Chapter 3 A literature review of assumptions on test characteristics and adherence in economic evaluations of colonoscopy and CT-colonography

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ABSTRACT

Colorectal cancer screening is an effective public health strategy for decreasing colorectal cancer mortality. Since many screening modalities exist, it needs to be determined what the most cost-effective strategy is. The aim of this review is to summarize the available cost-effectiveness evidence for colonoscopy vs. CT-colonography screening, and to pay special attention to assumptions regarding test characteristics and adherence. A literature search resulted in nine economic evaluations that could be included in the review. The incremental cost-effectiveness ratios of colonoscopy and CT colonography versus no screening remained under €20,000 and €30,000 per life year gained, respectively. Although both screening modalities were cost-effective according to most international thresholds, in most of the economic evaluations colonoscopy seemed more cost-effective than colonography screening. In many studies, model assumptions on major parameters (e.g. screening uptake) were more positive than real life data suggest. None of the models included indirect costs, which disproportionally favoured the relative cost-effectiveness of colonoscopy. For a good comparison of both screening methods, it is necessary that the assumptions used in economic evaluations are realistic, and include all costs.
Introduction
Colorectal cancer is one of the most frequent cancers in European countries. In 2006 in Europe, 3 191 600 incident cases of cancer were diagnosed. In women colorectal cancer is the second form of cancer diagnosed (13.1%) after breast cancer (28.9%). In men colorectal cancer is the third frequent cancer diagnosed (12.8%) after prostate cancer (20.3%) and lung cancer (17.2%). Colorectal cancer is the second most common cause of cancer related mortality (12.2% of total cancer mortality) after lung cancer, the most common cause of death (20%), followed by breast cancer (7.8%) and stomach cancer (6.9%) (Ferlay et al., 2007). The aim of colorectal cancer screening is to decrease mortality, caused by this disease. This can be reached by detecting and removing adenomas, a pre-cancerous lesion (Anderson et al., 2002). By screening, pre-malignant lesions and also cancer can be detected in an earlier stage than at the moment that a patient becomes symptomatic. It is known that colorectal cancer diagnosed in an earlier stage, has a better survival chance than discovered in a later stage (Markowitz et al., 2002). The 5 yearly survival rate is 93% for stage I, 82.5% for stage II, 59.5% for stage III and 8.1% for stage IV (Gollub et al., 2007; Ballinger & Anggiansah, 2007; O’Connell et al., 2004).

Based on observational research it is concluded that removal of adenomas by colonoscopy reduces the risk on cancer with 75% (Winawer et al., 1993; Hafner, 2007). Taking into account that most of the cases of colorectal cancer (>80%) start by a malign transformation of an adenoma to an adenocarcinoma, the early detection and removal of adenomas, before they develop to cancer, is a well established method preventing colorectal cancer.

There are different methods that can be used for screening on colorectal cancer. First biomarkers, like the faecal occult blood tests (FOBT) and faecal or blood DNA tests. Second, endoscope-based techniques, like the sigmoidoscopy and the colonoscopy. Finally, imaging techniques, like the CT- or MRI-colonography. The Advisory Committee on Cancer Prevention of the European Union has advised the member states to use the FOBT and to offer it to men and women aged 50 years to 74 years, with an interval of 1-2 years. If the FOBT is positive, colonoscopy should be used as
follow-up of test positive cases (ACCP, 2000). In 2007, twelve European Member States have adopted the (non invasive) FOBT screening (Bulgaria, Czech Republic, Finland, France, Hungary, Latvia, Portugal, Romania, Slovenia, Spain, Sweden, and the United Kingdom), six Member States use both FOBT and endoscopic test for primary screening (Austria, Cyprus, Germany, Greece, Italy, Slovak Republic), and one uses only an endoscopic test (Poland) (9). In these countries nation wide population-based screening programmes or nation wide non-population based programmes are have been implemented or started at present. In seven Member States there is no programme (Belgium, Denmark, Estonia, Ireland, Luxembourg, Lithuania and Malta) (von Karsa et al., 2008). In the Netherlands trials are going on and the implementation of population screening is planned for 2010 (Bakkenist & van den Berg, 2008). FOBT screening leads to a decrease of colorectal cancer related death, but the accuracy is low, especially in detecting adenomas in an early stage (Hewitson et al., 2007; Burch et al., 2007). Although no RCT-evidence of endoscopy-screening is available for colorectal cancer mortality reduction, it has better sensitivity and specificity than FOBT-screening (van Rijn et al., 2006). However, uptake of endoscopy-screening is relatively low, because the test is invasive and carries the risk of a perforation. There is a growing interest in CT-colonography, since colonography combines the sensitivity and specificity of colonoscopy, with the non-invasiveness of biomarker-screening.

Many economic evaluations were published in recent years, especially comparing the cost-effectiveness of colonoscopy and CT-colonography. Because there are no randomised controlled trials directly comparing the effectiveness of colonoscopy and CT-colonography, all the economic evaluations were based on models. In economic modelling, assumptions have to be made for instance on test characteristics and adherence. Such assumptions have an important influence on the cost-effectiveness. Parameter uncertainty leads to uncertainty of the incremental cost-effectiveness ratio (ICER) and consequently to decision uncertainty (Briggs et al., 2006).
The aim of this review is to summarize the available cost-effectiveness evidence for colonoscopy vs. CT-colonography screening, and to pay special attention to assumptions regarding test characteristics and adherence.

**Methods**

Economic evaluations were identified by searching PubMed for economic evaluations of colorectal cancer screening, in which colonoscopy and CT-colonography were compared among each other or to no screening. The search included the keywords colorectal cancer, cost-effectiveness, cost-utility, colonoscopy, endoscopy, CT-colonography, virtual colonoscopy, life years gained and life years saved. The search was restricted to articles published between October 1st, 1997 and October 1st, 2007, published in the English language. Over this period we found 34 articles. We followed the literature till October 1st, 2008, but no new articles connected to the purpose of this article were published. Relevant articles were selected based on title analyses and abstracts. Then we used reference tracking via the PubMed option ‘related articles’ and the references of articles retrieved. Based on the inclusion criteria (economic evaluation of colorectal cancer screening comparing colonoscopy and/or CT-colonography which each other or with no screening and sensitivity, specificity and adherence admitted in the model) 10 articles were included. A second search was done for test characteristics found in research on the effectiveness of screening. We did our search specific to meta-analyses. The key words used were colorectal cancer, faecal occult blood test, colonoscopy, endoscopy, CT-colonography, virtual colonoscopy, sensitivity and specificity. Separately a literature search for adherence was done using the same search terms for different forms of colorectal cancer screening, combined with adherence, compliance and participation. For adherence our search was directed on uptake of colorectal cancer screening in pilot projects.

To be able to compare the outcomes of economic evaluations with different base years and different currency units, all local currencies were first transferred to the Euro currency values of that time, following the advice of the Organisation for Economic
Co-operation and Development and then recalculated with the price index 2006 of Statistics Netherlands (CBS, 2007; OECD, 2007).

Results
Ten economic evaluations describing colonoscopy and/or CT-colonography, were included in this review. In three of them colonoscopy was compared with no screening, in six evaluations colonoscopy was compared with CT-colonography and either colonoscopy or CT-colonography or both were compared with no screening¹.

Incremental cost-effectiveness ratio (ICER)
In the base case scenario, all studies used a third payer’s perspective, implying that only the direct medical costs were incorporated in the studies. The time horizon used, differed from 3 years (Heitman et al., 2005) to 30 years (Hassan et al., 2007), 35 years (Khandker et al., 2000) to a life time horizon (Sonnenberg et al., 1999; Sonnenberg et al., 2000; Sonnenberg & Delco, 2002; Ladabaum et al., 2004; Vijan et al., 2001; Vijan et al., 2007; Pickhardt et al., 2007). All studies used a discount rate for both effects and cost of 3%. The ICERs of colonoscopy compared with no screening varied between dominant and €18,236, of CT-colonography compared with no screening between dominant and €27,839. The ICERs of colonoscopy compared with CT-colonography varied between dominant and €15,695. When a threshold of ≥6 mm. was used by CT colonography (and non-reporting diminutive lesions), the ICER of colonoscopy compared with CT-colonography was €58,149 (table 1). Model assumptions influence the ICER. For example, Sonnenberg and colleagues used a 100% adherence rate in their model. A decrease of adherence rate of 20% resulted in an increase of the ICER from €11971 to €14258 (Sonnenberg & Delco, 2002).

¹ From the literature describing also other methods, only colonoscopy and CT-colonogrpy data compared to doing nothing and to each other were used.
Model assumptions used in economic evaluations

Sensitivity of colonoscopy

When the sensitivity of colonoscopy was categorized in groups with polyp size <6 mm, 6-9 mm and >10 mm the sensitivity varied from 80% ≤ 6 mm, 85-94% from 6-9 mm and 90-96% > 10 mm (Heitman, 2005; Hassan, 2007; Pickhardt, 2007). When only the sensitivity of colonoscopy was reported by dividing polyps ‘<’ or ‘>’ 10 mm, the sensitivity was 85% <10 mm and 90-95% >10mm (Ladabaum, 2004; Vijan, 2007). Khandker and colleagues used in their model a sensitivity of 79% for small distal polyps and 85% for large distal polyps (Khandker, 2000). Vijan and colleagues reported only the overall sensitivity of colonoscopy for polyps, without dividing in sizes: 85% (Vijan, 2001). The sensitivity for colorectal cancer was 95-97% (Hassan, 2007; Ladabaum, 2004; Sonnenberg, 2000; Sonnenberg & Delco, 2002; Vijan, 2001; Pickhardt, 2007; Khandker, 2000). The unweighted average sensitivity for polyps <6 mm was 80%, for 6-9 mm 88% and the unweighted average sensitivity for polyps >10 mm was 92.5% (table 1).

Sensitivity of CT-colonography

The sensitivity of CT-colonography was presented in the same way. The sensitivity of screening in polyps ≤ 6 mm was 33-48%, between 6-9 mm 50-70% and > 10 mm 71-82% (Heitman, 2005; Hassan, 2007; Pickhardt, 2007; Vijan, 2007). Ladabaum reported a sensitivity of 70% if < 10 mm and 75% if larger than 10 mm (Ladabaum, 2004). The sensitivity for colorectal cancer was 95% (Hassan, 2007; Pickhardt, 2007; Ladabaum, 2004). Sonnenberg and colleagues reported an overall sensitivity of CT-colonography of 80% (Sonnenberg, 1999). The unweighted average sensitivity for polyps <6 mm was 43%, for sizes between 6 and 9 mm the unweighted average sensitivity was 62.7% and for polyps larger than 10 mm 79.8%. The unweighted average sensitivity for colorectal cancer was 95% (table 1).
Adherence

The adherence in the models ranged from 50% to 100%. When colonoscopy was compared with CT-colonography, the same adherence was used in the models. The unweighted average adherence was 78%.

Test characteristics and adherence in research on the effectiveness of screening:

Sensitivity of colonoscopy

A recent Dutch meta-analysis of back to back studies, shows a miss rate of 21% for all polyps. Non-adenomaeus polyps were more often missed than adenomas (27-22%). The sensitivity improves with increased polyp size: for little polyps (<6 mm) the miss rate is 26% (21-30%), for medium-sized polyps (6-9 mm) this is 13% (8-20%) and for large polyps (>9 mm) 2% (1-8%) (van Rijn, 2006).

Sensitivity of CT-colonography

Rosman and colleagues performed a meta-analysis including CT colonography and colonoscopy. Thirty studies were included in the meta-analysis. Studies were only included if all subjects who had undergone CT-colonography also underwent colonoscopy (as a reference standard). The pooled per-patient sensitivity of CT-colonography of big polyps (>10 mm) is about 82% (95% CI 76-88%). For medium sized polyps (6-10 mm) the pooled sensitivity is about 63% (95% CI 52-75%) and for little polyps (0-5 mm) the sensitivity is about 56% (95% CI 42-70%). No significant differences were found in CT-colonography done 2-dimensional and 3-dimensional (Rosman & Korsten, 2007). Lansdorp-Vogelaar and colleagues recalculated the per-patient sensitivity given in the a meta-analysis of Mulhall and colleagues (Mulhall et al., 2005) to the per-polyp sensitivity. For polyps < 6 mm the sensitivity was 29%, for medium sized polyps (6-9 mm), the per-polyp sensitivity was 66% and for large polyps (>10 mm) the per-polyp sensitivity was 97% (Lansdorp-Vogelaar et al., 2008).
Adherence:
In an Australian study performed by Scott and colleagues, a population (1400 subjects, randomly selected) with an average risk on colorectal cancer, was offered colorectal screening. One group was allocated to colonoscopy, a second group was offered CT-colonography and the third group was allowed a choice between both. The average adherence was 18%. There was no significant difference between the three groups (Scott et al., 2004). The Multicentre Australian Colorectal-neoplasia screening Group performed a randomised comparative study offering one of six screening strategies: 1. FOBT, 2. FOBT and flexible sigmoidoscopy, 3. CT-colonography, 4. colonoscopy, 5 and 6. two groups were offered a choice of these strategies In one group a FOBT kit was sent with the letter of invitation, while the other was required to request a FOBT kit by telephone if that was the test chosen. The average adherence was 21%. For CT-colonography it was 16% and for colonoscopy 18% (Macs-group, 2006). A recent Italian population-based randomized trial performed by Segnan and colleagues shows an adherence of colonoscopy of 27% (Segnan et al., 2007). In an editorial of this Journal, Coebergh reported that compliance with colonoscopy in trials is below 30% and there is no country in the world where this level has become higher than 20% (Coebergh, 2004).

Discussion
Compared with doing nothing, both colonoscopy and CT-colonography were cost effective, according to most international thresholds used. When colonoscopy was compared with CT-colonography, colonoscopy is the most cost effective solution. The ICERs varied from dominant to €16,000 per life year gained, not using a reporting threshold. However, assumptions on major parameters influencing cost-effectiveness were far more positive than real life data suggest. The biggest difference between the assumptions made in economic evaluations and the data presented in the effect studies were seen in the adherence. The average adherence in the economic evaluation models was 72.5%, while in trials the adherence of colonoscopy and CT-colonography was less than 30%, often even less than 20%. This affects both costs and health profits and
thus has a major influence on the cost-effectiveness. All sensitivity analyses done in the studies showed that a decrease of adherence results in an increase of the ICER, which means that an intervention becomes more expensive. Low adherence affects more costs because when more subjects opted not to use the opportunity of screening, the higher the healthcare expenditures are arising from treatment and terminal care of colorectal cancer cases. The sensitivity of both colonoscopy and CT-colonography for large polyps was underestimated in the models. The sensitivity for polyps smaller than 5 mm was overestimated for colonoscopy and for CT-colonography. The underestimation of the sensitivity of CT-colonography for large polyps means that in real life more polyps are found and therefore more colonoscopies are needed for removal of the polyps and thus more costs but also more effects. This also influences the cost-effectiveness. The present study shows that model assumptions on adherence are very unrealistic. These assumptions may have a major impact on the positive results of cost-effectiveness analyses. We speculate that real life effectiveness, in terms of number of colorectal cancer incidence and mortality will be less impressive than shown in the economic models.

All economic evaluations were done from the third payers’ perspective. That means that indirect costs, like productivity costs, were not included. For both colonoscopy and CT-colonography a bowel preparation is necessary. The intestine has to be completely clear, otherwise the miss rate is to high. This preparation takes time from a patient, starting the evening before the exam with taking laxatives. Furthermore, there is a difference in examination between colonoscopy and CT-colonography. For a colonoscopy almost every person gets a light anaesthetic (53%) or a total anaesthesia (30%) (Froehlich et al., 2006). In that case one has to go to a recovery after the examination and is not allowed to drive a car for the whole day. This has implications for the patients productivity and hence, it has a negative influence on the cost-effectiveness of colonoscopy (Jonas et al., 2008). This has consequences for the ICER, comparing colonoscopy and CT-colonography, which becomes probably more favourable for CT colonography. The described economic evaluations show cost-effectiveness for both used methods of colorectal screening of the whole population
between 50 and 75 years. Compared to each other colonoscopy is the most cost-effective method. However, should a more societal perspective be taken, thus including all indirect costs, we speculate that the CT-colonography would be more cost-effective than colonoscopy.

For a good comparison of both methods it is necessary that the assumptions used in economic evaluations are realistic and include all costs. An economic evaluation done from a societal perspective, including all direct and indirect medical and non medical costs is preferred. Further investigation is necessary on adherence, especially for differences between invasive screening methods and non invasive screening methods. Participant preferences have to be subject of research, to determine which screening method can consider the best adherence (Marshall et al., 2007). Only when the results of this kind of economic evaluations are available, it is for policy makers possible to take a well-informed decision which method for screening is the most worthwhile for the population.

**Conflict of interest statement**

We declare that no conflict of interest exists for any of the authors.

**Acknowledgement**

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**References**


Table 1 Colonoscopy compared with CT-colonography*

<table>
<thead>
<tr>
<th>Study</th>
<th>Se/Sp Colonoscopy</th>
<th>Se/Sp CT-Colonography</th>
<th>Adherence</th>
<th>ICER (per Life Year Gained)</th>
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<tr>
<td>Sonnenberg (2000, 2002)</td>
<td></td>
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<td>100%</td>
<td>CS*** (10 yearly) vs. no screening: €11,971</td>
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<td>Khandker</td>
<td>Se small polyp:</td>
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<td>100%</td>
<td>CS vs. no screening €22672</td>
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<td>79%</td>
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<td>big polyp: 85%</td>
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<td></td>
<td>CRC: 97%</td>
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<td></td>
<td>Sp: 100%</td>
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<td>Vijan (2001)</td>
<td>Se polyp: 85%</td>
<td></td>
<td>100%</td>
<td>CS (age 50 and 60 years) vs. no screening: €9,261</td>
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<td></td>
<td>CRC: 95%</td>
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<td>Sonnenberg (1999)</td>
<td>Se CRC: **</td>
<td>Se: 80%</td>
<td>65%</td>
<td>Screening every 10 year</td>
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<td></td>
<td></td>
<td>Sp: 95%</td>
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<td>CS vs. no screening: €12,237</td>
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<td>CT vs. no screening: €12,518</td>
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<td>CS vs. CT: €11,345</td>
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<td>Ladabum</td>
<td>Se: &gt;10mm: 90%</td>
<td>Se: &gt;10mm:75%</td>
<td>75%</td>
<td>CS vs. no screening: €18,236</td>
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<td></td>
<td>≤10mm: 85%</td>
<td>≤10mm:70%</td>
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<td>CT vs. no screening: €27,839</td>
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<td></td>
<td>CRC: 95%</td>
<td>CRC 95%</td>
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<td>CS vs. CT: dominant</td>
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<td>Sp: 85%</td>
<td>Sp: 85%</td>
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<td>Heitman</td>
<td>Se: 6-9mm:94%</td>
<td>Se: 6-9mm: 61%</td>
<td>50%</td>
<td>Screening one time CS vs. CT(at age 50 years): dominant</td>
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<td></td>
<td>≥10mm:96%</td>
<td>≥10mm 71%</td>
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<td>Sp: 100%</td>
<td>Sp: 84%</td>
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<td>Hassans</td>
<td>Se: ≤5mm:80%</td>
<td>Se:≤5mm: 48%</td>
<td>65%</td>
<td>CS vs. no screening: dominant</td>
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<td>6-9mm:85%</td>
<td>6-9mm:70%</td>
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<td>CT vs. no screening: dominant</td>
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<td>≥10mm:90%</td>
<td>≥10mm:85%</td>
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<td>CS vs. CT: €15,695</td>
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<td>CRC:95%</td>
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<td>Sp: 90%</td>
<td>Sp: 84%</td>
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<td>Pickhardt</td>
<td>Se: ≤5mm:80%</td>
<td>Se:≤5mm: 48%</td>
<td>65%</td>
<td>Screening every 10 year</td>
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<td></td>
<td>6-9mm:85%</td>
<td>6-9mm:70%</td>
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<td>CS vs. CT ( using a 6 mm. reporting threshold): €58,149</td>
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<td>≥10mm:90%</td>
<td>≥10mm:85%</td>
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<td>CRC:95%</td>
<td>CRC:95%</td>
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<tr>
<td></td>
<td>Sp: 90%</td>
<td>Sp: 86%</td>
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<td>Vijan (2007)</td>
<td>&lt; 1cm: 85%</td>
<td>Se:1-5mm:33%</td>
<td>60%</td>
<td>2-D CT vs. no screening: €16,762</td>
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<td></td>
<td>&gt; 1cm: 95%</td>
<td>6-9mm:50%</td>
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<td>3-D CT vs. no screening: €7,906</td>
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<td></td>
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<td>≥10mm 82%</td>
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<td>CS vs. no screening: €7,847</td>
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<td>Sp: 91%</td>
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<td>CS vs 3-D CT: dominant</td>
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*all local currencies were first transferred to the Euro currency values of that time and recalculated with the index 2006

**Sonnenberg did not use sensitivity in his models, but the efficacy preventing colorectal cancer (75%)

*** CS: Colonoscopy; CT: CT-colonography