomatous polyposis (FAP) has been excluded	Colorectal cancer diagnosed in two or more first- or second-degree relatives of any age

References

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