

## RESEARCH REPORT

### **Rapid review of existing literature on the cost-effectiveness of follow-up strategies after cancer treatment**

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## **Executive Summary**

**Introduction:** A rapid review has been conducted to explore the cost-effectiveness of follow up strategies of patients previously treated for cancer. The aim of the review was to assess whether existing literature could be useful in informing UK policy in these areas.

**Methods:** A systematic literature was undertaken. All papers that were considered to be economic evaluations in the subject areas described above were extracted. Data extracted included details of condition (type of cancer) examined, study design, findings (including incremental cost-effectiveness ratios (ICERs), assessment of uncertainty) and quality assessment. In order to maximise the usefulness of this report, papers deemed of high quality and high relevance have been considered as the priority for discussion. However, data extracted from all papers meeting the inclusion criteria are presented in an Appendix. Further appendices describe the search strategy methods, results and individual abstracts. Subsequently, interventions/strategies were assessed for their relevance to UK policy and decision making by a group of clinical experts in the relevant fields

**Results:** The search identified 1,637 references. After excluding papers that were duplicates, non-English, not economic evaluations, not focussed on cancer or not related to follow-up of patients previously treated for cancer, 78 papers were identified as potentially relevant and these articles were ordered or retrieved from the web. After full text assessment, a total of 34 articles were included in the analysis. Results are presented separately for each cancer

**Conclusions:** Colorectal cancer was the most common (n=9) cancer type considered. Breast (n=7), lung (n=4), bladder (n=3), cervical (n=2), skin (n=2), gastro-oesophageal (n=1), ovarian (n=1), renal (n=1), seminoma (n=1), Hodgkins (n=1), uterine (n=1) and general cancer (n=1) were also studied. The higher quality studies and expert opinion suggested the following:

### ***Colorectal***

- An intensive follow-up strategy for patients who had received curative resection for colorectal cancer appears a cost-effective strategy compared to minimal follow-up.
- The optimal follow-up time with an intensive programme for this patient population is likely to be between 2 and 4 years.
- Nurse-led follow-up appears a cost-effective option. Similarly, follow-up in primary care is likely to be less costly and similarly effective as follow-up at hospital by surgeons.

- Expert input suggested that the method of follow-up (eg remotely) is a potential method of reducing costs without impacting on patient outcomes.

### ***Breast***

- In general, intensive follow-up programmes do not appear a cost-effective option for women with previously treated breast cancer.
- A move to open access after a certain follow-up period (5 years) is popular with patients and clinicians, and is likely to reduce costs with no impact on outcomes.

### ***Lung***

- Follow-up programmes involving nurses or GPs rather than follow-up at hospital clinics might represent efficient strategies for patients previously treated for lung cancer. However, clinical input suggests that it is important to conduct the follow-up in the same place as imaging (hospital), though there is potential for nurse specialists to be involved.

### ***Cervical***

- PET-CT does not appear a cost-effective option in addition to standard imaging in the UK for follow-up of women treated for cervical cancer.

The suggestions described above should be interpreted with caution. Some of the studies were not UK based, several were dated and there was limited evidence that all relevant data had been synthesised or considered. In addition, the relevance of the comparators included may be questioned. In order to identify the most relevant studies for UK decision makers, an expert panel of clinicians has been assembled to provide advice. The following review combines evidence from the published literature with the opinion of clinical experts to highlight relevant studies of acceptable quality.

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## **GLOSSARY and ACRONYMS**

ACER	Average cost-effectiveness ratio
CEA	Carcinoembryonic antigen
CT	Computed tomography
CA15.3	Cancer antigen 15.3
EORTC	European Organisation for Research and Treatment of Cancer Quality of life
QLQ	Questionnaire
EQ-5D	EuroQol at 5 dimensions
FISH	Fluorescent in situ hybridization
HRQoL	Health related quality of life
ICER	Incremental cost-effectiveness ratio
LY	Life year
MRI	Magnetic resonance imaging
NICE	National Institute for Health and Care Excellence
NSCLC	Non-small-cell lung cancer
NHS	National Health Service
NMP22	Nuclear matrix protein 22
PET-CT	Positron emission tomography – computed tomography
QALY	Quality-adjusted life-years
SF-36	Short-form 36
SSC	Squamous cell carcinoma antigen

## 1. INTRODUCTION

The cost of treatment and follow-up of cancer patients in the UK is substantial. In particular, the UK has a relatively poor level of cancer survival compared to some other developed countries, and there is evidence that this may be related to the late diagnosis of treatable cancers. In a budget-constrained system such as the NHS, it is necessary to consider the cost-effectiveness of the range of management strategies at different points on cancer patients' care pathways to ensure that they provide an efficient use of scarce resources.

## 2. AIMS/OBJECTIVES

The specific objective of this project is to review the literature on the cost-effectiveness of follow-up strategies after cancer treatment including:

- i) *empirical* studies exploring the cost-effectiveness of alternative follow-up strategies in cancer patients
- ii) *methodological* papers examining how cost-effectiveness has been and should be assessed in the follow-up of patients after potentially curative treatment of any cancer

## 3. METHODS

The search was undertaken in the following databases: Medline, Embase, Web of Science (WOS), Cochrane Database of Systematic Reviews (CDSR) and the databases of the Centre for Reviews and Dissemination (CRD), DARE (Database of Abstracts of Reviews of Effectiveness), HTA (Health Technology Assessment) and NHS EED (NHS Economic Evaluation Database). In addition, the websites of relevant organisations and initiatives (e.g. Cancer Research UK, NAEDI (National Awareness and Early Diagnosis Initiative) were consulted. Reference list checking and citation searching were undertaken using studies selected for inclusion in the reviews. A keyword strategy was also developed (see Appendix 1 for additional details of the databases and search terms used).

### 3.1 Inclusion criteria

The citations retrieved were sifted by title and abstract and articles were retained if they conducted an economic evaluation of alternative follow-up strategies for patients with any type of cancer or they examined methodological features of how such analyses should be conducted. The articles were screened for inclusion and any ambiguity was reconciled through discussions by two reviewers. Only papers published in the English language were included. Conference abstracts or posters were also initially included but were subsequently excluded if they did not provide enough information to complete the study extraction template.

### 3.2 Data extraction

An extraction template was designed to capture relevant information from the studies identified. Evidence was reviewed by a single researcher and, where there was a lack of clarity or any uncertainty, the issues were discussed within the review team until a consensus was achieved. Table 1 shows the items considered in the template.

<b>A) DETAILS OF THE CONDITION</b>
<b>1. Type of cancer</b>
<b>2. Patient population</b>
<b>3. Interventions/strategies</b>
<b>B) DETAILS OF THE STUDY</b>
<b>1. Authors</b>
<b>2. Date</b>
<b>3. Country</b>
<b>4. Type of economic evaluation</b>
<b>5. Type of model used (if any)</b>
<b>6. Main sources of effectiveness data</b>
<b>7. Outcome measure</b>
<b>8. Perspective</b>
<b>9. Cost categories and main sources of resource use/costs</b>
<b>10. Base-case results</b>
<b>11. Analysis of uncertainty</b>
<b>12. Results of sensitivity analysis</b>
<b>13. Other issues</b>

**Table 1.** Data extracted from each included paper

The information extracted was used to assess the quality of the studies included and the relevance to the UK setting according to whether they met the NICE reference case methods. Table 2 shows the criteria considered in order to assess the quality of the studies.

<b>1. <u>Comparator(s)</u></b>
Is there a full range of comparators, limited set or just one comparator?
How appropriate are the comparator(s)?
<b>2. <u>Evidence synthesis</u></b>
Have authors attempted to bring together a full range of evidence and, if so, is this been done appropriately?
If the study was based on a single clinical study, have the authors made any attempt to relate to a more general evidence
<b>3. <u>Outcome measure</u></b>
Were quality-adjusted life-years (QALYs) assessed as main outcome measure?
How was measurement of health-related quality of life (HRQoL) conducted?
<b>4. <u>Time horizon</u></b>
Was an appropriate time horizon considered?
<b>5. <u>Incremental analysis</u></b>
Was an incremental analysis undertaken?
Do ICERs provide findings potentially useful to decision makers (e.g. cost per LYG, cost per QALYs)
<b>6. <u>Presentation of uncertainty</u></b>
Was a probabilistic sensitivity analysis conducted?
Were appropriate deterministic sensitivity analyses on relevant parameters made?

**Table 2. Quality assessment criteria**

The relevance of each study to the UK setting was based on the following criteria:

- 1) Comparators used in the UK NHS?
- 2) Does the study relate to UK resource use?
- 3) Clinical assessment of the relevant of the intervention/comparators.

## 4. RESULTS

### 4.1 Overview of results (literature searches)

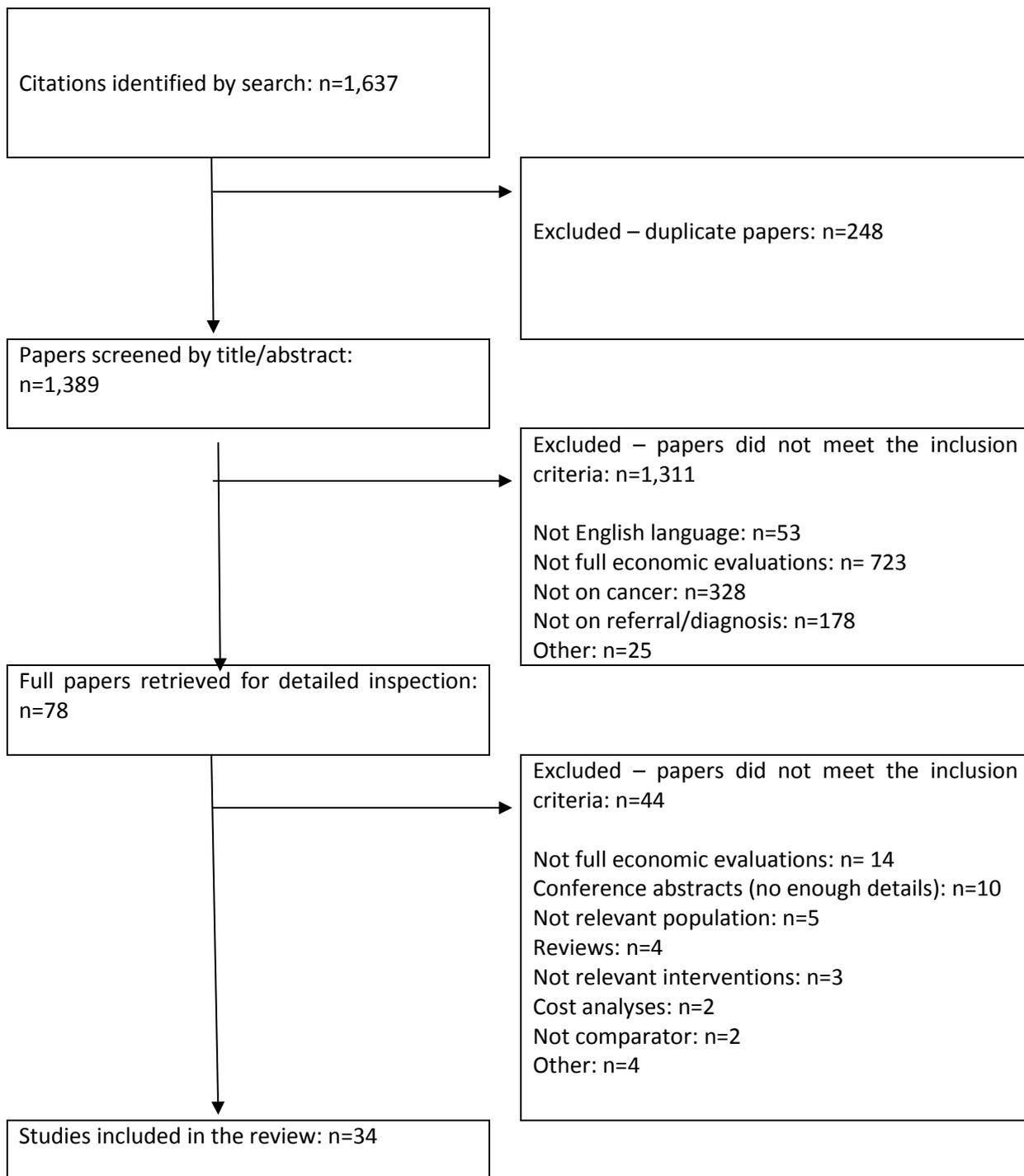
The search identified 1,637 references. After excluding duplicates (n=248), a total of 1,389 unique references were screened by one reviewer. Of these, 84 references were excluded because they were not in English language. Of the remaining 1,305 title/abstracts, 949 were excluded because they were not economic evaluations (e.g. clinical studies, editorials, reviews, cost analyses etc.); 130 were excluded because they did not focus on cancer; and 133 were excluded because they were not related to follow-up of patients previously treated for cancer. The remaining 93 references were initially considered as potentially relevant and discussed within the team (3 reviewers). Of these, 78 were finally identified as potentially relevant and these articles were ordered or retrieved from the web. After full text assessment, a total of 35 articles was included in the analysis. Reasons for exclusion of the 43 studies (after full text assessment) were not full economic evaluations (14 studies), reviews (4), conference abstracts of published studies already included (3) or without enough information (7), no comparator (2 studies), only cost analyses (2), not relevant interventions (3), not relevant population (5), other not relevant study design (2), not English language (1). Finally, 2 studies reported the same analysis on the same patient population, thus only one of the two was included.

Of the 34 follow-up studies included, 6 were conducted in the US,(1-6) 6 in the UK,(7-12) 6 in Germany,(13-18) 5 in the Netherlands,(19-23) 3 in Canada,(24-26) 2 in Italy,(27, 28) 2 in France,(29, 30) 2 in Spain,(31, 32) 1 in Australia(33) and 1 in Norway(34). Table 3 shows a breakdown of these studies by cancer type.

Type of cancer	Number of studies
Colorectal	9
Breast	7
Lung	4
Bladder	3
Cervical	2
Skin	2
Gastro-oesophageal	1
Ovarian	1
Renal	1
Seminoma	1
Hodgkin's	1
Uterine	1
General cancer	1
TOTAL	34

**Table 3. Follow-up papers by cancer type**

**Figure 1. Flow diagram for follow-up search**



## 4.2 Summary of results

### 4.2.1 Follow-up studies on colorectal cancer

Nine studies assessed the cost-effectiveness of follow-up strategies in patients previously treated for colorectal cancer,(9, 10, 12, 17, 20, 27, 29, 30) three of which were conducted in the UK.(9, 10, 12) Renehan et al (2004) (12) compared a strategy of conventional follow-up with a more intensive follow-up

strategy for patients who had received potentially curative resection for colorectal cancer. The study was based on a meta-analysis of 5 published clinical trials which had shown a reduction in mortality at 5 years for patients followed intensively. The perspective of the study was that of the UK NHS and costs of visits, tests, treatment of recurrences and palliative care were included in the analysis. Over a five-year follow up, the numbers of life years gained (LYG) by intensive follow up were 0.73 while the adjusted incremental cost for each patient was £2,479 leading to an incremental cost for each LYG of £3,402. Similar results were found when only 4 trials were considered in the meta-analysis. Intensive follow-up remained cost-effective (less than £10,000 per LYG) in all sensitivity analyses. The authors stated that there was heterogeneity in the tests included in the intensive follow-up programs of the five trials considered.

Macafee et al (2008)(10) also evaluated the cost-effectiveness of an intensive follow-up programme in the UK for patients previously surgically treated for colorectal cancer. A standard follow-up programme according to the broad principles of the British Society of Gastroenterology Guidelines was compared with a more intensive program involving more visits and tests for a longer period and carcinoembryonic antigen (CEA) measurement. Most clinical data and resource use were taken from a clinical trial (The Follow up after Colorectal Surgery trial) conducted in the UK. The time horizon of the study was 5 years and the perspective of the NHS was adopted. Considering the cohort of UK patients with colorectal cancer in 2003 which attended regularly a follow-up programme, intensive follow up would cost an additional £15.4 million and would detect 853 additional resectable recurrences over 5 years, with a cost per additional resectable recurrence of £18,077. It was concluded that *“intensive follow up will detect considerably more resectable recurrences but the financial cost and resource requirements are considerable. Resource limitations and the introduction of screening may mean that intensive follow up needs to be risk stratified to those with the highest likelihood of recurrent CRC”* (page 227).

The third UK study(9) (Jeyarajah et al, 2010) compared a Colorectal Nurse Specialist (CNS) follow-up protocol (nurse-led follow-up) with no follow-up in 193 patients who had undergone surgical intervention for colorectal cancer and who were followed-up to 5 years in a prospective study. The CNS protocol was based on a distinction between low- and high-risk patients, with different frequency of visits and tests. The perspective of the NHS was adopted and only the costs of tests and visits appear to have been included in the analysis. The adjusted cost for each QALY gained with CNS protocol versus no follow-up for lower-risk tumours was £1,914. The adjusted cost for each QALY gained was £2,180 for higher-risk tumours. It was concluded that nurse-led follow-up could be considered a cost-effective approach and that a 4-year follow-up is the optimal time since most recurrence were detected within 4 years.

Two studies were conducted in the French setting, both by Borie et al (2004).(29, 30) The two publications

report the same analysis over a different time horizon (5 or 7 years). Strategies compared were a more intensive follow-up programme versus minimal follow-up<sup>1</sup> in patients who had undergone curative resection for colorectal cancer. A sample of 231 patients was retrospectively analysed. A Markov model was constructed to project costs and QALYs of these patients over a 7-year follow-up from the perspective of the healthcare system. Transition probabilities and HRQoL weights were obtained from published studies. For the whole population the ICER for intensive versus minimal follow-up was €3,114. For patients who had Duke's stage A, B or C colorectal cancer, the ICERs were, respectively € 4693, €10,068 and €1,058 per QALY.

Staib et al (2000)(17) followed prospectively 1,054 patients previously treated for colorectal cancer in the German setting over a 5-year time horizon. Patients could receive endoscopy, chest radiography, abdominal ultrasound, computed tomography (CT) pelvis (or a combination of these tests) in an intensive follow-up programme. The cost per recurrence detected was calculated. Only tests and visits were included as cost categories from the payer perspective. In this sample of patients, the follow-up costs for 21 cured recurrence patients were €126,000, resulting in an average cost-effectiveness ratio of €6,000 per recurrence detected.

In a recent Norwegian study, Augestad et al (2013)(34) conducted an economic evaluation alongside a randomised clinical trial to assess the impact on costs and HRQoL of colon cancer follow-up organised by GPs in primary care instead than by surgeons in hospital. A total of 110 patients aged less than 75 years who had undertaken surgery for colon cancer with histological grade Dukes' stage A, B or C were randomised to be followed-up at GPs or at hospital by surgeons. Resource use and HRQoL data were collected alongside the trial (using both the EORTC QLQ C-30 and the EQ-5D questionnaires). The time horizon of the analysis was 2 years and a societal perspective was adopted. There were no significant differences in primary HRQoL measures between the two options. Overall, the mean cost per patient for 24 months follow-up was £9,889 in the surgeon group and £8,233 in the GP group ( $p < 0.001$ ). The length of sick leave was the main cost driver.

The remaining two studies compared several diagnostic tests for follow-up of patients after curative resection of colorectal cancer. Di Cristofaro et al (2012)(27) assessed the cost-effectiveness of various combinations of tests in a retrospective analysis of 373 Italian patients. Physical examination, colonoscopy, thorax-abdominal computed tomography (CT) scan, serum CEA, sigmoidoscopy, ultrasound and

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<sup>1</sup> The most intensive follow-up included CEA monitoring every 4–6 months for 3 years, then once a year for 2 years, physical examination every 3 months for 2 years, then every 6 months for 3 years, a colonoscopy every 3 years, an ultrasonography exploration every 4–6 months for 3 years, then once a year for 2 years, and an annual chest x-ray. Minimal follow-up schedule included CEA monitoring and ultrasonography exploration once a year for 3 years, a physical examination every 6 months for 5 years, a colonoscopy every 3 years, and a chest x-ray once a year for 2 years.

combinations of these tests were considered. Only test costs were included in the analysis on the basis of the Italian health care system. The combination of physical examination, colonoscopy, thorax-abdominal CT scan, and serum CEA was found to be the most cost-effective option to monitor stages I and II colon cancer; while physical examination, rigid sigmoidoscopy, thorax-abdominal CT scan, and serum CEA were found to be the most cost-effective surveillance strategies to monitor stages III and IV of colon cancer and rectal cancer. The authors concluded that any follow-up programme should be as intensive as possible in the first 2 years after resection.

Bleeker et al (2001)(20) analysed the clinical value and costs of different diagnostic tools used to identify potentially curable recurrent disease in patients treated adjuvantly for curatively resected Dukes' C colonic cancer. They followed 496 Dutch patients who could be managed on the basis of interim history, physical examination, liver ultrasonography, computed tomography CT, measurement of CEA levels, chest radiography and colonoscopy. The perspective of the healthcare system was adopted and the costs of tests, consultations and treatment of recurrence were considered. Of all treatable recurrences, 12 of 42 were identified by evaluation of symptoms only. Ultrasonography and colonoscopy identified 22 recurrences at a cost of US\$11,790 per patient, while routine follow-up by CEA measurement, chest radiography and physical examination identified a further six at a cost of US\$19,850 per patient. It was concluded that multiple diagnostic modalities are required to identify most patients with treatable recurrent disease; ultrasonography, CT and colonoscopy can identify most recurrences at a good value for money, while CEA, chest radiography and routine physician visits appear less cost-effective.

**Key messages:**

- An intensive follow-up strategy for patients who had received potentially curative resection for colorectal cancer appears a cost-effective strategy compared to minimal follow-up.
- However, current guidance and clinical opinion suggest that for a large number of patients, this could be remote monitoring
- The optimal follow-up time with an intensive programme for this patient population is likely to be between 2 and 4 years.
- Nurse-led follow-up appears a cost-effective option. Similarly, follow-up in primary care is likely to be less costly and similarly effective as follow-up at hospital by surgeons.
- Combination of CT scan, colonoscopy and ultrasonography appear the most cost-effective options in the follow-up of treated colorectal cancer patients. Contrasting results have been found for physical examination, CEA measurement and sigmoidoscopy, and their value for money might depend on patients' characteristics.

- Expert opinion suggested that how patients should be followed up (whether this can be remote) and which patients should be followed up and treated were more pressing issues (for example the over 80s)
- Input from an expert clinician suggested that although many of these papers were post-2000, studies quickly become dated in this field.
- Input from an expert clinician suggested that the big gain in terms of improving the effectiveness of follow-up would be to create an automated system enabling more efficient recall.
- The FACS trial which is due to report soon may have a substantial impact on practice.

#### 4.2.2 Follow-up studies on breast cancer

Seven studies included in the analysis estimated the cost-effectiveness of follow-up strategies in women previously treated for breast cancer.(8, 18, 19, 21, 31-33)

In a UK study, Beaver et al (2009)(8) assessed whether telephone follow-up by specialist nurses would be a cost effective approach compared to hospital follow-up. A sample of 374 women previously treated for breast cancer was randomised to receive either telephone or hospital follow-up. A cost-consequences analysis was conducted over a 2-year time horizon. The clinical impact of the two interventions was evaluated by the State–Trait Anxiety Inventory questionnaire. Costs were estimated both from the NHS and the societal perspective that also included travel and productivity costs. Telephone and hospital-based follow-up resulted in equivalent levels of anxiety for women, thus a cost-minimisation analysis was conducted. The total cost to the NHS of routine follow-up via telephone was significantly higher (£179 versus £124; mean difference £55) than hospital clinic follow-up. However, transport and productivity costs combined were a mean of £47 per patient lower in the telephone follow-up group. It was concluded that *“telephone nurse follow-up will not necessarily lead to cost or salary savings for the NHS. For some patients, the convenience and low cost of telephone follow-up appears to result in increased satisfaction with the process of care”*.

Two Spanish studies were identified.(31, 32) The most recent analysis by Baena-Canada et al (2013)(31) compared the cost-effectiveness of following up women treated for breast cancer either in primary care or by specialists/hospital. They retrospectively analysed data from 96 women who were still alive after 5 years of follow-up. A cost-consequence analysis was conducted and results were compared in terms of HRQoL (measured with the SF-36 questionnaire) and costs. The perspective of the healthcare system was used and only costs of visits and tests included in the analysis. It was found that the costs of follow-up in primary care were lower €112.86 versus €184.61 per patient/year (P = 0.0001). There was no statistically significant difference in any dimension of the SF-36 (when adjusted for age and type of chemotherapy). It was

concluded that primary care was more cost-effective. However, patients expressed greater satisfaction with specialist follow-up (80%), while only 10% of patients preferred primary care (10% indifferent).

In the other Spanish study, Oltra et al (2007)(32) compared an intensive follow-up programme to a standard clinical follow-up that only consisted of physical examination in 121 women diagnosed as having breast cancer at stages I, II, or III and who had completed an initial curative treatment. In the intensive follow-up group, in addition to physical examination, women received biochemistry, hematology, CEA and CA15.3 that were assessed at every outpatient visit together with an annual hepatic echography, chest x-ray, and bone scan. Patients were randomised to receive either standard or intensive follow-up; recurrences detected and costs were assessed alongside the trial. The perspective of the healthcare system was taken. After a median of 3 years of follow-up, there were 24 relapses, 11 in standard clinical follow-up, and 13 in the intensive follow-up group. The cost per patient in the standard clinical follow-up group was €390 while it was €1,278 in intensive follow-up group. It was concluded that no benefit for the more intensive strategy and, therefore, no justification for the higher cost.

Two studies were conducted in the Netherlands.(19, 21) Lu et al (2012)(21) assessed the cost-effectiveness of follow-up according to the National Screening Programme (NSP) versus less intensive follow-up options. NSP guidelines recommend hospital follow-up for 5 years with yearly mammography plus physical examination every 3 months for the first year, every 6 months the second year and then yearly up to 5 years. Three alternative less intensive programmes were considered where follow-up time in hospital was shortened by a shift of care from the hospital to the GP after 2 years of follow-up, the referral age was lowered from 60 to 50 years and yearly physical examination in general practice was excluded. A decision analytic model was developed to project costs and rate of recurrences of these options over patients' lifetime. The perspective of the healthcare system was taken. The model showed the less intensive programmes did not decrease the detection of small tumours. The current strategy of NSP was the most expensive option. The exclusion of physical examination after 2 years of follow-up was the most cost-effective strategy.

The other Dutch study (Benning et al, 2012)(19) aimed to show how to combine individual-specific parameter estimates from a random parameter model (mixed logit model) with cost data. It took the case of women treated with breast cancer as an example. Specifically, a customized programme for all patients based on individual patient preferences was compared with several non-customized programs. A 2-year time horizon was used and the hospital perspective adopted (including visits and mammography costs). It was found that the fully customized care programme leads to higher HRQoL and lower costs than the current standardized programme. There is significant preference heterogeneity amongst women assigned

to various attributes of the follow-up programmes. It was concluded that offering a fully customized follow-up programme may benefit both patients and hospitals in cases in which patients have heterogeneous preferences. For example, patients benefit from customized care because of obtaining higher HRQoL levels (i.e., receiving a more preferred follow-up program), while hospitals benefit because of cost savings and higher patient satisfaction rates.

Grogan et al (2002)(33) compared several follow-up schedules with a different number and frequency of visits in a retrospective analysis of 438 previously treated Australian women with stage I or II breast cancer. The cost of detecting a salvageable event was estimated over a 5-year time horizon. Only costs of visits and tests were considered from the perspective of the payer. A simulated follow-up programme involving monthly visits for 5 years, costing Australian \$3870 per woman, was the most successful in facilitating the detection of a salvageable recurrence (96%) but was also very expensive. The authors stated that three-monthly visits for 4 years and yearly visits in the 5th year was the more cost-effective option (52% detected at a cost of Australian \$1,097 per woman). However, this was not justified with an incremental analysis. It was acknowledged that a prospective assessment of the impact of different follow-up programmes on patients' HRQoL need to be performed to corroborate these findings.

Finally, Wojcinski et al (2012)(18) assessed the cost-effectiveness of adding ultrasound to routine follow-up programmes for women with a history of breast cancer. The analysis was based on a sample of 735 women using a before and after design. A time horizon of one year was applied and the perspective of the German insurance adopted. The rate of detected recurrences rose from 3.7% (95% CI: 2.3-5.0) in the routine follow-up program to 4.5% (95% CI: 3.0-6.0) in the study follow-up program ( $p = 0.041$ ). The costs per detected malignancy in the routine follow-up program were \$2455.69; the costs for each additionally detected malignancy in the study follow-up program were \$7580.30. Therefore the use of ultrasound detects a higher number of recurrences but at a relatively high cost.

**Key messages:**

- In general, intensive follow-up programmes do not appear a cost-effective option for women with previously treated breast cancer.
- The use of nurse-led telephone follow-up instead than hospital follow-up does not reduce detection of recurrences but it might be more costly from a NHS perspective.
- Customized programmes for all patients based on individual patient preferences could be cost-effective options.
- It is unclear whether follow-up by GPs should be preferred to specialists/hospital follow-up.

- The addition of ultrasound to routine follow-up programmes might detect more recurrence but at a relatively high cost.
- Input from experts suggested that there is a general move towards open access after a period without relapse. This is generally seen as a positive though limited cost-effectiveness evidence.
- Experts suggested that the big gain in follow-up of these patients would be from the set-up and maintenance of a database of patients. Information Technology is seen as the “stumbling block”

#### 4.2.3 *Follow-up studies on lung cancer*

Four studies estimated the cost-effectiveness of follow-up strategies for patients previously treated for lung cancer.(4, 11, 23, 25)

Moore et al (2002)(11) compared costs and HRQoL in 203 UK patients with lung cancer who had completed their initial treatment and were randomised to be followed-up either by nurses or with a conventional medical follow-up. Conventional care consisted of routine outpatient appointments (one post treatment appointment, then appointments at two or three month intervals) for medical assessment and investigations. Patients in the nurse-led follow-up group were assessed monthly by protocol over the telephone or in a nurse led clinic to identify signs of disease progression, symptoms warranting intervention, or serious complications. A one-year time horizon was used and the perspective of the NHS adopted that included the costs of tests, visits, procedures and hospitalisations. Patients’ HRQoL was assessed using the EORTC QLQ C-30 questionnaire. At 12 months, patients randomised to receive nurse led follow up had better scores for emotional functioning (P=0.03) and less peripheral neuropathy (P=0.05). All the other scores were not significantly different. Comparison of the overall costs of care for the three periods of follow up (3, 6, 12 months) showed no significant differences, although nurse-led follow-up was less expensive (€696.50 versus €744.50 for nurse-led versus medical FU). Clinical input suggests that this study is relevant to current decision making. However, while nurse specialists could be involved in the follow-up, their time is limited as much as physicians.

Gilbert et al (2000)(25) also assessed whether it is more efficient following-up patients treated for lung cancer at the hospital clinical or by their GPs. They estimated costs and recurrences detected in a retrospective analysis of 245 early stage (< IIB), non–small cell lung cancer (NSCLC) patients who had received resection in the Canadian setting. The perspective of the hospital was taken and a 5-year time horizon applied. Only costs of tests and visits were considered. It was found that, despite clinic follow-up,

66.7% (60 of 90) were identified by the family physician, and only 28.9% (26 of 90) by the surgeon. The cost per recurrence detected by surgeons was Can \$4,367 while the cost per recurrence detected by GP was Can\$1,105. Concern was expressed that in the UK, lung cancer patients struggle to get GP appointments for emergency issues let alone follow-up, so the generalisability of this finding to a UK setting may be limited.

The remaining two studies compared the value for money of diagnostic tests. Kent et al (2005),(4) in a US study, assessed the cost-effectiveness of chest computed tomography (CT) for patients who had undergone resection of NSCLC. They developed a Markov model to assess costs and benefits of CT over patients' lifetimes. Epidemiological and clinical data to populate the model were taken from a review of the literature, which was based mainly on US studies. Only a few estimates were pooled. HRQoL weights were also taken from published studies. The perspective of the analysis was that of the payer and both short-term costs (e.g. tests, visits, hospitalisations) and long-term costs (e.g. treatment of cancer recurrences) were considered. Annual CT scans resulted in an overall cost of \$47,676 per QALY gained compared to no CT scan. Test accuracy and patient age were key factors that could impact on the cost-effectiveness of CT scan (e.g. not cost-effective for patients aged more than 65 years). In the UK, some centres use CT scans, others do not, though international trials are underway comparing chest x ray with CT scans as a follow-up modality.

Van Loon et al (2010)(23) compared positron emission tomography – computed tomography (PET-CT) scan, chest CT scan and conventional follow-up (anamnesis, physical examination and a chest X-ray) for NSCLC patients after curative intent therapy in the Dutch context. A Markov model was used to project costs and HRQoL associated with these strategies over a 5-year time horizon. Clinical sources were based on a prospective study conducted at the authors' institution corroborated by published studies and expert opinion. HRQoL weights were taken from a published study. The analysis was conducted from the perspective of the healthcare system, and all direct costs incurred by these patients over 5 years were considered. CT-based follow-up was only slightly more effective than conventional follow-up, resulting in an ICER of € 264,033 per QALY gained. For PET-CT-based follow-up, the ICER was € 69,086 per QALY gained compared to conventional follow-up. The strategy in which a PET-CT was only performed in the asymptomatic subgroup resulted in an ICER of € 42,265 per QALY gained as opposed to conventional follow-up. Given a cost-effectiveness threshold of € 80,000 per QALY, PET-CT-based follow-up and conventional follow-up had a similar probability of being cost-effective (48% and 47%, respectively), while the probability of CT-based follow-up being cost-effective was only 5%. The expected value of perfect information was also assessed and showed it is worthwhile to perform additional research to reduce the uncertainty surrounding the decision whether to implement PET-CT. In the UK, PET is routinely used to

assess the stage of the cancer but not for post-treatment surveillance (largely due to the large costs and the lack of evidence of benefit)

**Key messages:**

- Follow-up programmes involving nurses or GPs instead of follow-up at hospital clinics might represent efficient strategies for patients previously treated for lung cancer and are generally preferred
- Expert opinion suggested that PET is widely used as a staging investigation for lung cancer in the UK (for patients with potentially radically treatable disease) but is not used at all in the follow-up context, though evaluations were underway to determine the effectiveness/cost-effectiveness
- Expert opinion suggested that there was some reluctance to move follow up into primary care, but that nurse specialists would be appropriate alternatives if they have sufficient capacity

*4.2.4 Follow-up of bladder cancer patients*

Three economic evaluations on follow-up options for patients with treated bladder cancer were found.(1, 3, 26)

Kamat et al (2011)(3) compared several diagnostic tests in a prospective trial to identify optimal bladder cancer surveillance protocol in the US. A total of 200 patients previously treated for bladder cancer was enrolled in the study and could receive: i) cystoscopy alone; (ii) cystoscopy and NMP22; (iii) cystoscopy and FISH; (iv) cystoscopy and cytology; and (v) cystoscopy and positive NMP22 confirmed by positive FISH. A median follow-up of 4.1 months was considered and recurrences detected estimated. Costs were assessed alongside the prospective study and included only the tests implemented. The costs per tumour detected were \$7,692, \$12,000, \$26,462, \$11,846; and \$10,292 for cystoscopy alone, cystoscopy and NMP22, cystoscopy and FISH, cystoscopy and cytology and cystoscopy and positive NMP22 confirmed by positive FISH, respectively. Cystoscopy plus FISH detected the highest number of recurrences (72%), but was associated with the highest cost per case detected due to the high number of false positives. It was concluded that cystoscopy alone was the option with the lowest cost per case detected.

In another US analysis (available only as conference abstract), Chen et al (2009)(1) estimated the cost-effectiveness of Urovysion (a genomic test) plus standard care compared to standard care alone (cystoscopy plus cytology). A prospective cohort of 80 patients previously treated for bladder cancer was followed-up to 2 years. Costs and recurrences detected were assessed and the perspective of the payer

adopted (only tests considered). The average cost per recurrent bladder cancer event detected was \$4,800 by using Urovysion and \$2,096 by the standard care, respectively. The incremental cost of Urovysion relative to the standard surveillance care was \$2,704 per case detected. The authors concluded that Urovysion test is unlikely to be cost-effective.

Finally, Nam et al(26) assessed the cost-effectiveness of urinary markers compared to a standard strategy of cystoscopy plus cytology. The analysis was based on a decision tree that assessed costs and recurrences detected for patients previously treated for bladder cancer. Probabilities were taken from a retrospective cohort of 361 patients. The authors stated that a societal perspective but only direct costs appear to have been considered including tests, visits and treatment of cancer. The cost of care based on urinary markers ranged from \$158 to \$228 for each follow-up visit while the cost of standard care was \$240 for each follow-up visit. No differences in recurrences rate were found. Accuracy of the urinary markers is the key determinant of cost differences between the two strategies.

**Key messages:**

- There is poor evidence and great uncertainty about the most cost-effective diagnostic strategies for the follow-up of patients with bladder cancer. Cystoscopy plus FISH might detect the highest number of recurrence but at a high cost
- It is unclear whether urinary markers and genomic tests could be preferred to standard care (cystoscopy plus cytology) in US and Canada at the time of these studies.
- Expert opinion suggested that the surveying and treatment of bladder cancer patients is very topical. A large National Cancer Research Institute (NCRI) trial is in set-up, with aim of recruiting 700+ patients.

*4.2.5 Follow-up studies on cervical cancer*

Two of the studies identified assessed the cost-effectiveness of diagnostic strategies to follow-up women previously treated for cervical cancer.(7, 28)

Auguste and colleagues (2014),(7) investigated the value for money of adding PET-CT to standard imaging (that consisted of clinical examination and either an MRI or CT scan alone, or both MRI and CT) in women at least 3 months after the completion of treatment, with either recurrent or persistent cervical cancer. A Markov model was developed to compare costs and QALYs associated to the two strategies over a 5-year time horizon. Clinical data were based on a systematic review of the literature and studies identified were selected on the basis of expert opinions. HRQoL weights were obtained from a single published study. The

perspective of the NHS was adopted and diagnostic test, visit and cancer treatment costs were included. The ICER for PET-CT plus standard care compared to standard care alone ranged between £1 million and £9 million per QALY depending on the subgroup of women considered. The probabilistic sensitivity analysis confirmed that it is very unlikely for PET-CT to be a cost-effective option. The expected value of perfect information was zero.

The other study identified was conducted in Italy by Forni et al (2007)(28) and assessed the cost-effectiveness of a squamous cell carcinoma antigen (SCC) assay plus gynaecologic examination versus standard follow-up protocol in follow-up of cervical cancer treated with radiotherapy. Standard protocol could include chest X-ray, abdominopelvic magnetic resonance imaging, gynecologic examination with colposcopy, Papanicolaou smear test. A sample of 135 women treated for cervical cancer was followed-up to 5 years in a prospective cohort study. The rate of missed recurrence and costs of tests and visits were estimated from the perspective of the Italian NHS. The number of recurrences missed by the SCC assay plus gynaecologic examination was 2.2%, but it was approximately 12.2-fold less costly than the standard approach over 5 years of follow-up (€298 per patient versus €3653 per patient). The authors concluded that a simple approach of SCC assay plus gynaecologic examination might be used as first-line follow-up tests.

**Key messages:**

- PET-CT does not appear a cost-effective option in addition to standard imaging in the UK for follow-up of women treated for cervical cancer.
- A simple approach of SCC assay plus gynaecologic examination could substantially reduce the costs of follow-up of women previously treated for cervical cancer missing a relatively low number of recurrences. However, the benefit of ANY routine regular investigations has not been demonstrated in these patients.
- Expert opinion suggested that ***“expensive imaging and other routine investigations are not justified – we do not do these in the UK and indeed investigate less than many of the “standards” considered as baselines in these papers”***

4.2.6 *Follow-up studies on skin cancer*

The two economic evaluations identified on follow-up of patients treated for cutaneous melanoma were both conducted in Germany.(15, 16)

Hoffman et al (2002)(15) assessed the cost-effectiveness of different diagnostic options for the follow-up of 661 patients previously treated for skin cancer. Diagnostic tests included history and physical examination,

chest X-ray, sonography of the abdomen, high resolution sonography of peripheral lymphnodes, scintigraphy of the bones, cranial CT-scan. A retrospective analysis of patients receiving these tests over an 8-year time horizon was conducted to estimate costs and metastasis detected. A subgroup analysis by cancer stages was also performed. The perspective of the healthcare system was adopted and costs associated to tests and visits were considered. Physical assessment was associated to a cost of €7,300 per detected metastasis while sonography cost €13,300 (follow-up of stage I/II) per detected metastasis. In contrast, chest X-ray cost to detect a metastasis was €2,800 (in stage III) and €13,300 in stages I/II. In general, all imaging techniques were more efficient at later stages. The authors stated that the findings of this study produce serious doubt on the efficiency of expensive routine imaging procedures at initial staging and during early phases of melanoma disease.

Leiter et al (2009)(16) also compared several diagnostic techniques in the German context including physical examination, lymph node ultrasound, chest radiograph, abdomen ultrasound, blood tests and CT. Resource use and diagnostic accuracy data were collected in a 2-year prospective study conducted in a single German centre. Cases detected and costs were estimated from the perspective of the payer; the costs of tests, visits and surgeries were considered. In stage I patients, costs for the detection of one recurrence were €4,289 for physical examination and €18,035 for lymph node sonography. Costs decreased in stage II to €500 for physical examination and to €1,333 for lymph node sonography and in stage III to €168 and to €1250, respectively. Chest radiograph generated the highest costs in stage I to detect one recurrence (€22,886). Abdomen ultrasound and blood tests did not identify recurrence.

#### **Key messages:**

- In the German context, physical examination appears the most cost-effective option for the follow-up of patients previously treated cutaneous melanoma
- Lymph node sonography and other imaging tests might be a cost-effective option at later stages.
- Clinical opinion suggested that the baseline level of tests/investigations in Germany is higher than in the UK and that the evidence for these additional tests in the NHS was limited.
- Expert opinion suggested that previously there was “no treatment for metastatic disease we had a very low intensity follow up regime but now that therapies are emerging which do have a survival benefit there has been a move to increase the intensity of follow up and radiological screening”. However, evidence of the effectiveness/cost-effectiveness is based on consensus rather than a robust evidence base.

#### **4.2.7 Follow-up studies on other cancer types**

Seven additional publications on follow-up strategies for other cancer types were found (one per type).

In a Dutch study, Polinder et al (2009)(22) compared two different protocols after surgery for oesophageal cancer: follow-up by surgeons at the outpatient clinic (standard follow-up) or by regular home visits of a specialist nurse (nurse-led follow-up). A total of 109 patients were randomised to one of the two protocols and followed-up to 1 year. HRQoL (EORTC QLQ C-30 and EQ-5D) and resource use data were collected alongside the clinical trial. The authors stated that a societal viewpoint was adopted and follow-up visits, intramural care, diagnostic procedures, additional treatments (for example, palliative treatment) were considered (but indirect costs were not included). At 4 and 7 months, slightly more improvement on the EQ-VAS was noted in the nurse-led compared with the standard follow-up group. No differences were found in most medical outcomes. Medical costs were lower in the nurse-led follow-up group (€2,600 versus €3800). At a cost effectiveness threshold of €4,000 or more for a one point gain on the EQ-VAS nurse-led follow-up had a probability of being cost effective of 76%. Expert opinion suggests that nurse led follow-up is likely to be cost-effective, but that the limiting factor may be the availability of suitably qualified nurses in this specialty.

Two US studies by Rettenmaier et al(5, 6) compared several diagnostic options in patients previously treated for ovarian, ovarian plus uterine and primary peritoneal cancer (PPC). The two publications were based on the same retrospective analysis, but different subgroups of patients and different time horizons were considered. Both studies adopted the perspective of the payer. The tests compared were CA-125 assay, physical examination, CT scanning of the abdomen, chest X-ray, pelvic ultrasound, PET scan and vaginal cytology. In both cases, serial imaging detected the highest number of progressive disease cases but CA-125 testing was the least expensive. However, clinical input on this paper suggested that “the value of routine clinical surveillance is unproven but appears to be accepted as a foregone conclusion in this paper.

Dion et al (2010)(24) assessed the cost-effectiveness of the new Canadian Urological Association (CUA) Guidelines compared to the old surveillance protocol for patients who had undergone radical nephrectomy for local renal cancer. Seventy-five patients who were followed-up using the old surveillance method in a Canadian hospital were retrospectively analysed. At each visit, patients underwent history, physical examination, laboratory testing (complete blood count, electrolytes, renal and liver panels), urinalysis and chest x-ray. At the 6-month visit, imaging of the chest/abdomen/pelvis with CT or abdominal ultrasound for patients with impaired renal function was performed. After 12 months, a stage-based strategy was implemented. The theoretical costs associated to the new guidelines that distinguished tests on the basis of patients' stage were calculated on the basis of this sample of patients. The perspective of the payer was used and only tests and visits were considered. Recurrence rate and disease survival associated to the two

protocols were estimated. The disease-free survival endpoints were 87.7% and 85.2%, respectively for old and new guidelines. Total medical costs were higher for old institutional surveillance strategy than the new guidelines (\$181,861 vs. \$135,054). For the complete follow-up of 75 patients, a cost-savings of \$46,806 could have been achieved following the CUA guidelines ( $p = 0.002$ ). Expert input suggested that there is a need to look at follow-up regimens and how they might impact cost, recurrence detection and survival, particularly with the availability of newer oral therapies.

In a German study, Classen et al (2009)(13) compared a follow-up strategy with diagnostic tests (chest X-ray, CT abdomen/pelvis, sonography abdomen) and tumour markers in patients with stage I seminoma treated with radiotherapy. Clinical data were based on a RCT that enrolled 675 patients who were followed-up (mean 61 months) after radiotherapy. Only the costs of diagnostic tests were included in the analysis from the perspective of the public and private healthcare funds. Study results showed that recurrence was diagnosed by symptoms or physical examination in 14 out of 26 relapsing patients. Among the technical follow-up investigations abdominopelvic imaging had the highest detection rate for relapse. Chest X-ray and CT abdomen were the most expensive diagnostic tests while sonography abdomen was the less costly option. The authors stated that sonography abdomen was the most cost-effective imaging option, but it is unclear how this was calculated as no average or incremental cost-effectiveness ratios were presented.

Guadagnolo et al. (2006)(2) evaluated the value for money of CT in the routine follow-up of patients after primary treatment for Hodgkin's disease (HD). A Markov model was used to estimate lifetime costs and QALYs in a hypothetical cohort of patients (25-year old) who have had a complete response to primary treatment for HD. Diagnostic accuracy and clinical data for transition probabilities were based on published studies, expert opinions and assumptions. HRQoL weights were also taken from published studies. The perspective of the analysis was that of the payer and included costs of tests, visits and cancer treatment. For patients at early stages (I-II), CT follow-up was dominated. For advanced-stage patients, annual CT for 5 years was associated with a very small quality-adjusted survival gain over non-CT follow-up with an incremental cost-effectiveness ratio of \$9,042,300/QALY. In all sensitivity analysis CT was dominated or associated with extremely high ICERs. Expert opinion suggested that annual CT is not an appropriate comparator and paper is of little relevance to current NHS.

Finally, Hengge et al (2007)(14) estimated the cost-effectiveness of different follow-up examinations in a sample of 526 melanoma patients at different stages previously treated. A Markov model was developed to

compare costs and QALYs associated to various tests such as physical examination, abdominal ultrasound, chest X-ray, lymph node ultrasound and blood tests over a 5-year time horizon. Costs were estimated both from the viewpoint of the German and the US payer (Medicare). Clinical examination (7,167 € or \$8,600 per detected metastasis) and lymph node ultrasound (9,118 € or \$10,942 per detected metastasis) represented the most effective methods to detect metastases of malignant melanoma at any stage.

Further details of all the studies included for the referral and follow-up reviews in the review are available in Appendix 2.

### **4.3 Quality assessment of follow-up studies**

#### **Comparators**

Nine of the 34 studies included in the analysis were based on a decision model. Of these, six studies undertook a review of the literature (1 systematic review) to identify model parameters. However, appropriate data synthesis was not conducted and values for model parameters were generally estimated from a (weighted) average of selected studies or chosen by the authors from one of the studies identified. The remaining 3 studies based on a decision model represented extrapolation on a longer-term of a single study. Among the 25 economic evaluations not based on a decision model, only two obtained clinical estimates from more than one published study. In one of these (Renehan et al, 2004), a meta-analysis of RCT was conducted. The remaining 23 studies are economic evaluations conducted alongside a single study (RCT, prospective cohort study, retrospective analysis etc.) and no data synthesis was needed. Generally, no comparison with other published studies was made.

Only six of 34 studies used QALYs as main benefit measure and utility weights were always taken from previously published studies. Little description of these published studies was generally provided: 3 studies reported the values used for utility weights but did not describe the instrument used to elicit these values; 1 study (Kent et al, 2005) did not report any information of utility values used; 1 study (Jeyarajah et al, 2010) did not provide information on sources used to obtain quality of life score only; Borie et al (2004) reported both the study used as source of quality of life scores and the questionnaire that was given to elicit these values. Four of the remaining studies assessed quality of life alongside the clinical study undertaken, with various instruments including the EQ-5D visual-analogue scale, the EORTC QLQ C-30 and the SF-36. The majority of studies (24) did not make any attempt to assess patients' quality of life.

A total of 20 of 34 studies appear to have used an adequate time horizon for this patient population (3 lifetime, 17 equal or more than 5 years). For the remaining studies it is unclear whether the time horizon

used is long enough to assess all costs and benefits (e.g. recurrences) for the patients that have been followed up.

Very few studies conducted an appropriate incremental analysis, and ICERs were calculated only in 10 of the 34 studies selected. Other 8 studies only presented average cost-effectiveness ratios, reducing the interpretability of the findings. Twelve studies only reported total costs and outcomes for each strategy without any attempt to calculate a ratio (cost-consequences analysis); the remaining 4 studies were cost-minimization analyses based on equal clinical effectiveness between the alternatives investigated. Among economic evaluations that had calculated ICERs, QALYs or LY saved were used in 5 and 2 studies, respectively. All the other analyses reported ratio with limited value for decision-making as, for example, incremental or average cost per recurrence or metastasis detected.

Finally, the analysis of uncertainty was overall rather poor. Only 3 studies adopted a probabilistic sensitivity analysis and 9 studies conducted deterministic sensitivity analysis on several parameters or considered several alternative scenarios. The majority of the analyses did not perform any sensitivity analysis (20/34) or only on few parameters (2/34). The very high number of studies without sensitivity analysis might be due to the limited use of decision models, since most analyses were economic evaluation conducted alongside a single study.

<p><u>Comparator(s)</u></p> <ul style="list-style-type: none"> <li>• Is there a full range of comparators, limited set or just one comparator?</li> <li>• How appropriate are comparator(s)?</li> </ul>	<p><b>Most studies were 2 arm trials with no attempt to use synthesis techniques. However, in most cases there was not an obvious comparator omitted.</b></p>
<p><u>Evidence synthesis</u></p> <ul style="list-style-type: none"> <li>• Have authors attempted this and if so is it done properly?</li> <li>• If the study was based on a single clinical study have the authors made any attempt to relate to a more general evidence</li> </ul>	<p><b>Only 8 of 34 studies were based on more than one (published) study. Only 1 study applied a meta-analysis of clinical trials to synthesise the clinical evidence</b></p> <p><b>26 based on a single study.</b></p>
<p><u>Outcome measure</u></p> <ul style="list-style-type: none"> <li>• Were QALYs assessed as main outcome measure?</li> <li>• How was measurement of health-related quality of life (HRQoL) conducted?</li> </ul>	<p><b>6/34 studies used QALYs</b>  <b>4/34 studies elicited quality of life by means of questionnaire alongside a clinical study</b></p> <p><b>Utility weights for QALYs always taken from published studies</b></p>
<p><u>Time horizon</u></p> <ul style="list-style-type: none"> <li>• Was an appropriate time horizon</li> </ul>	<p><b>3/34 lifetime</b></p>

considered?	<b>17/34 5 yrs or more</b> <b>5/34 more than 2 years and less than 5 years</b> <b>9/34 2 yrs or less</b>
<u>Incremental analysis</u> <ul style="list-style-type: none"> <li>Was an incremental analysis undertaken?</li> <li>Do ICERs provide findings potentially useful to decision makers (e.g. cost per LYG, cost per QALYs)</li> </ul>	<b>ICERs calculated in 10/34 studies</b> <b>Only ACERs calculated in 8/34 studies</b> <b>12 CCAs (ratios not calculated)</b> <b>4 CMAs</b>  <b>9 Cost per recurrence/metastasis detected</b> <b>6 Cost per QALY</b> <b>2 Cost per LYG</b> <b>1 Cost per increase of 1-point in EQ-VAS</b>  <b>16 studies did not report any ratio (either CCAs or CMAs)</b>
<u>Presentation of uncertainty</u> <ul style="list-style-type: none"> <li>Was a probabilistic sensitivity analysis conducted?</li> <li>Were appropriate deterministic sensitivity analyses on relevant parameters made?</li> </ul>	<b>3/34 PSA (and deterministic; 1 bootstrapping)</b> <b>20/34 SA not performed</b> <b>2/34 very few univariate</b> <b>9/34 univariate on several parameters and/or multivariate and/or scenario/subgroup analyses</b>

**Table 4. Quality assessment results**

#### **4.4 Relevance to the UK setting**

There were six studies conducted in the UK.(7-12) However, this does not imply that these were the only studies that could be of relevance to UK practice, nor that because they were UK based they were necessarily relevant to current UK practice. Three of these studies were in colorectal cancer(9, 10, 12), with a suggestion that an intensive follow-up strategy for patients after curative resection for colorectal cancer might be a cost-effective strategy. One study was in a lung cancer population(11) and suggested that nurse led follow-up might be cost-effective. Auguste et al(7) showed that using adjunct PET-CT is unlikely to be cost-effective in the follow-up of women with cervical cancer, while Beaver et al(8) concluded that follow-up of breast cancer patients by telephone was unlikely to reduce NHS costs.

## **5. DISCUSSION**

Interventions and strategies for follow-up in cancer patients were varied across type of cancer and setting. Drawing general conclusions about the cost-effectiveness of these interventions/strategies is difficult. The majority of studies were conducted outside the UK and this potentially limits the generalisability of the study findings to the UK NHS setting. In addition, the age of the papers coupled with the lack of

consideration of all relevant evidence means that reliance on the conclusions should be done cautiously. Nevertheless, the study identified some good quality papers which may provide useful information for UK decision makers. In particular, the existing literature suggests that intensive follow-up of patients with colorectal disease is likely to be cost-effective, but the opposite holds for breast cancer.

As regards the quality of the studies, it was disappointing that a relatively small number used an incremental analysis. Several papers reported (inappropriate) average cost-effectiveness analyses, compounding the problem by using an outcome measure that was difficult to value (such as recurrence). Also, the lack of sensitivity analyses (and particularly probabilistic sensitivity analysis) was a notable weakness of many studies as was the absence of evidence synthesis.

Finally, one issue that several clinicians stated would improve the quality of follow-up would be the provision of a routine database that would facilitate identification and routine follow-up of cancer patients.

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## 7. Appendix 1

### Draft Medline keyword strategies

#### Draft follow-up strategy

Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily, Ovid MEDLINE(R) and Ovid OLDMEDLINE(R) <1946 to Present>

Search Strategy:

- 
- 1 exp Neoplasms/ (2536685)
  - 2 cancer.tw. (1019562)
  - 3 1 or 2 (2740302)
  - 4 follow-up.ti. (70584)
  - 5 (follow-up adj3 (care or management or system or protocol or guideline or policy or package or program\$)).tw. (11120)
  - 6 (post treatment and monitor\$).ti. (2)
  - 7 (post treatment adj3 monitor\$).tw. (109)
  - 8 4 or 5 or 6 or 7 (79338)
  - 9 3 and 8 (16261)
  - 10 Economics/ (26517)
  - 11 exp "Costs and Cost Analysis"/ (178226)
  - 12 Economics, Dental/ (1863)
  - 13 exp Economics, Hospital/ (19240)
  - 14 Economics, Medical/ (8601)
  - 15 Economics, Nursing/ (3889)
  - 16 Economics, Pharmaceutical/ (2508)
  - 17 (economic\$ or cost or costs or costly or costing or price or prices or pricing or pharmaco-economic\$).tw. (455515)
  - 18 (expenditure\$ not energy).tw. (18159)
  - 19 value for money.tw. (952)
  - 20 budget.tw. (12996)
  - 21 or/10-20 (577497)
  - 22 ((energy or oxygen) adj cost).tw. (2857)
  - 23 (metabolic adj cost).ti,ab. (824)
  - 24 ((energy or oxygen) adj expenditure).tw. (16725)
  - 25 or/22-24 (19678)
  - 26 21 not 25 (573038)
  - 27 letter.pt. (829768)
  - 28 editorial.pt. (349068)
  - 29 historical article.pt. (299167)

30 or/27-29 (1463433)  
31 26 not 30 (544873)  
32 Animals/ (5245752)  
33 Humans/ (13264077)  
34 23 not (23 and 24) (9140)  
35 31 not 34 (544545)  
36 "Value of Life"/ec [Economics] (228)  
37 quality-adjusted life years/ (6766)  
38 exp models, economic/ (9935)  
39 36 or 37 or 38 (15637)  
40 35 or 39 (547636)  
41 9 and 40 (703)

## 1. Appendix 2.

Table 1a. Details of follow-up papers

AUTHORS	YEAR	COUNTRY	TYPE OF CANCER	PATIENT POPULATION	COMPARATORS	TYPE OF EE	TYPE OF MODEL USED	DISCOUNT RATE	TIME HORIZON	MAIN SOURCE OF EFFECTIVENESS DATA	MAIN OUTCOME MEASURE	PERSPECTIVE	COST CATEGORIES/ DATA SOURCES	MAIN RESULTS	TYPE OF SENSITIVITY ANALYSIS	MAIN FINDINGS SAS
K. M. Augustad, J. Norum, S. Dehof, R. Aspevik, U. Ringberg, T. Nestvold, B. Vonen, S. O. Skrovseth and R. O. Lindsetmo	2013	Norway	Colon	patients who had undertaken surgery for colon cancer with histological grade Dukes's Stage A, B or C (N=110)	follow-up at the surgical outpatient clinic or by GP	CMA	Not used	3% (costs and benefits)	2 yrs	RCT	QoL (EORTC QLQ C-30 and EQ-5D)	Society	Tests, consultations, surgeries, travel, productivity	There were no significant differences in primary QoL measures. Overall, the mean societal cost per patient for 24 months follow-up was £9889 in the surgeon group and £8233 in the GP group (p<0.001).	Univariate	The single factor with the greatest impact on overall societal costs was length of sick-leave, followed by cost of follow-up tests and cost of hospital travels.
P. Auguste, P. Barton, C. Meads, C. Davenport, S. Malaysiak, M. Kowalska, A. Zapalska, P. Guest, P. Martin-Hirsch, E. Borowiack, K. Khan, S. Sundar and T. Roberts	2014	UK	Cervical	Women at least 3 months after the completion of treatment, with either recurrent or persistent cervical cancer	positron emission tomography – computed tomography (PET-CT) imaging plus standard practice vs standard practice alone (clinical examination and either an MRI or CT scan alone, or both MRI and CT)	CUA	Markov	3.5% (costs and benefits)	5 yrs	Systematic review of literature (mainly trials) plus experts' opinions	QALYs	NHS	Clinical examination; diagnostic imaging (PET-CT, MRI, and CT); confirmatory biopsy; and treatment. Costs were obtained from the NHS reference costs and from the literature	The ICER for PET-CT plus SC compared to SC alone ranged between £1 million and £9 million per QALY depending on subgroup of women considered.	Deterministic and probabilistic	The probabilistic sensitivity analysis suggests that a strategy with PET-CT as an adjunct to standard practice is not likely to be considered cost-effective for any of the models and data used in the analysis given the current willingness-to-pay thresholds
J. M. Baena-Canada, P. Ramirez-Daffos, C. Cortes-Carmona, P. Rosado-Varela, J. Nieto-Vera and E. Benitez-Rodriguez	2013	Spain	Breast	women treated for breast cancer and survived at 5 yr FU (n=96)	primary care vs specialist care	CMA	Not used	not applied	5 yrs	Retrospective cohort study	QoL (SF-36)	Health care system	Visits and tests	The costs of follow-up in primary care were lower £112.86 (77.54) versus £184.61 (85.87) per patient and year (P = 0.0001). No differences were reported in HRQL.	not conducted	not conducted
K. Beaver, W. Hollingworth, R. McDonald, L. G. Dunn, D. Tysver-Robinson, L. Thomson, A. Hindley, S. Susnerwala and K. Luker	2009	UK	Breast	Women at low to moderate risk of recurrence of breast cancer (n=374)	hospital versus telephone follow-up by specialist nurses	CCA	Not used	3.5% costs	2 yrs	Clinical trial	State-Trait Anxiety Inventory	NHS, society	Hospital/telephone consultations, tests, visits (resource use taken from the trial, standard UK tariffs)	The total cost to the NHS of routine follow-up via telephone was significantly higher (£179 versus £124; mean difference £55 (95 per cent b.c.i. £29 to £77)) than hospital clinic follow-up. However, transport and productivity costs combined were a mean of £47 (95 per cent b.c.i. £40 to £55) per patient lower in the telephone follow-up group.	A couple of items were varied	If the unit cost of hospital consultations was increased by 100 per cent to reflect the high opportunity cost of clinic space, the mean cost of consultations in the hospital (£129) and telephone (£127) follow-up groups was very similar
T. M. Benning, M. L. Kimman, C. D. Dirksen, L. J. Boersma and B. G. Dellaert	2012	The Netherlands	Breast	women previously treated for breast cancer	Customized program for all patients based on individual patient preferences vs several non-customized programs	CEA	Discrete-choice model	not reported	2 yrs	Choices of attributes for the model based on a literature review and populated by means of two surveys	Utility attributed to each program by women	Hospital	Visits, mammography (Dutch standard tariffs)	The fully customized care program leads to higher utility and lower costs than the current standardized program. Compared with the single alternative program, the fully customized care program has increased benefits and higher costs.	This was a individual DCE	There is significant preference heterogeneity for all except two attributes of breast cancer treatment follow-up

<b>W. A. Bleeker, N. H. Mulder, J. Hermans, R. Otter and J. T. Plukker</b>	2001	The Netherlands	colon	patients treated adjuvantly for curatively resected Duke's C colon cancer (n=496)	interim history, physical examination, liver ultrasonography or computed tomography (CT), measurement of carcinoembryonic antigen (CEA) levels, chest radiography and colonoscopy	CEA	not used	not applied	median FU 43 mo	RCT	Recurrences detected	Health care system	Tests and treatment of recurrences	Of all treatable recurrences, 12 of 42 were identified by evaluation of symptoms only. Ultrasonography and colonoscopy identified 22 recurrences at a cost of US\$11 790 per patient, while routine follow-up by CEA measurement, chest radiography and physical examination identified a further six at a cost of US\$19 850 per patient	not conducted	not conducted
<b>F. Borie, C. Combesure, J. P. Daures, B. Tretarre and B. Millat</b>	2004	France	Colorectal	patients who had undergone curative resection for colorectal cancer	carcinoembryonic antigen (CEA) monitoring vs minimal follow-up strategy	CUA	Markov	not applied	7 yrs	Mainly from a retrospective analysis of a French cohort of patients	QALYs	Health care system	Tests and examinations	For the whole population the ICER for CEA vs minimal follow-up was €3,114. For patients who had Duke's stage A, B or C colorectal cancer, the cost-effectiveness ratios were, respectively € 4693, €10,068 and €1,058 per QALY	Deterministic	not strong impact on ICERs
<b>F. Borie, J. P. Daures, B. Millat and B. Tretarre</b>	2004	France	Colorectal	patients who had undergone curative resection for colorectal cancer (n=231)	carcinoembryonic antigen (CEA) monitoring vs minimal follow-up strategy	CUA	not used	not applied	5 yrs	Mainly from a retrospective analysis of a French cohort of patients	Survival	Health care system	Tests and examinations	Cost-effectiveness ratios (cost per patient alive) for CEA monitoring vs minimal FU were 2123 in Dukes' stage A patients, 4306 in Dukes' stage B patients, and 9600 in Dukes' stage C patients	not conducted	not conducted
<b>G. J. Chen, G. E. Amiel, K. Roville, D. M. Latini, H. J. Yu, H. Hornor and S. P. Lerner</b>	2009	US	Bladder	patients with bladder cancer previously treated (n=80)	Urovysion (a genomic test) plus standard care vs standard care alone (cystoscopy plus cytology)	CEA	not used	not reported	2 yrs	prospective cohort	Recurrences detected	Payer	Tests	The average cost per recurrent BC event detected was \$4,800 by using Urovysion and \$2,096 by the standard care, respectively. The incremental cost of Urovysion relative to the standard surveillance care was \$2,704.	not conducted	not conducted
<b>J. Classen, H. Schmidberger, R. Souchon, L. Weissbach, M. Hartmann, J. T. Hehr and M. Bamberg</b>	2009	Germany	Seminoma	patients with stage I seminoma treated with PA radiotherapy (n=675)	Chest X-ray CT abdomen/pelvis Sonography abdomen Tumour markers	CCA	not used	not applied	10 yrs	RCT	Recurrences detected	Public and private Health Care funds	Diagnostic tests	Recurrence was diagnosed by symptoms or physical examination in 14 out of 26 relapsing patients. Among the technical follow-up investigations abdominopelvic imaging had the highest detection rate for relapse. Chest X-ray and CT abdomen were the most expensive diagnostic tests. Sonography abdomen the most cost-effective	not conducted	not conducted

C. L. Di, M. Scarpa, I. Angriman, E. Perissinotto, C. Ruffolo, M. Frego and F. Erroi	2012	Italy	Colorectal	patients who underwent radical surgery for CRC (n=373)	physical examination, colonoscopy, thorax-abdominal computed tomography (CT) scan, and serum carcinoembryonic antigen (CEA), sigmoidoscopy, ultrasound (and combinations)	CEA	not used	not applied	median: 17.6 months	Retrospective analysis	Recurrences detected	Payer	Diagnostic tests	The combination of physical examination, colonoscopy, thorax-abdominal computed tomography (CT) scan, and serum carcinoembryonic antigen (CEA) dosage was found to be the most cost/effective one to monitor stages I and II colon cancer; while physical examination, rigid sigmoidoscopy, thorax-abdominal CT scan, and serum CEA dosage were found to be the most cost/effective surveillance to monitor stages III and IV of colon cancer and rectal cancer	not conducted	not conducted
M. Dion, C. H. Martinez, A. K. Williams, V. Chalasani, L. Nott and S. E. Pautler	2010	Canada	Renal	patients who had undergone radical nephrectomy for local renal cancer	Canadian Urological Association (CUA) guidelines vs old guidelines	CEA	not used	not applied	mean: 31.1 months	prospective cohort study	Recurrences detected, disease-free survival	Healthcare system	visits and tests	The overall and disease-free survival endpoints were 87.7% and 85.2%, respectively for old and new guidelines. Total medical costs were higher for old institutional surveillance strategy than the CUA guidelines (\$181 861 vs. \$135 054). For the complete follow-up of 75 patients, a cost-savings of \$46 806 could have been achieved following the CUA guidelines (p = 0.002).	not conducted	not conducted
F. Forni, G. Ferrandina, F. Deodato, G. Macchia, A. G. Morganti, D. Smaniotto, S. Luzzi, G. D'Agostino, V. Valentini, N. Cellini, B. Giardina and G. Scambia	2007	Italy	Cervical	patients treated for cervical cancer (n=135)	SCC assay plus gynecologic examination vs standard follow-up protocol (chest X-ray, abdominopelvic magnetic resonance imaging, gynecologic examination with colposcopy, Papanicolaou smear)	CEA	not used	not applied	5 yrs	prospective cohort study	rate of missed recurrences	NHS	Tests and examinations	The number of recurrences missed by SCC assay plus gynecologic examination was 2.2% but it was approximately 12.2-fold less costly than the standard approach over 5 years of FU (€298 per patient vs €3653 per patient)	not conducted	not conducted
S. Gilbert, K. R. Reid, M. Y. Lam and D. Petsikas	2000	Canada	Lung	early stage (<2 IIB) non-small cell lung cancer patients that had received resection (n=245)	follow-up at the surgical outpatient clinic or by GP	CEA	Not used	not applied	5 yrs	Retrospective analysis	recurrences detected	hospital	Visits and tests	Despite clinic follow-up, 66.7% (60 of 90) were identified by the family physician, and only 28.9% (26 of 90) by the surgeon. The cost per recurrence detected by surgeons was Can \$4,367. A 75% cost savings could ensure if patients were followed up by their family physician.	not conducted	not conducted
M. Grogan, A. Rangan, V. GebSKI and J. Boyages	2002	Australia	Breast	women with stage I or II breast cancer previously treated (n=438)	13 different number and frequency of visits in women's follow-up	CCA	not used	not applied	5 yrs	prospective cohort study	salvageable events detected	payer	Visits and tests	A simulated follow-up programme involving monthly visits for 5 years, costing A \$3870 per woman, was the most successful in facilitating the detection of a salvageable recurrence but was also very expensive. Three-monthly visits for 4 years and 12-monthly for 1 year was more efficacious	not conducted	not conducted

B. A. Guadagnolo, R. S. Punglia, K. M. Kuntz, P. M. Mauch and A. K. Ng	2006	US	Hodking's disease (HD)	patients (25-year old) who have had a complete response to primary treatment for HD	computed tomography (CT) vs non-CT follow-up	CUA	Markov	3% (costs and benefits)	lifetime	Published diagnostic studies and experts' opinions	LYs, QALYs	Payer	Tests, procedures, cancer treatments (Medicare)	For patients at early stages (I-II) CT follow-up was dominated. For advanced-stage patients, annual CT for 5 years is associated with a very small quality-adjusted survival gain over non-CT follow-up with an incremental cost-effectiveness ratio of \$9,042,300/QALY	Several one-way and two-way deterministic	CT was always dominated or associated with extremely high ICERS
U. R. Hengge, A. Wallerand, A. Stutzki and N. Kockel	2007	Germany	General melanoma	melanoma patients at different stages previously treated (n=526)	physical examination, abdominal ultrasound, chest X-ray, lymph node ultrasound, and blood tests	CUA	Markov	undiscounted costs and benefits	5 yrs	prospective cohort study	QALYs	Payer	Tests, examinations, program-related costs (German standard fees and Medicare)	Clinical examination (7,167 € or \$8,600 per detected metastasis) and lymph node ultrasound (9,118 € or \$10,942 per detected metastasis) represent the most effective methods to detect metastases of malignant melanoma	subgroup analysis by stage	Physical examination and lymph node ultrasound were the only cost-effective methods at all stages, while laboratory studies were generally not cost-effective
U. Hofmann, M. Szedlak, W. Rittgen, E. G. Jung and D. Schadendorf	2002	Germany	Cutaneous melanoma	patients with cutaneous melanoma treated (n=661)	History and physical examination; chest X-ray; sonography of the abdomen; high resolution sonography of peripheral lymphnodes; scintigraphy of the bones; cranial CT-scan	CEA	Not used	not applied	8 yrs	Retrospective analysis	Metastasis detected	Health care system	Tests and visits (German tariffs)	Costs for physical assessment was €7,300 per detected metastasis. Sonography of the lymph nodes proved to be the most cost consuming technical screening method with about 25% of total expenses at each phase of follow-up. Costs were €13,300 (follow-up of stage I/II) per detected metastasis. In contrast, chest X-ray cost to detect a metastasis was €2,800 (in stage III)	subgroup analysis by stage	Imaging tests more cost-effective at later stages
S. Jeyarajah, K. J. Adams, L. Higgins, S. Ryan, A. J. Leather and S. Papagrigroriadis	2010	UK	Colorectal	patients who had undergone surgical intervention for colorectal cancer (n=193)	nurse-led follow-up protocol vs no follow-up	CUA	Not used	not applied	5 yrs	Prospective study	QALYs	NHS	Tests and visits (UK Reference costs)	The total cost per patient for 3 years of follow up was £1506 and £1179 for lower-risk rectal and nonrectal cancers, respectively. The adjusted cost for each QALY gained for lower-risk tumours was £1914. The total cost per patient with higher-risk tumours was £1814 and £1487 for rectal and nonrectal tumours, respectively	not conducted	not conducted
A. M. Kamat, J. A. Karam, H. B. Grossman, A. K. Kader, M. Munsell and C. P. Dinney	2011	US	Bladder	patients with bladder cancer previously treated (n=200)	i) cystoscopy alone; (ii) cystoscopy and NMP22; (iii) cystoscopy and FISH; (iv) cystoscopy and cytology; and (v) cystoscopy and positive NMP22 confirmed by positive FISH	CUA	not used	not relevant	4.1 months median FU	Prospective study	Recurrences detected	Payer	Tests (Medicare)	The costs per tumour detected were \$7692, \$12 000, \$26 462, \$11 846; and \$10,292 for cystoscopy alone, cystoscopy and NMP22, cystoscopy and FISH, cystoscopy and cytology and cystoscopy and positive NMP22 confirmed by positive FISH, respectively	not conducted	not conducted
M. S. Kent, P. Korn, J. L. Port, P. C. Lee, N. K. Altorki and R. J. Korst	2005	US	Lung	patients who had undergone resection of non-small-cell lung cancer	chest computed tomography (CT) vs no CT	CUA	Markov	3% (costs and benefits)	lifetime	From a literature review (no data synthesis)	QALYs	Payer	Tests, visits, procedures and cancer treatment (Medicare)	Annual CT scans were determined to be a cost-effective intervention at an overall cost of \$47,676 per QALY gained.	Univariate	the factors that rendered surveillance CT cost ineffective were: an age at entry into the surveillance programme of older than 65 years; a cost of CT that was greater than \$700; an incidence of SPLC of less than 1.6% per patient per year of follow-up; and a false-positive rate of surveillance CT that was greater than 14%

U. Leiter, A. A. Marghoob, K. Lasithiotakis, T. K. Eigentler, F. Meier, C. Meisner and C. Garbe	2009	Germany	Cutaneous melanoma	patients with cutaneous melanoma previously treated	Physical examination, Lymph node ultrasound, Chest radiograph, Abdomen ultrasound, Blood tests, CT	CEA	not used	not applied	2 yrs	prospective study	Recurrences detected	Payer	Tests, examinations, surgeries (German tariffs and Medicare)	In stage I patients, costs for the detection of one recurrence were €4289 for physical examination and €18 035 for lymph node sonography. Costs decreased in stage II to €500 for physical examination and to €1333 for lymph node sonography, in stage III to €168 and to €1250, respectively. CR generated the highest costs in stage I to detect one recurrence €22 886. Abdomen ultrasound and blood tests did not identify recurrences	not conducted	not conducted
W. Lu, M. J. Greuter, M. Schaapveld, K. M. Vermeulen, T. Wiggers and G. H. de Bock	2012	The Netherlands	Breast	women with a history of breast cancer	follow-up according to the National Screening Programme (NSP) vs less intensive follow-up options	CEA	Decision tree	not applied	lifetime	Published studies (no data synthesis)	Recurrences detected	Health care system	Tests, visits, cancer treatment	Shortening the follow-up time in hospital by shifting care to the NSP or GP after 2 years instead of 5 years of hospital follow-up, lowering the age of referral to the NSP or GP from 60 to 50 years, and termination of annual physical examination by the GP after hospital follow-up did not decrease the detection of small tumours. The current strategy of NSP was the most expensive option. The exclusion of physical examination after 2 years of follow-up was the most cost-effective strategy	Confidence intervals around means were presented	not conducted
D. A. Macafee, D. K. Whynes and J. H. Scholefield	2008	UK	Colorectal	women previously treated (surgery) for colorectal cancer	'standard' follow-up protocol used the principles of the British Society of Gastroenterology (BSG) guidelines vs the 'intensive' follow-up protocol (more tests for longer period, CEA measurement etc)	CEA	Not used	3.5% (costs and benefits)	5 yrs	Data were taken from a clinical trial, and UK published studies	Recurrences detected	NHS	Visits, tests, operations, palliative care (NHS reference costs)	In total, intensive follow up would cost an additional £15.4 million and would detect 853 additional resectable recurrences over 5 years, with a cost per additional resectable recurrence of £18,077	Deterministic on selected data	The cost per additional resectable recurrence varied from £16,134 to £25,705
S. Moore, J. Corner, J. Haviland, M. Wells, E. Salmon, C. Normand, M. Brada, M. O'Brien and I. Smith	2002	UK	Lung	patients with lung cancer who had completed their initial treatment and were expected to survive for at least 3 months (n=203)	nurse led FU vs standard medical FU	CEA	not used	not relevant	12 months	RCT	QoL (EORTC QLQ C-30)	NHS	Tests, visits, procedures and hospitalisation (standard UK sources)	At 12 months, patients randomised to receive nurse led follow up had better scores for emotional functioning (P=0.03) and less peripheral neuropathy (P=0.05). All the other scores were not significantly different. Comparison of the overall costs of care for the three periods of follow up (3, 6, 12 months) showed no significant differences (£696.50 vs £744.50 for nurse-led vs medical FU)	not conducted	not conducted
R. K. Nam, D. A. Redelmeier, P. E. Spiess, H. A. Sampson, Y. Fradet and M. A. Jewett	2000	Canada	Bladder	patients with a history of superficial bladder cancer	cystoscopy and cytology (standard care) vs urinary markers (modified care)	CEA	Decision tree	not applied	3 yrs	Retrospective cohort study	Recurrences detected	Society	Tests, visits, cancer treatment	The cost of modified care ranged from \$158 to \$228 for each follow-up visit when using a urinary marker with a sensitivity and specificity of 95% and 77%, respectively. The cost of standard care was \$240 for each follow-up visit.	Univariate and multi-way deterministic	the minimum urinary sensitivity required for modified care to have a cost advantage was 70% at the 18-month follow-up and minimum specificity was 37% at the 36-month follow-up

<b>A. Oltra, A. Santaballa, B. Munariz, M. Pastor and J. Montalar</b>	2007	Spain	breast	women diagnosed as having breast cancer at stages I, II, or III and who had completed an initial curative treatment (n=121)	standard vs intensive follow-up	CCA	Not used	not applied	median FU: 3yrs	RCT	Recurrences detected	Health care system	costs of follow-up (not reported in detail)	The total cost of follow-up in the standard clinical follow-up group was 24,567 euros and 74,171 euros in the intensive follow-up group, making the individual mean costs 390 euros and 1,278 euros / patient in the standard clinical follow-up and intensive follow-up groups, respectively	not conducted	not conducted
<b>S. Polinder, E. M. Verschuur, P. D. Siersema, E. J. Kuipers and E. W. Steyerberg</b>	2009	The Netherlands	oesophageal	patients 3 weeks after hospital discharge following intentionally curative surgery for oesophageal or gastric cardia cancer (n=109)	outpatient follow-up vs nurse-led home follow-up	CUA	Not used	not relevant	1 yr	RCT	Patients' QoL (EQ-VAS, QLQ-C30)	Society	Visits, diagnostic procedures, hospitalisations, cancer treatment (resource use from the prospective study)	At 4 and 7 months, slightly more improvement on the EQ-VAS was noted in the nurse-led compared with the standard follow-up group. No differences were found in most medical outcomes. Medical costs were lower in the nurse-led follow-up group (€2600 vs €3800)	bootstrapping was performed	At a willingness to pay of €4000 or more for a one point gain on the EQ-VAS would find nurse-led follow-up cost effective with a probability of 76%
<b>A. G. Renehan, S. T. O'Dwyer and D. K. Whynes</b>	2004	UK	colorectal	patients who had received curative resection for colorectal cancer	conventional vs intensive FU	CEA	not used	6% costs, 1.5% benefits	5 yrs	Meta-analysis of 5 (or 4) RCTs	LYs	NHS	Visits, tests, treatment of recurrences, palliative care	Based on five year follow up, the numbers of life years gained by intensive follow up were 0.73 for the five trial model and 0.82 for the four trial model. For the five trials, the adjusted net (extra) cost for each patient was £2479 (€3550; \$4288) and for each life year gained was £3402. The corresponding values for the four trial model were £2529 and £3077, suggesting that targeted surveillance is more cost effective.	Univariate	surveillance cost was the most important determinant of cost effectiveness
<b>C. R. Rettenmaier, N. B. Rettenmaier, T. Wojciechowski, L. N. Abaid, J. V. Brown III, J. P. Micha and B. H. Goldstein</b>	2010	US	Uterine (n=364)	patients previously treated for uterine cancer	CA-125 assay, physical examination, vaginal cytology	CEA	not used	not applied	max 20 yrs	Retrospective analysis	Recurrences detected	Payer	Tests and visits (Medicare)	Serial imaging detected the highest number of progressive disease cases but CA-125 testing was the least expensive (USD 6,810 per patient recurrence).	not conducted	not conducted
<b>N. B. Rettenmaier, C. R. Rettenmaier, T. Wojciechowski, L. N. Abaid, J. V. Brown, III, J. P. Micha and B. H. Goldstein</b>	2010	US	Ovarian, ovarian plus uterine and primary peritoneal cancer (PPC) (n=288)	patients previously treated for ovarian or PPC	CA-125 assay, physical examination, CT scanning of the abdomen, chest X-ray, pelvic ultrasound, PET scan, vaginal cytology	CEA	not used	not applied	max 16 yrs	Retrospective analysis	Recurrences detected	Payer	Tests and visits (Medicare)	CA-125 (n=74; 49.0% of cases) and imaging studies (n=66; 43.7%) detected the highest number of initial disease recurrence cases. CA-125 testing was the least expensive (\$3924) per recurrent diagnosis.	not conducted	not conducted
<b>L. Staib, K. H. Link and H. G. Beger</b>	2000	Germany	colorectal	patients previously cured for colorectal cancer (n=1054)	endoscopy, chest radiography, abdominal ultrasound, computed tomography (CT) pelvis	CEA	not used	not applied	5 yrs	prospective study	Recurrences detected	Payer	Tests and visits	The follow-up costs for 21 cured recurrence patients were 126,000 euros, resulting in a cost-effectiveness ratio of €6,000 per recurrence detected	not conducted	not conducted

J. van Loon, J. P. C. Grutters, R. Wanders, L. Boersma, A. M. C. Dingemans, G. Bootsma, W. Geraedts, C. Pitz, J. Simons, B. Brans, G. Snoep, M. Hochstenbag, P. Lambin and D. De Ruyscher	2010	The Netherlands	NSCLC	NSCLC patients after curative intent therapy	PET-CT scan; chest CT scan; conventional follow-up with a chest X-ray	CUA	Markov	4% costs; 1.5% benefits	5 yrs	Prospective study at authors' institute, published literature	QALYs	Health care system	Visits, tests, procedures, terminal care, death (Dutch institute and published sources)	CT-based follow-up was only slightly more effective than conventional follow-up, resulting in an ICER of € 264,033 per QALY gained. For PET-CT-based follow-up, the ICER was € 69.086 per QALY gained compared to conventional follow-up. The strategy in which a PET-CT was only performed in the asymptomatic subgroup resulted in an ICER of € 42.265 per QALY gained as opposed to conventional follow-up.	Deterministic and probabilistic	Given this ceiling ratio of € 80,000, PET-CT-based follow-up and conventional follow-up had a similar probability of being cost-effective (48% and 47%, respectively), while the probability of CT-based follow-up being cost-effective was only 5%
S. Wojcinski, A. Farrokh, U. Hille, E. Hirschauer, W. Schmidt, P. Hillemanns and F. Degenhardt	2011	Germany	breast	patients with a history of breast cancer (n=735)	ultrasound examination in addition to routine FU	CEA	not used	not applied	possibly 1 yr	Before and after study	Recurrences detected	German private insurance	Tests and visits	The rate of detected recurrences rose from 3.7% (95% CI: 2.3-5.0) in the routine follow-up program to 4.5% (95% CI: 3.0-6.0) in the study follow-up program (p = 0.041). The costs per detected malignancy in the routine follow-up program were \$2455.69; the costs for each additionally detected malignancy in the study follow-up program were \$7580.30	not conducted	not conducted

