Cost effectiveness of a new strategy to identify HNPCC patients

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Background: Distinguishing hereditary non-polyposis colorectal cancer (HNPCC) from non-hereditary colorectal cancer (CRC) can increase the life expectancy of HNPCC patients and their close relatives. HNPCC is the most common hereditary form of colorectal carcinoma and is estimated to account for up to 5% of all CRC (CRC) patients. Identification of HNPCC is based on family history. The clinical criteria of HNPCC, the Amsterdam II criteria, are limited in sensitivity and rely on patients’ recall of family cancer history. Identification based on family history is expensive. However, due to small families and unawareness of family history only a proportion of the expected number of HNPCC patients in a CRC population is identified by family history.

In most families, HNPCC is caused by a defect in one of the mismatch repair (MMR) genes: MLH1 or MSH2 and, rarely, MSH6 or PMS2. Subjects carrying the mutation have a very high risk of developing CRC (50–85%), endometrial cancer (20–50%), and an increased risk for several other types of cancer (including carcinomas of stomach, small bowel, biliary tract, central nervous system, sebaceous gland, upper urinary tract, and ovaries; <10%).

Mismatch repair genes play a role in DNA repair. Inactivation of this pathway causes length variations of short repetitive DNA sequences in tumour DNA, called microsatellite instability (MSI). More than 90% of the CRC from patients with a pathogenic MMR gene mutations and 10–15% of sporadic CRC are characterised by MSI. According to the high prevalence of MSI in HNPCC associated tumours, testing for MSI can be used as a tool to select patients with a high risk for hereditary CRC. MSI analysis of tumour DNA and mutation analysis of germline DNA are expensive. MSI or DNA analysis should only be applied to those patients at risk for HNPCC.

The revised Bethesda guidelines (2001) appeared to be a good tool to identify individuals at high risk of HNPCC, especially in groups of patients with a positive family history of CRC. However, the Bethesda Guidelines as well as Amsterdam II Criteria are criticised for being too complex to use in daily clinical practice.

A new strategy for the detection of patients at high risk for HNPCC was developed based on selection of individual patients for MSI analysis with characteristics that are easy to use in clinical practice. This new strategy is an extension to ongoing current practice, with identification based on family history. Newly detected patients are selected for MSI testing if they fulfil one of the following selection criteria: (1) colorectal cancer diagnosed before the age of 50 years; (2) second CRC; (3) CRC and other associated extracolonic cancer (endometrium, ovarian, gastric, hepatobiliary, small bowel cancer, or transitional-cell carcinoma of the renal pelvis or ureter), or (4) a colorectal adenoma with high grade dysplasia diagnosed before the age of 40 years. An essential difference of the new strategy is that the pathologist can apply these criteria to select patients and tumour specimen for MSI testing. In the case of a positive MSI test result, referral for genetic counselling is suggested concerning the probability of hereditary colorectal cancer, and eventually mutation analysis of MLH1, MSH2, and MSH6. A more effective detection of HNPCC mutation carriers will improve the efficiency of cancer prevention in families with HNPCC, by allowing family members who do not carry the mutated gene to avoid costly and burdensome surveillance.

To evaluate this new strategy against current practice, an economic evaluation was performed using two decision models.
analytical models: one directed to a newly diagnosed CRC patient, and another directed to the siblings and children of an identified HNPCC patient.

METHODS
The incremental cost effectiveness of the new strategy to identify HNPCC patients from non-hereditary patients is compared with the current strategy, following a healthcare perspective. Effectiveness was expressed in life years and costs in Euros (indexed to 2002) using a time horizon of life expectancy. The “base case” cost effectiveness analysis was performed using our most reliable estimates for all model parameters. To study the impact of uncertainty concerning parameters one way sensitivity analyses were performed.14,15

Cost effectiveness model
Two decision analytic models were developed that integrated Markov chain analyses using the decision analysis program DATA (TreeAge Software, Inc, Williamstown, MA, USA). The first decision model focused on the incremental cost effectiveness of the new strategy in newly diagnosed patients compared with common practice (fig 1). This patient based model provided the intermediary outcome “extra MLH1 or MLH2 mutation carriers detected” that was used as input in the second, siblings and children oriented decision model (fig 2). Siblings and children follow in both arms (strategies) of the decision model the same pattern of healthcare consumption. But the input in both arms differs, because of the extra amount of true positive HNPCC patients detected in the patient based model. Markov chain analyses are added to the decision trees and evaluated the surveillance of a hypothetical cohort of HNPCC patients or their siblings and children.

Data sources and assumptions
It was assumed that 87% of the eligible patients would participate in genetic testing.17 Surveillance was defined as colonoscopy with polypectomy every two years, with the assumption of complete adherence with the surveillance programme. The average age of a HNPCC patient at diagnosis of a CRC was 46 years.18 The age of a first degree family member starting surveillance was 35 years, based on the midpoint age in the range of a child (20 years) and a sibling (50 years) that start surveillance. Parents were not included in this model. For both Markov models, the cancer mortality rate was assumed to be zero after 15 years. Future costs and effects were discounted at 4% to present values.19

Several specific databases (University Medical Centre Nijmegen (UMCN), University Hospital Groningen (AZG), Netherlands Foundation for the Detection of Hereditary Tumours (STOET), Comprehensive Cancer Centres east and south (IKO & IKZ), Dutch Registry of Pathology (PALGA)) were used as input for the decision analytic models (an extensive description of these databases is available upon request).

Where necessary the data were completed with literature and rarely by expert opinions (consensus group of medical experts UMCN and AZG). Table 1 shows the variables used as input and the data sources used to value them. In literature the probability that a patient with CRC below 50 years or with a double tumour, has a positive MSI result, and carries a deleterious MLH1 or MSH2 germline mutation ranges from 23–78%,20–28 with a mean of 50%. The probability that a patient fulfills the new selection criteria, has a positive MSI result, and carries a deleterious MLH1 or MSH2 germline mutation ranges from 16–63% explored with sensitivity analyses.

A meta-analysis was performed to estimate specificity values for the Amsterdam criteria and MSI analysis.29 Concerning the Markov chain models (fig 3), the probabilities to develop CRC for a HNPCC patient who does or does not participate in a surveillance programme were based on the findings of Järvinen et al.26 Data from the Netherlands Foundation for the Detection of Hereditary Tumours (STOET) were used to estimate the probability for a HNPCC patient to die from symptomatic or screened detected CRC. Non-CRC mortality rates were based on age related survival tables supplied by the Central Bureau of Statistics in the Netherlands (Statline).

Costs
Following a healthcare perspective, only direct medical costs were used for analysis. The volumes of care related to treatment and follow up of HNPCC patients were based upon the analysis of 30 records of HNPCC patients diagnosed with CRC (UMCN and AZG). Existing guideline prices for the Netherlands30 were used to value an outpatient visit and a hospital day. A full cost price was calculated based on UMCN

Figure 1 Patient based decision model (the figures refer to the probability of the variable; # is the complementary probability (1-p)).
Figure 2 Family based decision model (the figures refer to the probability of the variable; # is the complementary probability (1-p)).

Sensitivity analysis
One way sensitivity analyses were performed across a range of assumptions concerning the probabilities: compliance of newly diagnosed CRC patients with the new selection criteria; patients with an MSI positive tumour that had an MLH1 or MSH2 mutation. Furthermore, (MIN-MAX) specificity values for MSI analysis and DNA analysis were evaluated. In addition, the compliance rate with the Amsterdam Criteria was varied and finally the impact of the discount rate on the estimate of the incremental costs per life year gained was evaluated.

RESULTS
Patient based model
Using the new strategy more than twice the number of HNPCC mutation carriers were detected as compared with current practice. In the group of newly diagnosed CRC patients, 3.5% HNPCC patients carrying a mutation were detected with the new strategy, whereas with the current strategy this is 1.6% (table 2). The new strategy is more expensive (incremental discounted costs €141). This results in an incremental cost effectiveness ratio of €7330 per additional mutation carrier detected (table 2). This result was

Table 1 Basic input variables and sources used in the decision models (shown in figs 1 and 2).

<table>
<thead>
<tr>
<th>Input for the cost effectiveness models</th>
<th>Data source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Probability that a CRC patient has a positive MSI test result (given selection criteria)</td>
<td>AZG, Literature[20–28]</td>
</tr>
<tr>
<td>Has a DNA mutation (given MSI positive and given selection criteria)</td>
<td>AZG</td>
</tr>
<tr>
<td>Satisfies AC (given selection criteria and given MSI test negative)</td>
<td>AZG</td>
</tr>
<tr>
<td>Has a DNA mutation (given the selection criteria and given a negative MSI test and given AC criteria)</td>
<td>AZG, Literature[20–28]</td>
</tr>
<tr>
<td>Has a positive family history</td>
<td>Literature[11]</td>
</tr>
<tr>
<td>That the family history is taken by medical specialist</td>
<td>UMCN, AZG, Literature[20–28]</td>
</tr>
<tr>
<td>Has a DNA mutation (given a positive family history and given AC)</td>
<td>UMCN</td>
</tr>
<tr>
<td>Has a positive MSI test result (given a positive family history and not satisfying AC)</td>
<td>UMCN</td>
</tr>
<tr>
<td>Has a DNA mutation (given a positive family history and not satisfying AC and given a positive MSI test result)</td>
<td>UMCN</td>
</tr>
<tr>
<td>Probabilities that a first degree family member of a CRC patient satisfies selection criteria</td>
<td>Patient model</td>
</tr>
<tr>
<td>Has a positive MSI test result (given selection criteria)</td>
<td>Patient model</td>
</tr>
<tr>
<td>Has a DNA mutation (given MSI positive and given selection criteria)</td>
<td>Patient model</td>
</tr>
<tr>
<td>Satisfies AC (given selection criteria and given MSI test negative)</td>
<td>Patient model</td>
</tr>
<tr>
<td>Has a DNA mutation (given the selection criteria and given a negative MSI test and given AC criteria)</td>
<td>Patient model</td>
</tr>
<tr>
<td>Has a positive family history</td>
<td>Literature[11]</td>
</tr>
<tr>
<td>That the family history is taken by medical specialist</td>
<td>UMCN, AZG, Literature[20–28]</td>
</tr>
<tr>
<td>Has a DNA mutation (given a positive family history and given AC)</td>
<td>UMCN</td>
</tr>
<tr>
<td>Has a positive MSI test result (given a positive family history and not satisfying AC)</td>
<td>UMCN</td>
</tr>
<tr>
<td>Has a DNA mutation (given a positive family history and not satisfying AC and given a positive MSI test result)</td>
<td>UMCN</td>
</tr>
<tr>
<td>Costs</td>
<td>UMCN, Literature[20–28]</td>
</tr>
</tbody>
</table>

AZG means empirical data from the University Hospital Groningen, UMCN means empirical data from the University Medical Centre Nijmegen.
extended with a Markov chain analysis which showed an extra 2.5 life years per CRC patient, and found that the surveillance strategy was more expensive (€2249) than the non-surveillance strategy (€322). Integrating the results of the Markov chain analysis with the CRC patient based decision model resulted in an incremental cost effectiveness ratio of €3801 per life year gained (table 2).

**Family based model**

With the new strategy, more CRC patients are identified as HNPCC patients, leading to an enhanced number of relatives detected to carry a mutation that predisposes for HNPCC. In a group of children and siblings of newly diagnosed CRC patients, an extra 1% MLH1 or MSH2 mutation carriers will be detected when the new strategy is used, compared with the current strategy (table 2). The Markov chain analysis for a child or sibling showed that the surveillance strategy was more expensive (€6489) but more effective, with an extra three life years per relative. The incremental cost effectiveness ratio for a child or sibling detected to be a HNPCC mutation carrier is €853 per life year gained. Integrating the results of both the patient and family based model in one efficiency ratio for a child or sibling detected to be a HNPCC mutation, has a considerable effect on the percentage of patients detected with an MLH1 or MSH2 mutation, and consequently on the final outcome. The detection rate of the new strategy for mutation detected HNPCC patients among all newly diagnosed CRC patients varies between 2.1–4.1%; consequently the incremental cost effectiveness ratio varies between €1831–6196 per CRC patient, their siblings, and children. These, together with the other results of the sensitivity analyses, are displayed in table 4.

**DISCUSSION**

The new strategy for the detection of HNPCC is found to be effective and efficient; as over twice as many HNPCC patients were identified, and has an overall cost effectiveness ratio of €2184 per life year gained. An essential difference of the new strategy is that the pathologist can apply the criteria to select tumour specimens for MSI analysis. An explorative study about the feasibility of this new strategy showed, in four regional and one university hospital, a positive result realising 100% adoption of the new strategy within a few months.

The strength of this study is the use of databases. The results of our cost effectiveness study are in line (although the exact figures differ) with the literature investigating a related hypothesis. Reyes et al studied the cost effectiveness of a mixed strategy focussing on a set of criteria less stringent than the Bethesda criteria: (1) age under 50 years; (2) at least one first degree relative of the proband with CRC or endometrium cancer; (3) previous CRC or endometrium cancer in the proband. This mixed strategy was compared with mutation testing of patients complying with the Amsterdam criteria and shown to be efficient, based on a cost effectiveness ratio of €5500 per extra mutation carrier detected. In another study Ramsey et al concluded that a strategy in which all newly diagnosed CRC patients that meet the Bethesda guidelines are tested for MSI analyses was cost effective ($42 210 per life year gained). When considering the benefit for their immediate relatives, cost effectiveness increased to $7556. Our results differ considerably in magnitude compared with Ramsey’s. The difference in outcomes can be explained by the fact that Ramsey et al used prophylactic colectomy as the cancer prevention strategy, which is more expensive than surveillance. The price for a colectomy is (according to Ramsey) $30 673, whereas surveillance (in our study) is less than $2000. In our study the price for a subtotal colectomy and follow up for three years is a little over €8000. It is obvious that the choice of follow up strategies is principal with regard to the outcome of the efficiency ratio. Also it should be mentioned that our

**Sensitivity analysis**

The probability that a newly diagnosed CRC patient complies with our selection criteria, as well as the probability that a patient with a MSI positive tumour had an MLH1 or MSH2 mutation, has a considerable effect on the percentage of patients detected with an MLH1 or MSH2 mutation, and consequently on the final outcome. The detection rate of the new strategy for mutation detected HNPCC patients among all newly diagnosed CRC patients varies between 2.1–4.1%; consequently the incremental cost effectiveness ratio varies between €1831–6196 per CRC patient, their siblings, and children. These, together with the other results of the sensitivity analyses, are displayed in table 4.

**Table 3 Full costs prices of the different units of care used in the cost effectiveness model**

<table>
<thead>
<tr>
<th></th>
<th>Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>MSI analysis</td>
<td>€529</td>
</tr>
<tr>
<td>DNA analysis for CRC index patient</td>
<td>€1308</td>
</tr>
<tr>
<td>DNA analysis for family member from a mutation detected family</td>
<td>€286</td>
</tr>
<tr>
<td>Genetic counselling CRC patient, intake visit</td>
<td>€95</td>
</tr>
<tr>
<td>Genetic counselling CRC patient, average costs per visit*</td>
<td>€17</td>
</tr>
<tr>
<td>Genetic counselling family member, total costs</td>
<td>€54</td>
</tr>
<tr>
<td>Colonoscopy</td>
<td>€144</td>
</tr>
<tr>
<td>Subtotal colectomy</td>
<td>€6557</td>
</tr>
<tr>
<td>Follow up after subtotal colectomy (for 3 years)</td>
<td>€1634</td>
</tr>
</tbody>
</table>

*Average of all possible visits to the genetic counsellor.

**Table 2 Incremental effects, costs, and cost effectiveness of the new strategy for detection and surveillance of CRC patients and relatives compared with the current strategy (detected for carrying a deleterious mutation that predisposes for HNPCC)**

<table>
<thead>
<tr>
<th></th>
<th>CRC patients</th>
<th>Children and siblings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Extra HNPCC mutation carriers detected (%)</td>
<td>1.9</td>
<td>1</td>
</tr>
<tr>
<td>Incremental screening costs (€)</td>
<td>141</td>
<td>9</td>
</tr>
<tr>
<td>Incremental costs/mutation carrier detected (€)</td>
<td>7330</td>
<td>950</td>
</tr>
<tr>
<td>Incremental survival costs (€)</td>
<td>1927</td>
<td>1675</td>
</tr>
<tr>
<td>Life years gained</td>
<td>2.5</td>
<td>3</td>
</tr>
<tr>
<td>Incremental costs per life year gained (€)</td>
<td>3801</td>
<td>855</td>
</tr>
<tr>
<td>Overall incremental costs per life year gained:</td>
<td>€2184</td>
<td></td>
</tr>
</tbody>
</table>

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study was mainly based on databases from a European setting, as opposed to published data from a transatlantic origin (see Methods section). This might have caused the difference in effect between Ramsey et al and us (1.25 life years gained for a CRC patient found by Ramsey v 2.5 life years gained found in the patient model by us). The combination of higher incremental costs and lower incremental effects probably explains the difference in magnitude of the cost effectiveness ratio of Ramsey et al compared with our study.

From other studies, the gains in life expectancy from colonoscopy programmes for relatives is known to range from 7–13 years, whereas our data showed a life expectancy gain for relatives of three years. However, if more gain in life expectancy is to be expected the new strategy will give further support to our main conclusion on cost effectiveness.

Our findings must be considered within the context of some limiting factors. Firstly, we focus on HNPCC patients with a MLH1 and MSH2 mutation; MSH6 mutation carriers are not considered. The exclusion of MSH6 mutations may not have a large impact, because in the group of CRC patients under 50 years of age, only a small amount of HNPCC patients are expected to carry an MSH6 mutation. Additionally, this study does not address surveillance for other HNPCC related carcinomas. In particular, female HNPCC carriers have a lifetime risk up to 40% to develop endometrium cancer. Although the effectiveness of surveillance for that type of cancer is not well known, surveillance for endometrium cancer is recommended.

As the new strategy is shown to be cost effective and feasible, we believe it should be implemented in daily practice. Testing for MSI is straightforward, but the consequences can be diverse because many colorectal cancers show MSI without evidence of germline abnormalities. MSI analysis tests for somatic changes in the tumour and not for germline changes. Among patients with MSI in the tumour DNA there will be sporadic cases and inherited cases. MSI analysis selects patients at high risk for HNPCC that need further analysis to determine whether they do or do not have HNPCC. Discussing the complex information of a positive MSI test result needs to be done with great care because it is given at a time when these patients are adjusting to the diagnosis of cancer and not all patients may want to know their genetic risk for cancer.

We did not include immunohistochemistry (a relatively inexpensive method which can identify loss of MLH1, MSH2, or MSH6 protein products) as a screening technique for several reasons. The most important reason is that the variation in interpretation of immunohistochemistry does not yet permit firm conclusions concerning its use in daily practice.

Very recently, in 2004, a newly revised version of the Bethesda criteria was published, which are very much inline with our criteria list.

Overall, it can be concluded that the proposed new strategy is more effective and efficient than current practice. It underlines that MSI testing in selected, newly diagnosed colorectal cancer patients may serve as a powerful method to identify patients at risk for HNPCC in cases where they are not recognised by their family history.

ACKNOWLEDGEMENTS

This work was supported by a financial grant from the Netherlands Organisation for Health Research and Development (ZonMW). We are indebted to R Niessen, MD, from the University Hospital Groningen and the Comprehensive Cancer Centre East and South for their valuable input in the cost effectiveness study. We thank the departments of Pathology and Surgery of Jeroen Bosch Hospital Hertogenbosch, Canisius-Wilhelmina Hospital Nijmegen, Catharina Hospital Eindhoven, and Rijnstate Hospital Arnhem for participation in the feasibility study.

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REFERENCES


| Table 4 Results of the sensitivity analysis on HNPCC mutation carriers detected and on incremental costs per life year gained |
|---|---|---|---|---|---|
| Variable | Base case | Range | Low | High | Low | High |
| Probability of complying with selection criteria | 0.13 | 0.10–0.20 | 3.4 | 4.9 | 2130 | 2013 |
| Probability of mutation is positive given MSI-H | 0.50 | 0.16–0.63 | 2.1 | 4.1 | 6196 | 1831 |
| Specificity of the Amsterdam criteria | 0.60 | 0.46–0.69 | 3.9 | 3.9 | NE | NE |
| Specificity of MSI analysis | 0.79 | 0.59–0.91 | 3.9 | 3.9 | NE | NE |
| Specificity of DNA analysis | 0.90 | 0.90–0.95 | 3.9 | 3.9 | NE | NE |
| Discount rate costs | 0.04 | 0–0.06 | NE | NE | 2145 | 2106 |
| Discount rate effect | 0.04 | 0–0.06 | NE | NE | 2038 | 2157 |

*The variables had no effect on the outcomes of the current strategy, therefore only the outcomes of the new strategy are presented.
†Based on data from the Comprehensive Cancer Centre East, whereas the range was based on expert opinions.
‡Empirical data varied between 16–63%, whereas the data from literature varied between 23–78%.
§The result of a meta-analysis and the range was based on the lowest and highest value found in literature.
||The base case and the range were both expert opinions.

NE, no effect found.
EDITOR’S QUIZ: GI SNAPSHOT

Answer

From question on page 90

Endoscopic examination revealed marked ecchymosis in the first part of the duodenum with significant luminal compression consistent with a periduodenal haematoma. As the patient was clinically and haemodynamically stable, his conservative management was continued and his condition subsequently ameliorated. The haematoma rapidly resolved and his duodenum appeared entirely normal on a final endoscopic examination six months later. Spontaneous duodenal ulceration is an unusual complication of anticoagulant therapy but may also occur after blunt abdominal trauma. Symptoms of gastric outlet obstruction may only become apparent sometime after the initial development of the haematoma (the mass effect of which increases as fluid shifts into the hyperosmotic degraded haematoma). A conservative approach to treatment is preferable as laparotomy and evacuation of the haematoma may exaggerate the injury to the viscera. Once suspected, a computerised tomogram or, more sensitively, a barium follow through contrast study should be performed to make the diagnosis and examine for mural perforation.