Fourfold increased detection of Lynch syndrome by raising age limit for tumour genetic testing from 50 to 70 years is cost-effective

A. S. Sie1, A. R. Mensenkamp1, E. M. M. Adang2, M. J. L. Ligtenberg1,3 & N. Hoogerbrugge*

Departments of 1Human Genetics; 2Health Evidence; 3Pathology, Radboud University Medical Center, Nijmegen, The Netherlands

Received 20 March 2014; revised 11 June 2014; accepted 21 July 2014

Background: Recognising colorectal cancer (CRC) patients with Lynch syndrome (LS) can increase life expectancy of these patients and their close relatives. To improve identification of this under-diagnosed disease, experts suggested raising the age limit for CRC tumour genetic testing from 50 to 70 years. The present study evaluates the efficacy and cost-effectiveness of this strategy.

Methods: Probabilistic efficacy and cost-effectiveness analyses were carried out comparing tumour genetic testing of CRC diagnosed at age 70 or below (experimental strategy) versus CRC diagnosed at age 50 or below (current practice). The proportions of LS patients identified and cost-effectiveness including cascade screening of relatives, were calculated by decision analytic models based on real-life data.

Results: Using the experimental strategy, four times more LS patients can be identified among CRC patients when compared with current practice. Both the costs to detect one LS patient (€9437/carrer versus €4837/carrer), and the number needed to test for detecting one LS patient (42 versus 19) doubled. When family cascade screening was

Footnotes:

---

© The Author 2014. Published by Oxford University Press on behalf of the European Society for Medical Oncology. All rights reserved. For permissions, please email: journals.permissions@oup.com.
Conclusion: Testing all CRC tumours diagnosed at or below age 70 for LS is cost-effective. Implementation is important as relatives from the large number of LS patients that are missed by current practice, can benefit from life-saving surveillance.

Key words: genetic, hereditary, colorectal cancer, Lynch syndrome, screening

methods

Efficacy (proportion of LS patients identified among CRC index patients) was compared between the experimental strategy (CRC ≤70) versus current practice (CRC ≤50). Only age at diagnosis for one CRC tumour was considered, excluding criteria based on additional tumours or family history [3, 9]. Cost-effectiveness analyses included both index patients and relatives tested by cascade screening. Effectiveness was expressed in life-years gained and direct medical costs in Euros (€), based on the Dutch health care system, using a time horizon of average life expectancy.

cost-effectiveness models

Three decision analytic models were developed using TreeAge version 2013. The first model (Figure 1) was aimed at efficacy, focusing on CRC index patients tested for MSI at age of diagnosis 70 or below (experimental strategy) versus 50 or below (current practice). The second model was aimed at cost-effectiveness (supplementary Data S2, available at Annals of Oncology online) using the same decision tree, but focusing on additionally tested index patients diagnosed with CRC between 51 and 70 years. Integrated Markov chain analyses (supplementary Data S3a, available at Annals of Oncology online) evaluated survival and follow-up (intensive if tested in experimental strategy; standard if not tested in current practice) of a hypothetical cohort of CRC 51–70 patients using stochastic data (means with standard deviations) to perform probabilistic sensitivity analyses (N = 1000 Monte Carlo simulations). The third model (Figure 2) focused on cost-effectiveness in relatives of CRC 51–70 patients identified as LS patients, with an integrated Markov model (supplementary Data S3b, available at Annals of Oncology online) for survival and surveillance (intensive if tested; none if not compliant or tested). First CRC in LS relatives non-compliant to surveillance was assumed to be treated as LS-related. Future costs and effects were discounted at 4% to present values [15]. Acceptable cost-effectiveness threshold was €80 000 per life-year gained, assumed equal to quality-adjusted life-years [16].

cost data sources and assumptions

Costs per care unit are shown in supplementary Data S4, available at Annals of Oncology online. Procedures for genetic counselling, colonoscopy, CRC treatment and follow-up were considered unchanged from 2005 [10]: costs were corrected for the Dutch consumer price index for health care [14]. Genetic testing costs have changed substantially thus were newly assessed (August 2013) locally. Average costs for DNA analysis of index patients were based on pair wise testing of genes MLH1/MSH2 or MSH2/MSH6 (single-DNA isolation processing). Average costs for DNA analysis of relatives were based on gene distribution in a local database including all index LS patients diagnosed between May 1996 and August 2013 (N = 182: MLH1 32%, MSH2/EPCAM 34%, MSH6 23%, PMS2 12%). Overhead costs (35.5%) were included [15].

patient data sources and assumptions

Data for patient-based models (supplementary Data S5, available at Annals of Oncology online) were based on a literature review, searching the PubMed

original articles

Identification of Lynch syndrome (LS: confirmed germline mutation) among patients with colorectal cancer (CRC) leads to effective surveillance and can prevent premature deaths of these patients and their relatives [1]. LS is the most common hereditary form of CRC, accounting for 1%–3% of all CRC [2]. Identification of LS is based on family history and young age at diagnosis of CRC (below age 50) as in the Amsterdam-II and Bethesda criteria (supplementary Data S1, available at Annals of Oncology online [3, 4]). Due to small families, unawareness of family history and current age limits, only a proportion of the expected number of LS patients is identified [5]. Unawareness of LS patients of their increased cancer risk and prevention options leads to unnecessary CRC incidence.

LS is caused by a mutation affecting one of the mismatch repair (MMR) genes: MLH1, MSH2, MSH6 and PMS2 [6, 7]. LS patients have a high risk of developing CRC (25%–70%), endometrial cancer (30%–70%), and an increased risk for several other types of cancer (stomach, ovaries, urinary tract, brain, small bowel, hepatobiliary tract, skin) [2]. Over 90% of LS-related CRC and 10%–15% of sporadic CRC are characterised by microsatellite instability (MSI) [8]. MSI testing in newly diagnosed CRC patients fulfilling MIPA criteria (MSI Indicated by a Pathologist [9]: supplementary Data S1, available at Annals of Oncology online) based on Bethesda guidelines, including diagnosis below age 50, was shown to be cost-effective (€3801/life-year gained) [10].

Recently, a European meeting of experts specialised in LS recommended an age limit of 70 instead of 50 years [2], thereafter incorporated in ESMO guidelines [11]. Updated NCCN guidelines advocate universal screening or selectively testing all CRC ≤70 and CRC >70 fulfilling Bethesda criteria [12]; both strategies equally result in a higher diagnostic yield in comparison to the limit of 50 years [13]. However, no cost-effectiveness analyses were carried out to justify the costs for additionally testing CRC patients diagnosed between ages 51 and 70 years.

Increasing the age limit from 50 to 70 years will greatly increase numbers to test: only 5%–6% of CRC is diagnosed below age 50 versus 50% below age 70 [14]. MSI testing at higher age may be less effective as young age at diagnosis is a hallmark of hereditary cancer, and MSI-high tumours at older age more often are caused by non-hereditary MLH1 promoter hypermethylation [8].

To evaluate genetic testing of CRC diagnosed at age 70 or below (experimental strategy) versus age 50 or below (current practice), an economic evaluation was carried out for newly diagnosed CRC index patients (i.e. first CRC patient tested within one family) including family cascade screening.
Figure 1. Patient-based decision analytic model for identifying Lynch syndrome (LS) among colorectal cancer (CRC) index patients to determine the efficacy (LS patients detected) of the experimental strategy testing CRC at 70 years or below (CRC ≤70) versus current practice testing CRC at 50 years or below (CRC ≤50). Numbers reflect the probability [mean ± standard deviation as derived from literature, see (online only) supplementary Data S5, available at Annals of Oncology online] of the variable; # is the complementary probability (1 – P).
family data sources and assumptions

Data for family-based models (supplementary Data S6, available at Annals of Oncology online) were based on a local database containing all relatives tested before August 2013 (N = 935) of 112 index LS patients diagnosed between May 1996 and August 2011 (supplementary Data S7, available at Annals of Oncology online) allowing a minimum 2 years for relatives to undergo DNA screening. Mean numbers of relatives tested (X) and identified as LS patients (Y) per index LS patient were calculated. Surveillance compliance among relatives was 88% [25]. Yearly risks of CRC for compliant and non-compliant LS patients were calculated from Jarvinen et al. [26]. Risks of LS-related CRC mortality and second CRC were assumed equal to index patients [24]. Markov chain analyses (supplementary Data S3b, available at Annals of Oncology online) were run for 50 years [14].

results

patient-based models

Using the experimental strategy, four times as many LS patients were identified than current practice. Costs and number needed to test for detecting one LS patient doubled (Table 1: €9437/carrier versus €4837/carrier and 42 versus 19). Within the age group of 51–70, the incremental costs were €11 541 per additional LS patient detected. Mutation detection rate was lower in patients diagnosed at or below 70 versus 50 years (2.4% versus 5.4%). In additionally tested CRC 51–70 patients, 58.8% of MSI-high tumours was due to MLH1 promoter hypermethylation (not LS) versus 7.1% in CRC ≤50.

Markov chain analyses of CRC 51–70 patients showed 0.01 extra life-years gained versus current practice at incremental costs of €212, resulting in a ratio of €25 130 per life-year gained (Table 2; supplementary Data S8, available at Annals of Oncology online).

family-based model

With the experimental strategy, more CRC patients were identified as LS patients, leading to a proportionally increased number of relatives detected as additional LS patients. In our setting, every index LS patient led to genetic testing of one additional LS patient detected. Mutation detection rate was lower in MSI- group of 51–70 patients than current practice. Costs and number needed to test for detecting one LS patient doubled (Table 1: €9437/carrier versus €4837/carrier and 42 versus 19). Within the age group of 51–70, the incremental costs were €11 541 per additional LS patient detected. Mutation detection rate was lower in patients diagnosed at or below 70 versus 50 years (2.4% versus 5.4%). In additionally tested CRC 51–70 patients, 58.8% of MSI-high tumours was due to MLH1 promoter hypermethylation (not LS) versus 7.1% in CRC ≤50.

Markov chain analyses of CRC 51–70 patients showed 0.01 extra life-years gained versus current practice at incremental costs of €212, resulting in a ratio of €25 130 per life-year gained (Table 2; supplementary Data S8, available at Annals of Oncology online).
Markov chain analyses of relatives showed that the experimental strategy resulted in −€292 lower costs and 0.32 extra life-year gained versus current practice (Table 2; supplementary Data S9, available at Annals of Oncology online). Therefore, the experimental strategy was dominant over current practice, which would miss these LS relatives, denying them CRC surveillance.
combined patient-family results

For an average LS family, the results of 8 relatives were added to results of CRC 51–70 patients identified as LS (2.0%), resulting in an overall ratio of €2703 per extra life-year gained (Table 2) per additionally tested CRC 51–70 patient. Smaller family sizes of four or six relatives resulted in €5301 or €3659 per extra life-year gained.

discussion

The experimental strategy for detecting LS is found to be cost-effective, as four times as many LS patients were detected for €2703 per extra life-year gained in additionally tested patients, including family cascade screening. This fourfold efficacy among index patients was achieved at only twice the cost (€9437/carryer versus €4855/carryer) and numbers needed to detect one carrier (42 versus 19), despite half of MSI-high CRC ≤70 tumours being caused by non-hereditary MLH1 promoter hypermethylation. In additionally tested CRC 51–70 patients, the experimental strategy resulted in more costs for negligible survival gains (€25 130 per life-year gained). But higher benefits were found in relatives using their LS knowledge for CRC prevention, resulting in a more favourable ratio of €2703 per life-year gained. Although the cost-effectiveness threshold of €80 000 in Dutch standards uses quality-adjusted life-years [16] and our study used non-quality-adjusted life-years, the experimental strategy seems good value for money. This recommendation could greatly improve the identification of LS, allowing more LS patients to prevent CRC mortality and simplifying the LS diagnostic process considerably. Half of all CRC patients would be tested immediately; only those with CRC >70 would require evaluation of other tumours and family history, lowering the burden on clinical genetic services. Such simplification may lead to high uptake at implementation of the new strategy.

To identify 100% of LS patients, testing all CRC patients could be considered [27]. But the diagnostic yield of testing without any age limit is comparable with testing only CRC ≤70 and CRC >70 fulfilling Bethesda guidelines, with 35% fewer patients requiring tumour genetic testing and 29% fewer requiring DNA analysis [13]. Testing without age limit compared with testing up to 50 years showed an incremental cost-effectiveness ratio of $37 010 per life-year gained [28]. But Ladabaum et al. [29] demonstrated rising costs with each 10-year increase: testing up to 60 versus 50 years cost $33 800 per life-year gained; testing up to 70 versus 60 years cost $44 200 per life-year gained; and testing all ages versus up to 70 years cost $88 700 per life-year gained. Although gynaecological screening was included and genetic testing costs have decreased since 2011, this shows a trend for higher ratios thus lower likelihood to be cost-effective by including CRC >70.

In our study, the experimental strategy led to only 0.01 extra life-years gained in index patients due to higher average age of CRC 51–70 patients than CRC ≤50 with higher population mortality rates. This is comparable with Ladabaum et al. [29]: Bethesda-based versus no testing led to 0.18 extra life-years gained. In relatives, our study showed 0.32 extra life-years were gained; lower than other conclusions that surveillance starting at 25 years gave 13.5 extra life-years [30], as average age in our study was 45 years. But it remains evident that although index patients may not benefit greatly from improved LS identification, their relatives do.

The main strength of our study is the use of stochastic data for most input variables (supplementary Data S5 and S6, available at Annals of Oncology online), allowing assessment of 95% confidence intervals, showing cost-effectiveness even at these upper limits. Several variables were based on a previous cost-effectiveness study [10] although different methods were used. The previous study compared two different strategies with full patient- and family-based criteria. The current study evaluated only the raised age limit from 50 to 70 years in one patient with one CRC tumour, not considering other tumours or family history. Those with CRC ≤50 overlapped in both guidelines therefore cost-effectiveness analyses focused on the additionally tested CRC 51–70 index patients, comparing costs and effects if LS patients within this group were tested (experimental strategy) or not tested (current practice). This may explain higher benefits in the family-based model, where CRC surveillance in additional LS patients detected led to lower costs and higher effects than if they were missed. The previous study only considered costs and effects if those detected (€855 per life-year gained), not weighed against those missed [10]. Additional risks of a second CRC tumour [24] were incorporated, allowing more robust simulation of LS patient lifetimes and higher benefits than previous analyses only considering the first CRC tumour [10].

Preference for MSI or IHC as first-pass LS testing is the subject of debate: sensitivity is equal, but IHC has the advantage of pinpointing which MMR genes to examine for germline mutations [11]. Conversely, IHC shows higher inter-observer variability depending on observer experience, leading to preferred centralisation of IHC testing within specialised centres [31]. Thus, MSI remained the gold standard for first-pass LS testing [23], determining our testing algorithm. Including the MLH1 promoter hypermethylation test is important to detect non-hereditary MSI-high CRC (nearly half of CRC ≤70) and minimise the proportion of patients undergoing expensive DNA analysis.

The generalisability of our study results may be influenced by the assumptions made. Analyses were based on the Dutch health care system using MSI as first-pass LS testing, but MSI may be second to IHC elsewhere. MIPA criteria [9] are used in the Netherlands to select CRC ≤50 patients for direct tumour genetic testing, but may not reflect current practice in other countries. Some family-based variables were calculated using a local and long-term database, not considering regional variances or degree of relatedness. Cascade screening may—through initial screening of first/second-degree relatives—reach third or more degree, leading to more relatives tested per family and fewer relatives identified as LS patients (in our setting 39%) than expected for close relatives (50%). Some LS patients among CRC patients may belong to the same family. Genetic testing costs were based on local data and may vary. However, our main conclusion that increasing the upper age limit for MMR deficiency testing from 50 to 70 is cost-effective is probably relevant for most western countries.

In conclusion, the proposed experimental strategy, testing all new CRC patients diagnosed at age 70 or below for LS, is more effective than current practice using an age limit of 50 years. Implementation is important as relatives from many LS patients...
missed by current practice, can benefit from life-saving surveillance.

**acknowledgements**

The authors acknowledge F. Ahmadpour, M. Ariaans, J. Hol, Y. Peters, M. Shabani and N. van Vliet for initial data gathering and analysis, and W. Kievit and J. M. M. Groenewoud for providing additional data from the LIMO study [19]; and R. A. van Soest and H. W. Willems for providing current genetic testing costs.

**funding**

This work was supported by the Radboud University Medical Center (no grant number attached).

**disclosure**

The authors have declared no conflicts of interest.

**references**