The cost-effectiveness of follow-up strategies after cancer treatment: A systematic literature review

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Introduction

The cost of treatment and follow-up of cancer patients in the UK is substantial. 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 adequate value for money.

Sources of data

We conducted a systematic literature review to explore the cost-effectiveness of follow up strategies of patients previously treated for cancer with the aim of informing UK policy. All papers that were considered to be economic evaluations in the subject areas described above were extracted.

Areas of agreement

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.

Areas of controversy

Interventions and strategies for follow-up in cancer patients were variable across type of cancer and setting. Drawing general conclusions about the cost-effectiveness of these interventions/strategies is difficult.

Growing points

The search identified 2,036 references but applying inclusion/exclusion criteria a total of 44 articles were included in the analysis. Breast cancer was the most common (n=11) cancer type followed by colorectal (n=10) cancer. In general, there were relatively few studies of cost-effectiveness of follow-up that could influence UK guidance. Where there was evidence, in the most part, NICE guidance broadly reflected this evidence.

Areas timely to develop research

In terms of future research around the timing, frequency and composition of follow-ups, this is dependent on the type of cancer being considered. Nevertheless, across most cancers, the possibility of remote follow-up (or testing) by health professionals other than hospital consultants in other settings appears to warrant further work.

1. Background

Expenditure on cancer in the UK NHS was £5.8 billion in 2012/13,[1] with an estimated total spend of £13bn by 2020/21.[2] Despite this, the UK has a relatively poor level of cancer survival compared to some other developed countries[3] This in turn may be related a number of factors including sub-optimal follow-up of existing cancers.

These concerns have been reflected in the policy arena. A report by the Independent Cancer Taskforce in 2015 [4] set out a five year plan, with a strategic emphasis on stratified follow up pathways.

In addition to the creation and report of this taskforce, NHS England has also launched an programme calling for better care and after care for those diagnosed with cancer [5], However, implementing interventions to improve follow up in cancer are unlikely to be costless activities. What evidence is there that these policy initiatives are likely to provide value for money? In a budget-constrained system such as the NHS, it is necessary to consider the cost-effectiveness of the range of management strategies/interventions at different points on cancer patients' care pathways to ensure that they provide an efficient use of scarce resources.

This paper presents a review of the existing cost-effectiveness literature on the follow up of cancer patients. We discuss how current policies reflect this literature and whether alternative strategies could be considered for either investment or disinvestment.

2. Methods

We conducted a systematic literature review to explore the existing literature on the cost-effectiveness of interventions/strategies for follow-up of patients with cancer or suspected cancer. Literature searches were undertaken that considered for inclusion all economic evaluations in the subject areas described above. 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. Further details of all papers and search strategies have been reported elsewhere.[6]

2.1 Search methodology

A first search was undertaken for the period 1946 to March 2014 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). This search was updated in June 2016 to cover the period from March 2014 to June 2016 using the same databases. In addition, two websites (NICE.org.uk and SIGN.ac.uk) were reviewed to identify any cost-effectiveness analysis that has been included in guidance on cancer follow-up by UK government agencies.

2.2 Inclusion criteria

The citations retrieved were reviewed by title and abstract, and all articles were retained if they conducted a cost-effectiveness evaluation on alternative follow-up strategies for patients with any type of cancer. Papers were excluded if not full economic evaluations (e.g. cost studies, studies without a clear comparator etc.), not on relevant patient populations (e.g. not focused on patients with any type of cancer) or not on relevant interventions/strategies for follow-up (e.g. curative interventions). Reviews were also excluded, although references were checked in order to assess whether relevant studies were not caught in our review. The selected articles were screened for inclusion and any ambiguity was reconciled through discussions by two reviewers. Only papers published in English language were included. Conference abstracts or posters were also initially included but were subsequently excluded if they do not provide enough information to complete our study template as described in the following paragraph.

2.3 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. Appendix 1 shows the items considered in the template.

The information extracted was used to assess the quality of the studies included as well as their relevance to the UK setting according to whether they met the NICE reference case methods. The criteria considered in order to assess the quality and relevance of the studies is presented in Appendix 2 but briefly comprised an assessment of:

i) range and appropriateness of comparators

ii) whether all relevant evidence was included

iii) appropriateness of outcome measure(s)

iv) appropriateness of analysis (reasonable time horizon, use of incremental analysis, use of probabilistic sensitivity analysis)

v) relevance to a UK setting

3. Results

The detailed results of the systematic review are presented elsewhere [6]. Briefly, the first search identified 1,389 references, while the second search 396 references. All these records were screened and a total of 112 references were considered as potentially relevant and full articles were obtained. After full text review, 44 studies were included in the analysis. Main reasons for exclusion included not economic evaluations and/or not related to cancer. Prisma diagrams with included and excluded studies with reasons for exclusions are presented in figures 1 and 2.

3.1 Overview of results

Overall, a total of 44 studies were included in the analysis. Of these, seven were conducted in the US, six in Germany, six in the Netherlands, five in Canada, five in Australia, two in Italy, two in France, two in Spain, one in Norway, one in Sweden and one in Ireland. Table 1 shows a breakdown of these studies by cancer type.

Type of cancer	Number of studies
Breast	11
Colorectal	10
Lung	4
Bladder	4
Cervical	4
Skin	3
Gastro-oesophageal	1
Ovarian	1
Renal	1
Seminoma	1
Hodgkin's	1
Uterine	1
Prostate	1
Head and neck	1
TOTAL	44

Table 1. Follow-up papers by cancer type

3.2 Studies of follow-up strategies by cancer type

3.2.1 Breast cancer

Eleven studies included in the analysis estimated the cost-effectiveness of follow-up strategies in women previously treated for breast cancer.(14, 24, 25, 27, 37-39, 44-47)

In a UK study, Beaver et al (2009)(14) 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 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.

Two Spanish studies were identified (37, 38). 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. 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), although scores were generally higher for patients with specialist attention. 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)(38) 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 initial curative treatment. 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.(25, 27) Lu et al (2012)(27) 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 in 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 the rates of recurrences of these options over patients' lifetime. The model showed that 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)(25) 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. It was found that the fully customized care programme leads to higher HRQoL and lower costs than the current standardized programme.

Wojcinski et al (2012)(24) 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. The rate of detected recurrences rose significantly with 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.

Grogan et al (2002)(39) 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. 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). In more recent Australian studies, Bessen and colleagues (2014 and 2015) (46, 47) estimated the cost-effectiveness of routine annual mammography for women who have completed their primary treatment for early breast cancer. The 2014 study included a sample of 407 postmenopausal women diagnosed with moderate-prognosis early breast cancer from 2000 to 2008; while the 2015 study considered 1,100 women diagnosed with early breast cancer (again from 2000 to 2008). The 2014 study showed that 2-year mammography was generally more likely to be the most cost-effective option (at both Aus$25,000 and Aus$50,0000 cost-effectiveness thresholds), but there was high uncertainty, especially when adherence was set at 75%. The authors concluded that annual mammography which was that recommended in Australia appears not cost-effective and that less frequent surveillance might assure better value for money, especially in the older population. In the 2015 study, Bessen and colleagues was found that yearly mammography was generally not a cost-effective option, except for women aged 50-69 and with a poor prognosis tumour (assuming a 75% adherence and a Aus$50,000 cost-effectiveness threshold). Two-yearly mammography was cost-effective for all women with excellent prognosis tumours and for women with good prognosis tumours if high compliance rates can be achieved.

The analysis by Armstrong and colleagues (2015) (44) assessed the cost-effectiveness of replacing the conventional, in-person postoperative follow-up care with mobile app follow-up care following ambulatory breast reconstruction in post-mastectomy breast cancer patients. A 30-day time horizon was considered and a cost-minimisation analysis was conducted. The total cost difference between mobile app and in-person follow-up care was $245 CAD, with in-person follow-up being more expensive ($381 CAD) than mobile app follow-up care ($136 CAD). Considering health care system costs alone, in-person follow-up was $38 more expensive than mobile app follow-up care. In another Canadian study, Coyle and colleagues (2014) (45) assessed the cost effectiveness of a survivorship care plan (SCP) for women with early-breast cancer who had successfully completed primary treatment compared to routine follow-up care with their own primary care physician (PCP) using data from a randomized controlled trial (RCT). The no-SCP group had lower total costs per patient compared to SCP (Canadian $698 v $765), and total QALYs were almost equivalent (1.42 for standard care v 1.41 for the SCP). The probability that the SCP was cost effective was 0.26 at a cost-effectiveness threshold of $50,000 per QALY. Sensitivity analyses did not change the conclusions of the analysis.

3.2.2 Colorectal cancer

Ten studies assessed the cost-effectiveness of follow-up strategies in patients previously treated for colorectal cancer,(15, 16, 18, 19, 26, 33, 35, 36, 40, 43) three of which were conducted in the UK (15, 16, 18).

Renehan et al (2004)(18) 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 in the UK. Over a five-year follow up, the numbers of life years gained (LYG) by intensive follow-up were 0.73 per patient while the adjusted incremental cost for each patient was £2,479 leading to an incremental cost for each LYG of £3,402. Macafee et al (2008)(16) 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 programme involving more visits and tests for a longer period and carcinoembryonic antigen (CEA) measurement. Considering the cohort of UK patients with colorectal cancer in 2003 who regularly attended 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. The third UK study (15) (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 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.

Two studies were conducted in the French setting, both by Borie et al (2004).(35, 36) 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[1] in patients who had undergone curative resection for colorectal cancer. The incremental cost-effectiveness ratio (ICER) for intensive versus minimal follow-up was €3,114 per QALY. 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)(23) prospectively followed 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)(40) 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 of surgeons in hospital. There were no significant differences in primary HRQoL measures between the two options, although improvement in EQ-5D was higher in patients followed by GPs compared to those followed by surgeons. 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 patients' sick leave was the main cost driver.

Two other studies compared several diagnostic tests for follow-up of patients after curative resection of colorectal cancer. Di Cristofaro et al (2012)(33) assessed the cost-effectiveness of various combinations of tests in a

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[1] 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.

retrospective analysis of 373 Italian patients. Physical examination, colonoscopy, thorax-abdominal computed tomography (CT) scan, serum CEA, sigmoidoscopy, ultrasound and combinations of these tests were considered. 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) (26) 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 in the Netherlands. 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. Finally, in a more recent Dutch study, Verberne and colleagues (2015) (43) estimated whether an intensified follow-up schedule with more frequent CEA measurements but fewer outpatient visits is cost-effective compared with the usual follow-up protocol in colorectal cancer patients. The mean yearly cost per patient was €548 in the intensified protocol and €497 in the control protocol. The cost-effectiveness analysis showed an incremental cost of €94 (95% CI €76–€157) to detect a 1% greater recurrence in the intervention protocol compared with the control protocol. For curable recurrences, the incremental cost per additional recurrence detected was €607 (95% CI €5695–€5728). The authors concluded that the new protocol of intensified follow-up was likely to be a cost-effective option.

3.2.3   Lung cancer

Four studies estimated the cost-effectiveness of follow-up strategies for patients previously treated for lung cancer.(10, 17, 29, 31)

Moore et al (2002)(17) 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. 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)(31) 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 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 at al (2005),(10) in a US study, assessed the cost-effectiveness of chest computed tomography (CT) for patients who had undergone resection of NSCLC. 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)(29) 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 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%. 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)

3.2.4   Bladder cancer

Four economic evaluations of follow-up options for patients with treated bladder cancer were found.(7, 9, 32, 50)

Kamat et al (2011)(9) compared several diagnostic tests in a prospective trial to identify an 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. 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, Chen et al (2009)(7) estimated the cost-effectiveness of Urovysion (a genomic test) plus standard care compared to standard care alone (cystoscopy plus cytology). 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 additional case detected. The authors concluded that Urovysion test is unlikely to be cost-effective.

Nam et al. (2000) (32) assessed the cost-effectiveness of urinary markers compared to a standard strategy of cystoscopy plus cytology in Canada. 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 between the options. Accuracy of the urinary markers was the key determinant of cost differences between the two strategies. Finally, in a Swedish study Dansk and colleagues (2015) (50) explored the value for money of introducing hexaminolevulinateblue-light flexible cystoscopy (HAL BLFC) as an adjunct to white-light flexible cystoscopy (WLFC), compared with WLFC alone, for the detection and management of non-muscle invasive bladder cancer (NMIBC) recurrences in the first year after successful initial transurethral resection of the bladder tumour (TURBT). Total costs for 231 patients (initial cohort of the model) were SEK 14,033,834 with HAL BLFC plus WLFC and SEK, and 13,815,155 for WLFC alone. The additional costs of HAL BLFC were only estimated over the first year of the analysis, while cost savings occur from year 2 onwards. The authors concluded that the introduction of HAL BLFC in addition to WLFC resulted in a minimal cost impact compared to WLFC alone over 5 years, with improved patient clinical outcomes.

3.2.5   *Cervical cancer*

Four of the studies identified assessed the cost-effectiveness of diagnostic strategies to follow-up in women previously treated for cervical cancer.(13, 34, 42, 48)

Auguste and colleagues (2014),(13) 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. 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.

Another study identified was conducted in Italy by Forni et al (2007)(34) and assessed the cost-effectiveness of a squamous cell carcinoma antigen (SSC) assay plus gynaecologic examination versus a standard follow-up protocol in patients who had been treated for cervical cancer. The standard protocol could include chest X-ray, abdominopelvic magnetic resonance imaging, gynaecologic examination with colposcopy and Papanicolaou smear test. 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.

The two remaining studies were both available as conference abstracts. Phippen and colleagues (2015) (42) estimated the cost-effectiveness of the routine use of post-chemoradiation positron emission tomography/computed tomography (PET/CT) to direct completion hysterectomy for locally advanced cervical cancer compared to routine surveillance in the US. A Routine use of PET/CT to determine eligibility for completion hysterectomy was associated with a higher average cost ($15,429 vs $14,757) and a lower recurrence rate (26% vs 32%) when compared to

standard surveillance. The ICER of PET was $12,364 per recurrence prevented. In sensitivity analysis, when the probability of recurrence following hysterectomy was assumed to be less than 37%, PET/CT was a dominant strategy.

Hou and colleagues (2014) (48) compared [18]FDG-PET-guided follow-up, where patients undergo an [18]FDG-PET scan within six months of completing chemo-radiotherapy for locally advanced cervical cancer, with routine surveillance in the Australian setting. The model showed that [18]FDG-PET-guided follow-up would cost $15,543, compared with $12,925 for routine follow-up. The estimated QALY gained was 3.33 and 2.34, respectively, producing an ICER of $2,656 per QALY gained. Basecase results were robust to changes in key model parameters and the authors concluded that [18]FDG-PET guided follow-up is likely to provide good value for money.

3.2.6 *Skin cancer*

The three economic evaluations identified on follow-up of patients treated for cutaneous melanoma were both conducted in Germany.(20, 21, 22)

Hoffman et al (2002)(21) 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. Physical assessment was associated with a cost of €7,300 per detected metastasis while sonography has an estimated cost €13,300 per detected metastasis (follow-up of stage I/II). In contrast, chest X-ray cost €2,800 per detected metastasis (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 cast serious doubt on the efficiency of expensive routine imaging procedures at initial staging and during early phases of melanoma disease.

Hengge et al (2007)(20) 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. 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.

Leiter et al (2009)(22) also compared several diagnostic techniques in the German context including physical examination, lymph node ultrasound, chest radiograph, abdomen ultrasound, blood tests and CT. In stage I patients, the costs per recurrence detected 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 cost per recurrence detected in stage I (€22,886). Abdomen ultrasound and blood tests did not identify recurrence.

3.2.7 *Other cancers*

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

In a Dutch study, Polinder et al (2009)(28) 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 by a specialist nurse (nurse-led follow-up). 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 76While nurse led follow-up is likely to be cost-effective, capacity issuesof the availability of suitably qualified nurses in this specialty may be a limiting factor.

Two US studies by Rettenmaier et al(11, 12) 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.

Dion et al (2010)(30) assessed the cost-effectiveness of the new Canadian Urological Association (CUA) Guidelines compared to an old surveillance protocol for patients who had undergone radical nephrectomy for local renal cancer.. The costs associated to the new guidelines that distinguished tests on the basis of patients' stage were calculated on the basis of a sample of Canadian patients. Total medical costs were higher for the old institutional surveillance strategy than the new guidelines ($181,861 vs. $135,054). For the complete follow-up of 75 patients, a cost-saving of $46,806 could have been achieved following the CUA guidelines (p = 0.002).

In a German study, Classen et al (2009)(19) 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. 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 estimate of cost-effectiveness was not presented.

Guadagnolo et al. (2006)(8) evaluated the value for money of CT in the routine follow-up of patients after primary treatment for Hodgkin's disease (HD). A For patients at early stages (I-II), CT follow-up was dominated (less effective and more costly). 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

analyses CT was dominated or associated with extremely high ICERs. However, the choice of annual CT as an appropriate comparator rendersthe paper is of little relevance to current NHS.

In a recent Australian study, Shah and colleagues (2015) (49) analysed the cost-effectiveness of stratifying follow-up intensity by post-treatment [18]FDG-PET-CT response for head and neck cancers treated with primary radiation or chemoradiation. Specifically, in Australia, in 2008 clinical review after radical head and neck radiotherapy was reduced from 3- to 6-monthly for patients with complete [18]FDG-PET-CT response at 3 months. Time to detection of recurrence was similar between two cohorts (hazard ratio 1.05, 95%CI 0.45–2.52), as was overall survival (HR 0.91, 95%CI 0.36–2.29). The proportion of radically treatable recurrences was also similar (42% Standard vs. 47% PET Stratified). The hospital cost savings per patient from reduced review were AUD$2606 over 2 years and AUD$5012 over 5 years. It was concluded that the use of [18]FDG-PET-CT to stratify follow-up intensity after radical radiotherapy for head and neck cancer reduces costs with no impact on clinical outcomes.

Finally, Pearce and colleagues (2015) (51) conducted a cost-minimisation analysis comparing three different strategies for follow-up of prostate cancer in the Irish setting: the European Association of Urology (EAU) guidelines, the National Institute of Health Care Excellence (NICE) guidelines and current practice in Ireland. Strategies differed in frequency of PSA testing, setting of treatment, and tests during follow-up. Average cost per cancer survivor was €852.73 with NICE guidelines, €1057.32 with EU guidelines and €1149.81 with current practice in Ireland. It was estimated that, for the 2562 new cases of prostate cancer diagnosed in 2009, the Irish health care system could have saved €760,000 over a 10-year period if the NICE guidelines were adopted.

Further details of all the studies included for the follow-up reviews in the review are available in Table 1 in the Appendix.

3.3 Quality assessment of follow-up studies

Table 2 summarises the quality assessment of the studies included in this review. Details on the quality assessment for ach single study are provided in table 2 in the appendix.

Most studies were two arm trials with no attempt to use synthesis techniques. However, in most cases there was not an obvious comparator omitted.

Fourteen of the 44 studies included in the analysis were based on a decision model. Of these, seven studies undertook a review of the literature (1 systematic review) to identify model parameters. However, appropriate data synthesis was generally 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. One study did not report any information on methods to synthesise data (available only as abstract). The remaining 6 studies based on a decision model represented long-term extrapolation from 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[18] , a meta-analysis of RCTs was conducted. The remaining 23 studies are economic evaluations conducted alongside a single study (RCT, prospective cohort study, retrospective analysis etc.) so no evidence synthesis was needed. Generally, no comparison with other published studies was made.

Only eleven of 44 studies used QALYs as the main benefit measure and HRQoL weights were always taken from previously published studies. Little description of these published studies was generally provided: 4 studies reported the values used for HRQoL weights but did not describe the instrument used to elicit these values; 1 study [10] did not report any information on HRQoL values used; 1 study [15] did not provide information on the sources used to obtain HRQoL weights; three studies[36,45,46] reported both the study used as source of HRQoL weights and the instrument that was used to collect these data. Five of the remaining studies assessed HRQoL 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 (28) did not make any attempt to assess patients' HRQoL.

A total of 29 of 44 studies appear to have used an adequate time horizon for this patient population (5 lifetime, 24 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.

The majority of studies did not conduct an appropriate incremental analysis, and ICERs were calculated only in 16 of the 44 studies selected (but six out of ten for the more recent studies). Eight other studies only presented average cost-effectiveness ratios, reducing the interpretability of the findings. Fifteen studies only reported total costs and outcomes for each strategy without any attempt to calculate a ratio (cost-consequences analysis); the remaining 5 studies were cost-minimization analyses based on equal clinical effectiveness between the alternatives investigated. Among economic evaluations that had calculated ICERs, QALYs or life-years saved were used in 10 and 2 studies, respectively. All the other analyses reported ratios with limited value for decision-making such as, for example, incremental or average cost per recurrence or metastasis detected.

Finally, the analysis of uncertainty was generally poor, although it was better addressed in more recent studies. Overall, only 9 studies adopted a probabilistic sensitivity analysis, but 6 of these were published between 2014 and 2016. Twelve studies conducted deterministic sensitivity analysis on several parameters or considered several alternative scenarios. The majority of the analyses did not perform any sensitivity analysis (21/34) 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 evaluations conducted alongside a single study.

Comparator(s) • Is there a full range of comparators, limited set or just one comparator?	Most studies were 2 arm trials with no attempt to use

• How appropriate are comparator(s)?	synthesis techniques. However, in most cases there was not an obvious comparator omitted.
Evidence synthesis • Have authors attempted this and if so is it done properly? • If the study was based on a single clinical study have the authors made any attempt to relate to a more general evidence	Only 13 of 44 studies were based on more than one (published) study. Only 1 study applied a meta-analysis of clinical trials to synthesise the clinical evidence 31 based on a single study.
Outcome measure • Were QALYs assessed as main outcome measure? • How was measurement of health-related quality of life (HRQoL) conducted?	11/44 studies used QALYs 5/44 studies elicited quality of life by means of questionnaire alongside a clinical study Utility weights for QALYs always taken from published studies
Time horizon • Was an appropriate time horizon considered?	5/44 lifetime 24/44 5 yrs or more 5/44 more than 2 years and less than 5 years 10/44 2 yrs or less
Incremental analysis • Was an incremental analysis undertaken? • Do ICERs provide findings potentially useful to decision makers (e.g. cost per LYG, cost per QALYs)	ICERs calculated in 16/44 studies Only ACERs calculated in 8/34 studies 15 CCAs (ratios not calculated) 5 CMAs 11 Cost per recurrence/metastasis detected 11 Cost per QALY 2 Cost per LYG 1 Cost per increase of 1-point in EQ-VAS 20 studies did not report any ratio (either CCAs or

	CMAs)
Presentation of uncertainty • Was a probabilistic sensitivity analysis conducted? • Were appropriate deterministic sensitivity analyses on relevant parameters made?	9/44 PSA (and deterministic; 2 bootstrapping) 21/44 SA not performed 2/44 very few univariate 12/44 univariate on several parameters and/or multivariate and/or scenario/subgroup analyses

Table 2. Quality assessment results

4. Discussion

In general, there were relatively few studies of cost-effectiveness of follow-up that could influence UK guidance. Where there was evidence, in the most part, NICE guidance broadly reflected this evidence.

In breast cancer, the identified studies suggested that intensive follow-up was not likely to be cost-effective. This is consistent with current guidance that stresses that "intensive, hospital based follow-up is not beneficial". For colorectal cancer, the main message from the identified studies was that intensive follow-up is likely to be cost-effective but that this could be conducted outside the hospital setting. NICE guidance states that follow-up visits should start soon after curative treatment and include testing every 6 months in first three years. However, stopping follow-up is more to do with patient preferences and weighing up advantages and disadvantages of further testing.

In lung cancer, there were limited studies, with the main message being that hospital follow-up might not be cost effective and that others (GPs, nurses) might provide the same level of care at lower cost in other settings. NICE guidance recommends initial specialist treatment with clinical follow up by a clinical nurse specialist and is therefore consistent with findings from literature. In bladder cancer, biomarkers are perceived as a potentially cost-effective mechanism for identifying the condition. The evidence around this is weak however, and while current NICE guidance suggests that biomarkers should be included in follow-ups, the evidence at present is equivocal.

Though guidance from NICE tended to be supported by the literature where it was identified, it is less clear where guidance is adhered to. Anecdotal evidence suggests that adherence to guidance varied by type of cancer, geographical region as well as by individual consultant practise.

The studies identified were based largely on single randomised controlled trials with limited follow-up period and no attempt at synthesising results across studies. Future methods work could attempt to extrapolate results

to a more appropriate time horizon (such as the lifetime of the patient) and use existing data to complement the results of individual trials.

Most of the studies did not consider capacity issues around the introduction of new interventions or strategies for follow-up of cancer patients. The consideration of capacity issues and how these interact with demand is a current focus of NHS Improvement [52]. Current concerns over shortages of key personnel such as nurses may also limit the feasibility of some services. [53]

In terms of future research around the timing, frequency and composition of follow-ups, this is dependent on the type of cancer being considered. Nevertheless, across most cancers, the possibility of remote follow-up (or testing) by health professionals other than hospital consultants in other settings appears to warrant further work.

References

1. Nuffield Trust. http://www.nuffieldtrust.org.uk/data-and-charts/nhs-spending-top-three-disease-categories-england

2 National Audit Office 2015, Progress in improving cancer services and outcomes in England. 2015, National Audit Office

3.Alberry J. Improving Outcomes :A strategy for Cancer.
https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/213785/dh_123394.pdf

4   Independent Cancer Taskforce. Achieving Owlrd Class Cancer Outcomes.
http://www.cancerresearchuk.org/sites/default/files/achieving_world-class_cancer_outcomes_-_a_strategy_for_england_2015-2020.pdf

5 NHS England. https://www.england.nhs.uk/2015/01/beat-cancer/. Jan 2015

6 Barbieri M, Richardson G, Paisley S and Sculpher M. Rapid Review of existing literature on the cost-effectiveness of follow-up strategies after cancer. http://www.eepru.org.uk/Follow-up%20review%20-%20cancer%20treatment.pdf

7 Chen GJ, Amiel GE, Roville K, Latini DM, Yu HJ, Hornor H, et al. Cost implication of using Urovysion in surveillance care for non-invasive bladder cancer. Journal of UrologyConference: 2009 American Urological Association (AUA) Annual Meeting Chicago, IL United StatesConference Start: 20090425 Conference End: 20090430Conference Publication: (varpagings). 2009;181(4 SUPPL.#1):April.

8. Guadagnolo BA, Punglia RS, Kuntz KM, Mauch PM, Ng AK. Cost-effectiveness analysis of computerized tomography in the routine follow-up of patients after primary treatment for Hodgkin's disease. Journal of Clinical Oncology. 2006;24(25):4116-22.

9. Kamat AM, Karam JA, Grossman HB, Kader AK, Munsell M, Dinney CP. Prospective trial to identify optimal bladder cancer surveillance protocol: reducing costs while maximizing sensitivity. BJU International. 2011;108(7):1119-23.

10. Kent MS, Korn P, Port JL, Lee PC, Altorki NK, Korst RJ. Cost effectiveness of chest computed tomography after lung cancer resection: a decision analysis model. Annals of Thoracic Surgery. 2005;80(4):1215-23.

11. Rettenmaier CR, Rettenmaier NB, Wojciechowski T, Abaid LN, Brown Iii JV, Micha JP, et al. The utility of routine follow-up procedures in the surveillance of uterine cancer: a 20-year institutional review. Oncology. 2010;79(3-4):262-8.

12. Rettenmaier NB, Rettenmaier CR, Wojciechowski T, Abaid LN, Brown JV, III, Micha JP, et al. The utility and cost of routine follow-up procedures in the surveillance of ovarian and primary peritoneal carcinoma: a 16-year institutional review. British Journal of Cancer. 2010;103(11):1657-62.

13. Auguste P, Barton P, Meads C, Davenport C, Malysiak S, Kowalska M, et al. Evaluating PET-CT in routine surveillance and follow-up after treatment for cervical cancer: a cost-effectiveness analysis. BJOG: An International Journal of Obstetrics & Gynaecology. 2014;121(4):464-76.

14. Beaver K, Hollingworth W, McDonald R, Dunn G, Tysver-Robinson D, Thomson L, et al. Economic evaluation of a randomized clinical trial of hospital versus telephone follow-up after treatment for breast cancer. British Journal of Surgery. 2009;96(12):1406-15.

15. Jeyarajah S, Adams KJ, Higgins L, Ryan S, Leather AJ, Papagrigoriadis S. Prospective evaluation of a colorectal cancer nurse follow-up clinic. Colorectal Disease. 2011;13(1):31-8.

16. Macafee DA, Whynes DK, Scholefield JH. Risk-stratified intensive follow up for treated colorectal cancer - realistic and cost saving? Colorectal Disease. 2008;10(3):222-30.

17. Moore S, Corner J, Haviland J, Wells M, Salmon E, Normand C, et al. Nurse led follow up and conventional medical follow up in management of patients with lung cancer: Randomised trial. British Medical Journal. 2002;325(7373):16.

18. Renehan AG, O'Dwyer ST, Whynes DK. Cost effectiveness analysis of intensive versus conventional follow up after curative resection for colorectal cancer. BMJ. 2004;328(7431):81.

19. Classen J, Schmidberger H, Souchon R, Weissbach L, Hartmann M, Hartmann JT, et al. What is the value of routine follow-up in stage I seminoma after paraaortic radiotherapy?: An analysis of the German Testicular Cancer Study Group (GTCSG) in 675 prospectively followed patients. Strahlentherapie und Onkologie. 2009;185(6):June.

20. Hengge UR, Wallerand A, Stutzki A, Kockel N. Cost-effectiveness of reduced follow-up in malignant melanoma. [German, English]. JDDG - Journal of the German Society of Dermatology. 2007;5(10):October.

21. Hofmann U, Szedlak M, Rittgen W, Jung EG, Schadendorf D. Primary staging and follow-up in melanoma patients--monocenter evaluation of methods, costs and patient survival. British Journal of Cancer. 2002;87(2):151-7.

22. Leiter U, Marghoob AA, Lasithiotakis K, Eigentler TK, Meier F, Meisner C, et al. Costs of the detection of metastases and follow-up examinations in cutaneous melanoma. Melanoma Research. 2009;19(1):50-7.

23. Staib L, Link KH, Beger HG. Follow-up in colorectal cancer: cost-effectiveness analysis of established and novel concepts. Langenbeck's Archiv fur Chirugie. 2000;385(6):412-20.

24. Wojcinski S, Farrokh A, Hille U, Hirschauer E, Schmidt W, Hillemanns P, et al. Optimizing Breast Cancer Follow-up: Diagnostic Value and Costs of Additional Routine Breast Ultrasound. Ultrasound in Medicine and Biology. 2011;37(2):February.

25. Benning TM, Kimman ML, Dirksen CD, Boersma LJ, Dellaert BG. Combining individual-level discrete choice experiment estimates and costs to inform health care management decisions about customized care: the case of follow-up strategies after breast cancer treatment. Value in Health. 2012;15(5):680-9.

26. Bleeker WA, Mulder NH, Hermans J, Otter R, Plukker JT. Value and cost of follow-up after adjuvant treatment of patients with Dukes' C colonic cancer. British Journal of Surgery. 2001;88(1):101-6.

27. Lu W, Greuter MJ, Schaapveld M, Vermeulen KM, Wiggers T, de Bock GH. Safety and cost-effectiveness of shortening hospital follow-up after breast cancer treatment. British Journal of Surgery. 2012;99(9):1227-33.

28. Polinder S, Verschuur EM, Siersema PD, Kuipers EJ, Steyerberg EW. Cost comparison study of two different follow-up protocols after surgery for oesophageal cancer. European Journal of Cancer. 2009;45(12):2110-5.

29. van LJ, Grutters JP, Wanders R, Boersma L, Dingemans AM, Bootsma G, et al. 18FDG-PET-CT in the follow-up of non-small cell lung cancer patients after radical radiotherapy with or without chemotherapy: an economic evaluation. European Journal of Cancer. 2010;46(1):110-9.

30. Dion M, Martinez CH, Williams AK, Chalasani V, Nott L, Pautler SE. Cost analysis of two follow-up strategies for localized kidney cancer: a Canadian cohort comparison. Cuaj-Canadian Urological Association Journal. 2010;4(5):322-6.

31. Gilbert S, Reid KR, Lam MY, Petsikas D. Who should follow up lung cancer patients after operation? Annals of Thoracic Surgery. 2000;69(6):1696-700.

32. Nam RK, Redelmeier DA, Spiess PE, Sampson HA, Fradet Y, Jewett MA. Comparison of molecular and conventional strategies for followup of superficial bladder cancer using decision analysis. Journal of Urology. 2000;163(3):752-7.

33. Di CL, Scarpa M, Angriman I, Perissinotto E, Ruffolo C, Frego M, et al. Cost-effectiveness analysis of postoperative surveillance protocols following radical surgery for colorectal cancer. Acta Chirurgica Belgica. 2012;112(1):24-32.

34. Forni F, Ferrandina G, Deodato F, Macchia G, Morganti AG, Smaniotto D, et al. Squamous cell carcinoma antigen in follow-up of cervical cancer treated with radiotherapy: Evaluation of cost-effectiveness. International Journal of Radiation Oncology Biology Physics. 2007;69(4):1145-9.

35. Borie F, Combescure C, Daures JP, Tretarre B, Millat B. Cost-effectiveness of two follow-up strategies for curative resection of colorectal cancer: comparative study using a Markov model. World Journal of Surgery. 2004;28(6):563-9.

36. Borie F, Daures JP, Millat B, Tretarre B. Cost and effectiveness of follow-up examinations in patients with colorectal cancer resected for cure in a French population-based study. Journal of Gastrointestinal Surgery. 2004;8(5):552-8.
37. Baena-Canada JM, Ramirez-Daffos P, Cortes-Carmona C, Rosado-Varela P, Nieto-Vera J, Benitez-Rodriguez E. Follow-up of long-term survivors of breast cancer in primary care versus specialist attention. Family Practice. 2013;30(5):525-32.

38. Oltra A, Santaballa A, Munarriz B, Pastor M, Montalar J. Cost-benefit analysis of a follow-up program in patients with breast cancer: a randomized prospective study. Breast Journal. 2007;13(6):571-4.

39. Grogan M, Rangan A, Gebski V, Boyages J. The value of follow-up of patients with early breast cancer treated with conservative surgery and radiation therapy. Breast. 2002;11(2):163-9.

40. Augestad KM, Norum J, Dehof S, Aspevik R, Ringberg U, Nestvold T, et al. Cost-effectiveness and quality of life in surgeon versus general practitioner-organised colon cancer surveillance: a randomised controlled trial. BMJ Open. 2013;3(4):2013.

41. Warde P, Gospodarowicz MK, Panzarella T, Chow E, Murphy T, Catton CN, et al. Long term outcome and cost in the management of Stage I testicular seminoma. Canadian Journal of Urology. 2000;7(2):967-73.

42. Phippen NT, Havrilesky LJ, Barnett JC, Hamilton CA, Stany M, Lowery WJ. Does routine post-treatment PET/CT add value to the care of women with locally advanced cervical cancer? Gynecologic Oncology. 2015; 137(3).

43. Verberne CJ, Wiggers T, Grossmann I, de Bock GH, Vermeulen KM. Cost-effectiveness of a carcinoembryonic antigen (CEA) based follow-up programme for colorectal cancer (the CEA Watch trial). Colorectal Disease 18(3): O91-O96

44. Armstrong KA, Semple JL, Coyte PC. Replacing ambulatory surgical follow-up visits with mobile app home monitoring: modeling cost-effective scenarios. Journal of Medical Internet Research 2014; 16(9): e213.

45. Coyle D, Grunfeld E, Coyle K, Pond G, Julian JA, Levine MN. Cost effectiveness of a survivorship care plan for breast cancer survivors. Journal of Oncology Practice 2014; 10(2): March

46. Bessen T. Keefe, D. M. K. Karnon, J. Does One Size Fit All? Cost Utility Analyses of Alternative Mammographic Follow-Up Schedules, by Risk of Recurrence." International Journal of Technology Assessment in Health Care 2015; 31(5): 281-288.

47. Bessen T, Karnon J. A patient-level calibration framework for evaluating surveillance strategies: a case study of mammographic follow-up after early breast cancer. Value in Health 2014, 17(6): 669-678.

48. Hou C, Siva S. Haas M, Viney R. Cost-effectiveness of post-therapy pet and telephone interview in the clinical follow-up of patients treated with locally advanced cervical cancer. Value in Health 2015; 17(7)

49. Shah K. Marvelde TL, Collins M, De Abreu, Lourenco R, D'Costa I et al. Safety and cost analysis of an (18)FDG-PET-CT response based follow-up strategy for head and neck cancers treated with primary radiation or chemoradiation. Oral Oncology 2015; 51(5): 529-535.

50. Dansk V, Malmstrom P, Blackberg M, Malmenas M. Hexaminolevulinate Blue-Light Flexible Cystoscopy In Addition To Standard White-Light Cystoscopy In The Follow-Up Of Non-Muscle Invasive Bladder Cancer: Cost-Consequences During Outpatient Surveillance In Sweden. Value in Health 2015: 18(7): A354.

51. Pearce AM, Ryan F. Drummond FJ, Timmons A, Thomas AA, Sharp L. "Comparing the costs of three prostate cancer follow-up strategies: A cost-minimisation analysis." Supportive Care in Cancer. (2016) 24:879–886

52. NHS Improvement. Delivering cancer waiting times. A good practice guide. 2016

53. NHS Digital. NHS Workforce statistics. 2017

Figure 1. Flow diagram for follow-up search up to March 2014

Citations identified by search: n=1,637

Excluded – duplicate papers: n=248

Papers screened by title/abstract: n=1,389

Excluded – papers did not meet the inclusion criteria: n=1,311

Not English language: n=53

Not full economic evaluations: n= 723

Not on cancer: n=328

Not on referral/diagnosis: n=178

Other: n=25

Full papers retrieved for detailed inspection: n=78

Excluded – papers did not meet the inclusion criteria: n=44

Not full economic evaluations: n= 14

Conference abstracts (no enough details): n=10

Not relevant population: n=5

Reviews: n=4

Not relevant interventions: n=3

Cost analyses: n=2

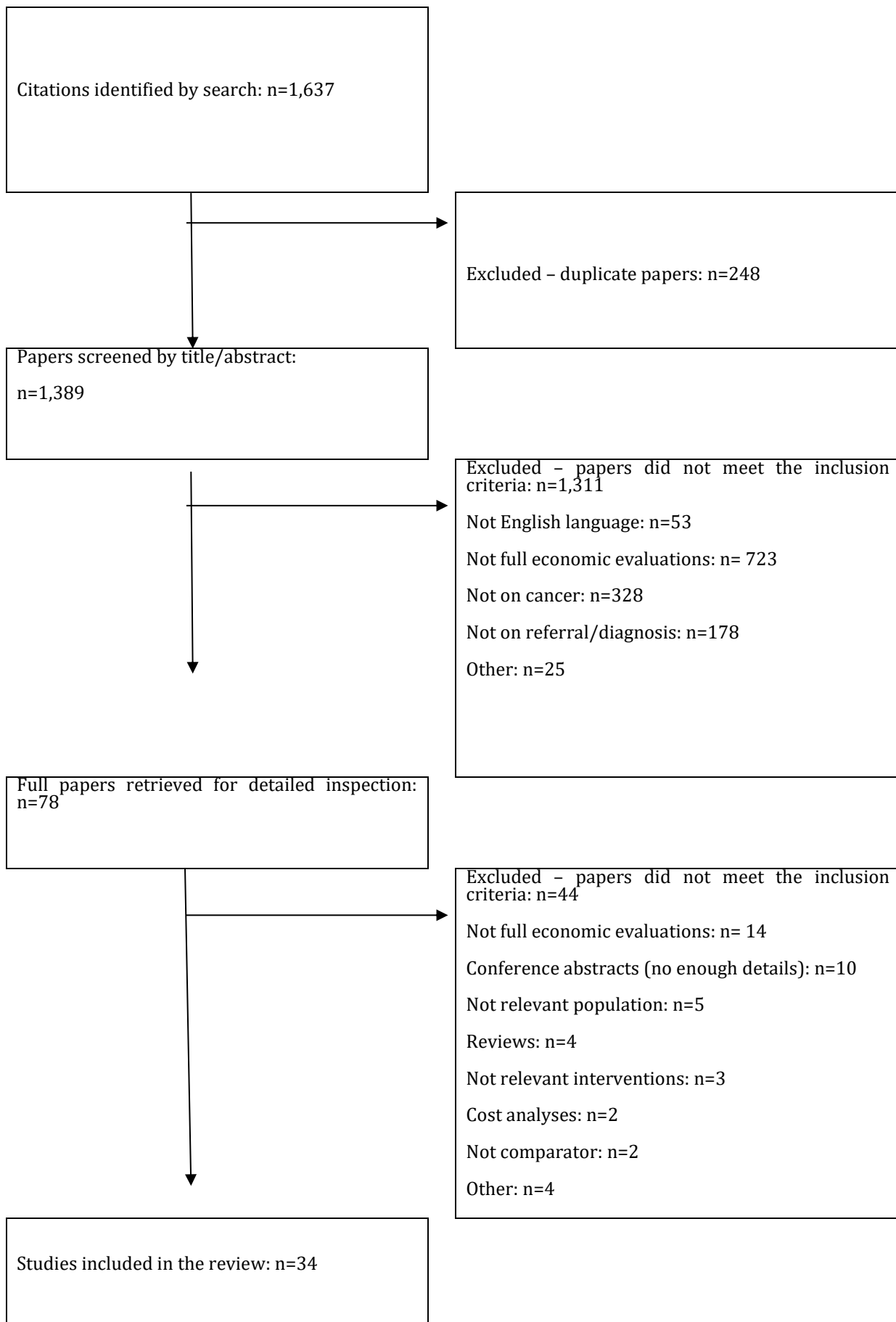Not comparator: n=2

Other: n=4

Studies included in the review: n=34

Figure 2. Flow diagram for follow-up search 2014-2016

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│ Citations identified by search: n=399│
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            │              │ Excluded – duplicate papers: n=3      │
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│ Papers screened by title/abstract: │
│ n=396                   │
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            │──────────────▶ Excluded – papers did not meet the inclusion
            │              │ criteria: n=362                       │
            │              │                                      │
            │              │ Not English language: n=8             │
            │              │ Not full economic evaluations: n= 303 │
            ▼              │ Not on cancer: n=18                   │
                           │ Not on follow-up/curable patients: n=33│
┌─────────────────────────┐└──────────────────────────────────────┘
│ Full papers retrieved for detailed inspection: │
│ n=34                    │
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            │──────────────▶ Excluded – papers did not meet the inclusion
            │              │ criteria: n=24                        │
            │              │                                      │
            │              │ Not full economic evaluations: n= 4   │
            │              │ Not enough data reported n=3          │
            │              │ Not relevant population: n=3          │
            │              │ Reviews: n=6                          │
            │              │ Not on cancer follow-up: n=2          │
            │              │ Guidelines: n=4                       │
            ▼              │ Other types of studies: n=2           │
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│ Studies included in the review: n=10│
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