Sundhedsstyrelsen
National Board of Health

HEREDITARY NONPOLYPOSIS COLORECTAL CANCER IN DENMARK
– a health technology assessment
– summary

2007

Danish Health Technology Assessment – Projects funded by Dacehta 2007; 7(3)

Sundhedsstyrelsen
National Board of Health

Danish Health Technology Assessment (DACEHTA)

HEREDITARY NONPOLYPOSIS COLORECTAL CANCER IN DENMARK
– a health technology assessment – summary

Bojesen, SE[1], Bernstein, I[2], Gerdes, AM[3], Hartlev, M[4], Koch, L[5], Lindorff-Larsen, K[6], Olsen, KE[7], Wille-Jørgensen, P[8], Hansen, MS[9]

1. Department of Clinical Biochemistry, Herlev Hospital
2. HNPCC-registry, unit of Gastroenterology, Hvidovre Hospital
3. Department of Biochemistry, Pharmacology and Genetic, Odense Universitetshospital
4. University of Copenhagen
5. Institute of Public Health, University of Copenhagen
6. Surgical Gastroenterological Department, Aalborg Sygehus, Århus Universitetshospital
7. DSI – Danish Institute for Health Services Research
8. Cochrane Colorectal Cancer Group, Bispebjerg Hospital
9. Diagnostic Centre, Rigshospitalet

Danish Health Technology Assessment – Projects funded by Dacehta 2007; 7(3)

Hereditary nonpolyposis colorectal cancer in Denmark – a health technology assessment

URL: http://www.sst.dk

Key words: HNPCC, hereditary, genetic, counselling, nonpolyposis, colon, colorectal, cancer, HTA, health technology assessment

Language: Danish, with an English summary

Format Pdf
Version: 1,0
Version date: July 9, 2007

Published by: National Board of Health, Denmark, July 2007

Design: National Board of Health and 1508 A/S
Layout: P.J. Schmidt Grafisk

ISBN (electronic version): 97887-7676-450-0
ISSN (electronic version): 1601-586X

This report should be referred as follows:
Bojesen, SE; Bernstein, I; Gerdes, AM; Hartlev, M; Koch, L; Lindorff-Larsen, K; Olsen, KE; Wille-Jørgensen, P; Hansen, MS;
Hereditary nonpolyposis colorectal cancer in Denmark – a health technology assessment
Copenhagen: National Board of Health, Danish Centre for Health Technology Assessment, 2007
Danish Health Technology Assessment – Projects funded by Dacehta 2007; 7(3)

Series Title: Danish Health Technology Assessment – Projects funded by Dacehta
Series Editorial Board: Finn Børlum Kristensen, Mogens Hørder, Leiv Bakketeig
Series Editorial Manager: Stig Ejdrup Andersen

For further information please contact:

National Board of Health
Danish Centre for Health Technology Assessment
Islands Brygge 67
DK-2300 Copenhagen
Denmark
Phone: +45 72 22 75 48
E-mail: dacehta@sst.dk
Home page: www.dacehta.dk

The publication can be down-loaded free of charge at www.dacehta.dk

Summary

The fraction of colorectal cancer caused by hereditary factors is not known. The well-known syndromes FAP (Familial Adenomatous Polyposis) and HNPCC (Hereditary Nonpolyposis Colorectal Cancer) comprises 5% of all patients with colorectal carcinoma (CRC). It is estimated that hereditary factors are involved in up to 35% of all cases with CRC, although neither biological mechanisms nor heredity are known.

HNPCC is by far the most frequent hereditary syndrome causing CRC and in this HTA report it is defined as both manifest hereditary CRC and suspicion of hereditary CRC, where further elucidation and assessment are relevant. All aspects of the HNPCC syndrome are described with recommendations after each chapter. The medical chapters are written on the basis of a systematical review of the literature and the level of evidence has been estimated according to Oxford Centre for Evidence-Based Medicine (http://www.cebm.net/levels_of_evidence.asp). The evidence is noted with bold numbers followed by a minuscule (e.g. **2c**) and the evidence of the recommendations is noted with bold capitals (e.g. **B**).

Target group

The target group of this HTA report is all professional health care persons involved in diagnostics and treatment of HNPCC patients and political decision-makers involved in prioritizing health care services concerning diagnostics, treatment and prophylaxis of CRC.

Aim

The aim of this HTA analysis is to review the present situation for patients suspected of having hereditary CRC and to provide recommendations for the future.

The analysis covers registration, clinical genetic work-up, molecular diagnosis, treatment, prophylaxis, ethics, legal basis and economy.

In this summary only the main recommendations are given. Detailed recommendations and their levels of evidence are given in the individual chapters.

Registration

The HNPCC families are primarily identified in the surgical departments. The guidelines for referral to clinical genetic work-up and counselling differ between the different regions of the country.

The HNPCC patients/families are registered at every contact with the health care system. Increased solicitude is required when handling genetical information. It also contains information on relatives, and may not be handed over to others without regard for these special circumstances.

The HNPCC registry is the national centre of competence and registers epidemiological and genetical data on all Danish HNPCC families and analyzes the effect of identification, diagnostics and prophylaxis in HNPCC families.

The different electronical registrations of HNPCC families are not compatible and electronical merging of data is not directly possible. A prerequisite for the global evaluation of the effort is

therefore that all HNPCC families and all families under suspicion of having HNPCC are reported to the registry, including data on diagnostics and treatment.

It is recommended to:

- establish a national classification system of HNPCC diagnoses as a common database
- continue the national registration and establish a lasting model to finance the national tasks of the registry
- continuously develop nationally integrated IT solutions
- make reporting to the HNPCC registry compulsory.

Clinical genetic work-up

Patients are referred to clinical genetic work-up and counselling from general practitioners, hospitals and private clinics. It is also possible for patients to consult a clinical geneticist without referral. Several departments for clinical genetics have published guidelines for referral.

Genetic work-up and risk assessment begin with working out a pedigree of at least 3 generations, where all relevant cancer diagnoses have been confirmed. Based on an analysis of the pedigree, the probability for hereditary colorectal cancer is assessed. Increased risk of CRC is seen in several genetic syndromes among which HNPCC is probably the most frequent. Each syndrome is characterized by its candidate genes and clinically characterized by increased risk of cancer in various organs.

Genetic counselling includes informing the counselee and the patient's family about genetic aspects of genetic disease, such as the development and risk of such a disease, as well as providing support in the choices to be made as regards molecular diagnostics, information of relatives, regular clinical control visits, prophylactic surgery and other topics.

Persons with increased risk of cancer are referred to regular clinical control visits according to national and international guidelines.

It is recommended:

- that molecular diagnostics – resequencing for mutations, as well as presymptomatic tests – of HNPCC or other genetical dispositions to CRC is always carried out in the context of genetic counselling performed by a clinical geneticist or other medical specialist having regular contact with HNPCC patients or potential HNPCC patients
- that it becomes possible to obtain personalized extracts concerning family members – including diagnosis and time period – from the Danish Cancer Registry in order to facilitate the clinical genetic work-up
- that it becomes possible and compulsory to file the genetic patient charts for more than 10 years – ideally at the national HNPCC-registry
- that the costs for genetic work-up, counseling and molecular diagnosis are covered across the borders of the different health administrative geographical areas without the need for advance permission
- to establish nationally uniform guidelines for informed consent to genetic counselling.

Molecular diagnosis

Molecular diagnosis of HNPCC is a tool to distinguish between mutation carriers and mutation non-carriers in the HNPCC families. Non-carriers are presumed to have the same risk of CRC as the background population. The laboratory techniques of the three Danish laboratories are identical.

The precondition for presymptomatic testing of persons at risk is that the disease-causing mutation of the family is known. By the end of August 2002, 293 families were examined and a disease-causing mutation was identified in 61 of these families. In these families, 431 persons at risk were examined and 214 did not have the disease-causing mutation of the family. These persons and their descendants do not need clinical control visits. Dividing the total (2002) costs of the molecular diagnostic services by the number of tested persons without the mutation amounts to a cost of 37,864 DKK per person relieved of suspicion. This cost has to be compared with the cost of the life-long clinical control visits for the person and her or his descendants.

The search for the mutation in a given family is complex and a success rate of 20% as in Denmark is not unusual. Therefore it has been tried internationally to develop methods in order to pre-select the families with the highest probability of finding a mutation. For this purpose different examinations of tumour tissue are applied.

It is recommended:

- to establish a higher integration of the different medical specialities: surgery, pathology, clinical genetics and clinical biochemistry
- to carry out a clinical validation of the ability of tumour examinations to identify possible mutation carriers.

Treatment and prophylaxis

Families with hereditary CRC (HNPCC) also have increased risk of other types of cancer – most frequently in the womb, stomach, small intestine, bile tract, upper urinary tract, brain and ovaries. The risk of cancer in the womb is about 7 times higher than in the background population and as for the other types of cancer the age-of-onset is lower than the age-of-onset of sporadic cancer not being a part of the HNPCC syndrome.

Lifetime risk of developing intestinal cancer is more than 80% for mutation carriers. In families where the mutation is unknown, but the diagnosis is based on the pedigree alone, the lifetime risk of first-degree relatives developing the disease is 40%.

The effect of clinical control visits has not been examined in randomized trials. In a Finnish study of 252 HNPCC family members without sign of disease, the risk of CRC was reduced by 62% in the group with regular control colonoscopic examination of the large intestine compared with the group who had chosen not to do so. This is the reason why regular colonoscopic examination of the large intestine in HNPCC families is recommended in order to remove precursors of cancer or to detect cancer at an early stage. Precursors of cancer develop faster in HNPCC than in other types of intestinal cancer.

For other types of cancer, the effect of the clinical control visits is uncertain. Arranging prophylactic examinations of persons without symptoms has to consider – not only risk of cancer – but also whether early treatment of precursors of cancer is of significant benefit for the individual as opposed to the disadvantages of the clinical control visits.

The risk of metachronous CRC (a new cancer originating at a later occasion) in HNPCC patients versus patients with sporadic CRC is 4 – corresponding to a life-time risk of 50%. The recommended operation by CRC in a HNPCC patient is to remove the whole large intestine and also rectum if the tumour is situated there. In most cases it is possible to avoid permanent stoma (artificial opening of the intestine on the abdomen), but it will still be necessary with regular colonoscopic examinations of the part of rectum left behind.

It is necessary that the effect of clinical control visits to prevent the different malignant diseases of HNPCC is validated by a prospective central registration of the HNPCC patients, their diseases, the results of the clinical control visits and any surgical treatment.

It is recommended

- that persons at risk with or without identified mutation are examined by colonoscopy every other year from the 25th birthday
- that the womb and urinary tract are examined by a gynaecological examination and ultrasound scanning and that microscopy of the urine and examination for blood in the urine are performed every other year from the 25th birthday
- that families with an increased frequency of stomach or urinary tract cancer are advised to follow a more intensive control programme, including gastroscopy
- that the whole large intestine (in some cases including the rectum) is surgically removed in case of CRC in HNPCC patients
- that these control programmes are monitored in a national database.

Ethics

Getting to know about a genetic risk of cancer has advantages as well as disadvantages. This dualism is an unavoidable condition when we discuss problems related to patient knowledge of risk and the relationship between the individual and the family in the context of genetic knowledge. Thus, our recommendations do not develop naturally from the study of how people experience genetic knowledge, but take into consideration research, established procedures and health policy. The recommendations reflect bio-ethical decisions based on certain conceptions of impartiality and fairness.

Patient perspectives on the knowledge of risk

Counselees consider genetic knowledge an implement to assure health through the prevention of genetic disease. Genetic counseling creates hope by giving people access to means whereby they can reduce the risk of a life-threatening illness. A feeling of despair is also created because counselees tend to interpret a high genetic risk of cancer as indicating the certainty of disease in the future.

Persons who actively seek counseling and undergo their examinations diligently concomitantly employ other explanatory models or outright doubt the genetic knowledge. Thus, acceptance and contestation of genetic explanations go hand in hand. This coexistence of different understandings in each individual is not necessarily experienced as a conflict by the individual.

The relation between the individual and the family

Notions of individual autonomy and bodily integrity represent core values in established medical ethics. These values are challenged by the concept of prevention (the societal wish to save lives), which in concert with the establishment of the family tree in genetic counselling makes information to family members a concrete possibility. Counselees are both to get hold of health information from relatives and deliver information to them. Many counselees consider this circumstance problematic. The duty to look after the interests of the individual and at the same time manage the obligation of the health care system towards other citizens represents a dilemma for the physician. These other citizens may be e.g. relatives with wishes and needs that differ from those of the subject whose heredity is being investigated. The physician's duty to watch over the interests of the individual patient may conflict with the societal interest of improving the treatment of hereditary diseases.

If the health care system is to improve the prevention and treatment of inheritable colon cancer, the involvement of family members in genetic counselling is required. Respect for the individual's autonomy in the strict sense of the word cannot be upheld neither when it comes to a risk assessment based on the family tree nor in case of a risk assessment made on the basis of mutation screening or presymptomatic testing. Given that family members are to be informed it is in accordance with the principle of equality that all family members are given the same access to information. This information should be given in a way that is independent of good or bad personal relationships within the family.

It is recommended that

- individuals in counselling should be supported if they feel ambivalent about the amount and character of the information
- contact to family members in order to obtain information from patient records and/or a blood sample should be taken by the individual in counselling or by the health care personnel
- family members must give their consent to letting health care personnel obtain information from patient records. If the family member refuses to give consent, the information may still be passed on provided the information is necessary for the treatment of the patient (Act on Patients' Rights, § 26, section 2).
- family members at high risk of developing HNPCC may be contacted directly by health personnel provided this is medically indicated.

The recording of information on family members shall be possible without consent from the family member in order to allow the HNPCC registry to perform investigative activities.

Legal basis

Several laws define the legal framework for collection, registration and application of information in the HNPCC registry. The Personal Data Act (persondataloven) contains rules for handling personal data, including rules for collection, registration, use, passage and erasure. The Health Act (sundhedsloven) and before that the Act on the Legal Status of the Patient (patientretsstillingsloven) contains regulations important for passage of information to other health care persons involved in the treatment of the patient and to persons not involved in the treatment – relations, employer and insurance companies. Special laws deal with the handling of personal health information in scientific projects, employment and insurance relations. Most of these regulations are not specifically elaborated for genetic matters except for the regulations on personal health information in employment and insurance matters.

Collection and registration of information must be founded upon factual arguments. In some cases, collection and registration without the consent of the patient is possible. This is the case where health care persons collect information necessary for the diagnosis and treatment of the patient or in the case of prophylactic health care. In other situations explicit consent is necessary. This could be the case when the health care person collects and registers the information not only about the patient, but also about the relatives. Then the health care person is obliged to inform about the type of information collected and the purpose.

Usage and passage of information must also be founded upon factual arguments and may not conflict with the purpose of the original collection. Usage and passage of information without specific consent is possible if it is necessary for current medical treatment. If treatment necessitates passage of information on relatives of the patient, it might be necessary to obtain specific consent. Normally, for registry-based scientific projects, information can be passed on without consent from the patient. Genetic examinations can make it necessary to contact and inform the relatives of the patient. This raises several problems in conjunction with the right-to-not-know of the relatives and

the right to confidentiality of the patient. The balancing of these conflicting rights is based on concrete assessment of the situation. In some cases a consent form signed by the patient is necessary. Special and limiting regulations apply to passage of information to employers and insurance companies. In these cases, passage of information is impossible even if the patient should consent to it.

Economy

Calculations of the costs of the prophylactic colonoscopies of HNPCC patients are presented. The costs surveillance programme for the 2500 participating persons at risk consists of two different components: Non-recurrent expenses and operating costs. Non-recurrent expenses for genetic counselling and molecular diagnostics amount to 16.9 million DKK in total or 6,764 DKK per person at risk. The operating costs of colonoscopy, gynaecological examinations, ultrasound scanning, examination and microscopy of the urine and gastroscopy amount to 10.9 million DKK in total per 2 years or 4,349 DKK per person per 2 years.

Cost-effectiveness

Is the surveillance programme offered to the persons at risk cost-effective in terms of reducing costs due to treatment and consequences of CRC? This question is analyzed by calculating the average costs for a 25-year-old person referred to the HNPCC registry. A simulation model calculates and compares the costs of life courses for a person who chooses to follow the surveillance programme and for a person who does not:

The average CRC-related lifetime costs for a referred person with and without prophylactic colonoscopy are (with 5% discounting) 16,387 DKK and 12,667 DKK.

The baseline assumption is that the referred population consists of 31% with CRC risk as the background population, 33% with moderate increased risk, and 36% with highly increased risk (members of HNPCC families and/or mutation carriers). The average referred person gains (0% discounting) 3.1 life years. Persons belonging to the high-risk group (members of HNPCC families and/or mutation carriers) gain 9.6 life years and the moderate-risk person gains 2.2 life years.

The price per gained life year obtained by prophylactic colonoscopy amounts by 5% discounting of both costs and life years to 7,294 DKK, which is extremely cost-effective.

If the number of referred persons belonging to the low-risk group, i.e. erroneously referred persons, could be reduced from 31% to 10%, the price per gained life year would decrease to 4,497 DKK.

If all referred persons belonged to the high-risk group (members of HNPCC families and/or mutation carriers), the price per gained life year would decrease to 3,783 DKK.

Realistic changes in the presumptions as regards effects of prophylactic colonoscopies, costs of molecular diagnostics, and incidence of CRC and metachronous CRC, give a confidence interval of the price per gained life year spanning from 2,696 to 17,600 DKK. Thus, the sensitivity analysis does not change the conclusion that prophylactic colonoscopies are extremely cost-effective.

www.dacetha.dk

National Board of Health
Danish Centre for Health Technology Assessment
Islands Brygge 67
DK-2300 Copenhagen
Telefon +45 72 22 74 00
E-mail: dacehta@sst.dk
Homepage: www.dacehta.dk

The summary can be down-loaded at www.dacehta.dk