EEPRU

Economic Evaluation of Health and Social Care Interventions Policy Research Unit

RESEARCH REPORT

Rapid review of existing literature on the cost-effectiveness of alternative systems for diagnosis and referral of any cancer in primary care

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Executive Summary

Rapid review of existing literature on the cost-effectiveness of alternative systems for diagnosis and referral of any cancer in primary care

Introduction: A rapid review has been conducted to explore the existing literature on the cost-effectiveness of interventions/strategies for diagnosis and referral of patients with symptoms that might be suspected 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 search was 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. In order to maximise the usefulness of this report, papers deemed of high quality represented the priority for discussion. However, data extracted from all papers meeting the inclusion criteria have been 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 1,478 references. After excluding papers that were duplicates, non-English language, not economic evaluations, not focussed on cancer or not related to diagnosis/referral for symptoms potentially related to cancer, 28 were finally identified as potentially relevant. These articles were ordered or retrieved from the web. After exclusion of non-relevant studies based on examination of full text, a total of 16 articles were included in the analysis.

Conclusions: Cervical cancer was the most common (n=4) cancer type in these studies. Breast (n=2), colorectal (n=2), gastro-oesophageal (n=2), back pain related to cancer (n=2), skin (n=1), lung (n=1), hepatocellular (n=1) and endometrial (n=1) were also studied. The higher quality studies and expert opinion suggested the following:

Cervical

- In the UK, referral to colposcopy after one mild result during cervical screening rather than after two consecutive mild results appears a cost-effective option.

- Published studies suggest that the addition of HPV triage to standard repeat of Pap smear for women with ASC-US might provide good value for money, but that this is already implemented in the NHS

Colorectal

- Colonoscopy might be the most cost-effective strategy in patients presenting to their GP with rectal bleeding compared to other diagnostic options as sigmoidoscopy or watchful waiting.
- Immediate colonoscopy could lead to cost savings compared to a traditional system of "waiting list" for colonoscopy.

Breast

- Immediate fine needle aspiration cytology (FNAC) appears a cost-effective option for patients with a suspicious lesion identified with mammography and clinical examination, and this is fairly routine in the NHS.

Low back pain related

- Magnetic resonance imaging (MRI) might not be a cost-effective option for patients with low-back pain related to cancer and implementation would likely cause capacity problems in primary care.

Gastro-oesophageal

- Performing early endoscopy in all patients presenting with dyspepsia would lead to very large costs per malignancy detected.
- Endoscopy appears a cost-effective option only in a selected subgroup of patients, namely those considered "appropriate" on the basis of American Society of Gastrointestinal Endoscopy (ASGE) or European Panel on the Appropriateness of Gastrointestinal Endoscopy (EPAGE) guidelines.

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. Subsequent evidence from expert clinicians indicates that, where there was a demonstrably cost-effective intervention or strategy, this is often in place in the UK NHS setting.

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GLOSSARY and ACRONYMS

ACER	Average cost-effectiveness ratio
ALD	Alcoholic liver disease
AFP	Alpha-fetoprotein
ASGE	American Society for Gastrointestinal Endoscopy
ASC-US	Abnormal squamous cells of undetermined significance
CEA	Carcinoembryonic antigen
CT	Computed tomography
EB	Endometrial biopsy
EPAGE	European Panel on the Appropriateness of Gastrointestinal Endoscopy
ESR	Erythrocyte sedimentation rate
FNAC	Fine-needle aspiration cytology
GP	General Practitioner
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HPV	Human papilloma virus
HRQoL	Health related quality of life
ICER	Incremental cost-effectiveness ratio
LYG	Life-years gained
MRI	Magnetic resonance imaging
NICE	National Institute for Health and Care Excellence
NHS	National Health Service
OPH	Outpatient hysteroscopy
QALYs	Quality-adjusted life-years
TTS	Triple test score
USS	Ultrasonography

1. INTRODUCTION

Expenditure on cancer in the UK NHS was £5.8 billion in 2010/11,[1] with a considerable burden on other sectors of society, while within this the cost of diagnosis and treatment of cancer patients in the UK is also substantial.[2] 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.[3] This in turn may be related to a sub-optimal identification and referral in primary care. 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. This report focusses on the identification of existing literature on the cost-effectiveness of diagnosis and referral for any cancer in primary care. Knowledge of the existing literature could identify potentially cost-effective strategies that are not yet implemented and/or identify promising areas for future research as well as providing useful data for future work.

2. AIMS/OBJECTIVES

The specific objective of this project is to review the literature exploring the cost-effectiveness of alternative referral systems in primary care including:

i) alternative strategies for the diagnosis of patients with symptoms potentially indicative of cancer in primary care

ii) decision support strategies in primary care relating to testing and referral for symptoms potentially related to cancer

3. METHODS

3.1 Search methodology

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.

3.2 Inclusion criteria

The citations retrieved were reviewed by title and abstract, and all articles were retained if they conducted a cost-effectiveness evaluation on either strategy: the diagnosis of patients with symptoms potentially indicative of cancer in primary care; or decision support strategies in primary care relating to testing and referral for symptoms potentially related to cancer. The 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.

3.3 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. Table 1 shows the items considered in the template.

A) DETAILS OF THE CONDITION
1. Type of cancer
2. Patient population
3. Interventions/strategies
B) DETAILS OF THE STUDY
1. Authors
2. Date
3. Country
4. Type of economic evaluation
5. Type of model used (if any)
6. Main sources of effectiveness data
7. Outcome measure

8. Perspective
9. Cost categories and main sources of resource use/costs
10. Base-case results
11. Analysis of uncertainty
12. Results of sensitivity analysis
13. Other issues

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:

1. <u>Comparator(s)</u>
Is there a full range of comparators, limited set or just one comparator?
How appropriate are the comparator(s)?
2. <u>Evidence synthesis</u>
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
3. <u>Outcome measure</u>
Were quality-adjusted life-years (QALYs) assessed as main outcome measure?
How was measurement of health-related quality of life (HRQoL) conducted?
4. <u>Time horizon</u>
Was an appropriate time horizon considered?
5. <u>Incremental analysis</u>
Was an incremental analysis undertaken?
Do ICERs provide findings potentially useful to decision makers (e.g. cost per LYG, cost per QALYs)
6. <u>Presentation of uncertainty</u>
Was a probabilistic sensitivity analysis conducted?
Were appropriate deterministic sensitivity analyses on relevant parameters made?

Table 2. Quality assessment criteria

In addition to issues of quality, the relevance of these studies to the UK setting was based on the following criteria:

1) Comparators that are used, or could potentially be used, in the UK NHS

2) Resource use estimates relate to practice in the UK

3) Assessment of relevance by clinicians

4. RESULTS

4.1 Overview of results

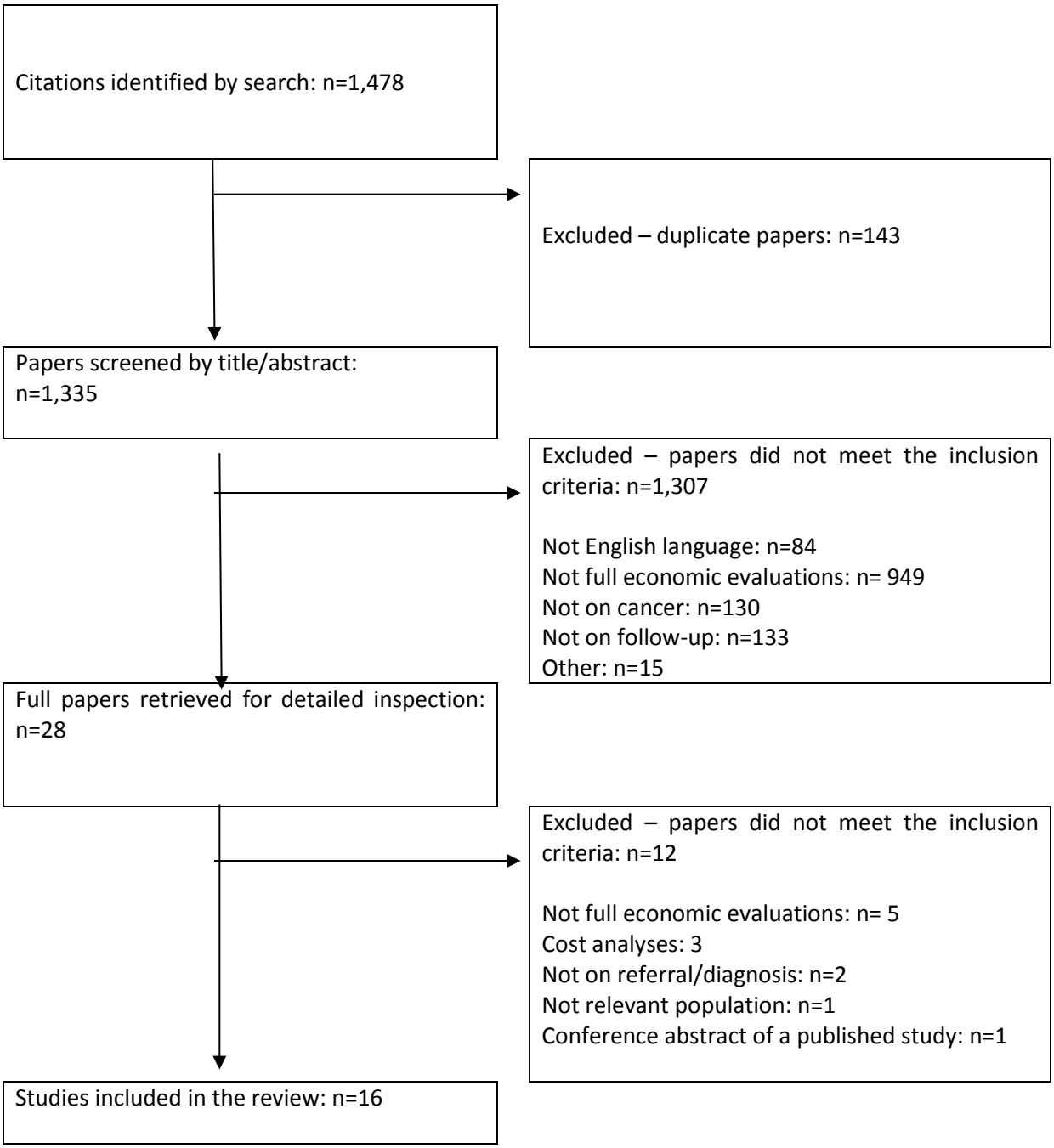
The search identified 1,478 references. After excluding duplicates (n=143), a total of 1,335 unique references were screened by one reviewer. Of these, 53 references were excluded because they were not in English language. Of the remaining 1,282 title/abstracts, 723 were excluded because they were not economic evaluations (e.g. clinical studies, editorials, reviews, methodological papers, cost analyses etc.); 328 were excluded because they did not focus on cancer; and 178 were excluded because they were not related to diagnosis/referral for symptoms potentially related to cancer (e.g. treatments, follow-up etc.). The remaining 53 references were initially considered as potentially relevant and discussed within the team (3 reviewers). Of these, 28 were finally identified as potentially relevant and these articles were ordered or retrieved from the web. After further assessment of relevance for the review based on full text assessment, a total of 16 articles were included in the analysis. Reasons for exclusion of the twelve studies (after full text assessment) were not full economic evaluations (5 studies), only cost analyses (3), screening as main intervention (2), conference abstract of a published study (1) and not relevant population (1).

Of the 16 studies included in the analysis, 8 were conducted in the US,[4-11] 5 in the UK,[12-16] 1 in Germany,[17] 1 in Canada[18] and 1 in the Netherlands.[19] Table 3 presents these studies by type of cancer investigated.

Type of cancer	Number of studies
Cervical	4
Breast	2
Gastro-oesophageal	2
Colorectal	2
Cancer-related low-back pain	2
Skin	1
Endometrial	1
Hepatocellular	1
Lung	1
TOTAL	16

Table 3. Referral study by cancer type

Figure 1. Flow diagram literature search



4.2 Summary of results

4.2.1 Referral studies on cervical cancer

Four studies assessed the cost-effectiveness of diagnosis/referral for patients with symptoms potentially indicative of cervical cancer.[8, 14, 17, 18]

One of these analyses was conducted in the UK[14] with the aim of assessing the value for money of new guidelines recommending referral to colposcopy after one mild result during cervical screening rather than after two consecutive mild results. The patient population included women aged 25 to 64 years with mild dyskaryosis. A Markov model was developed to assess cost and benefits associated with the alternative referral strategies over a lifetime horizon (90 years). Model parameters were mainly based on a systematic review of the literature, but it is unclear whether the data obtained from the studies selected were pooled. Data on costs and quality of life weights (utilities) were obtained from a previously published health technology assessment[20]. The analysis (conducted from the perspective of the UK NHS) showed that the cost per QALY of changing referral guidelines depends on screening frequency and it was £13,477 for an age-related screening, while it ranged between £6,244 and £21,893, for a 5-year and a 3-year screening frequency, respectively. Most of the sensitivity analyses showed that referral to colposcopy after one mild result rather than two mild results from cervical screening may represent a cost-effective option at conventional threshold values of a QALY.

Hughes and colleagues (2005),[8] in a US analysis, compared costs and cases detected for 4 management strategies of this patient population: 1) immediate colposcopy, (2) repeat cytology after an abnormal squamous cells of undetermined significance (ASC-US) Pap smear result, (3) conventional Pap with reflex human papilloma virus (HPV) testing, and (4) liquid-based cytology with reflex HPV testing. A decision model appears to have been used to estimate costs and benefits of these strategies although it was not described. Sensitivity and specificity data for the diagnostic strategies were taken from a systematic review of the literature and mean estimates were used (but it was not stated how these means were obtained). Costs were taken from Medicare tariffs. The analysis showed that, for the repeat Pap smear strategy, the incremental cost per true positive result was $331 when compared with immediate colposcopy. Comparing liquid-based cytology with reflex HPV testing with conventional cytology resulted in an additional cost of $306 to detect each additional true positive result. The immediate colposcopy strategy was more costly and less effective than liquid-based cytology with reflex HPV testing. It was concluded that that using reflex HPV testing in the management of an ASC-US Pap smear resulted in lower overall management costs and fewer women with false positive results being referred to colposcopy. In general, strategies offering HPV test, and in particular liquid-based cytology, were considered cost-effective options.

Sheriff and colleagues (2007),[17] in a German study, also compared three strategies for women with atypical and ASC-US: (1) repeat Pap smear, (2) triage with HPV DNA testing, or (3) immediate treatment. A decision tree was used to model costs and risks of women aged 21 to 64 years with PapIIw or PapIII/PapIIId findings at screening. Published studies and experts' opinions were used to estimate model parameters. The analysis was conducted from the perspective of the German payer over a short time-horizon. Similar conclusions to those of the study by Hughes et al were reached, with HPV triage generally being the most cost-effective option. For women with initial screening result of PapIIw, III, and IIId, incremental cost effectiveness ratios (ICERs) for HPV triage versus repeat Pap smears were €2,232, €815, and €487 per additional case of CIN2+ detected and treated. For patients with an initial screening result of PapIII or IIId, immediate treatment and HPV triage detected only four and 11 additional cases of CIN2+ at incremental cost effectiveness ratios of €39,684 and €10,716 per case, respectively.

Finally, Lytwin et al (2003)[18] compared a strategy of repeating Pap smear test alone (at 6, 12, 18 and 24 months) with a strategy of HPV triage plus Pap smear test in 257 Canadian women aged 18 to 50 years with low-grade squamous intraepithelial lesions (LSILs) or ASC-US. An economic evaluation of the two strategies was conducted alongside a RCT with a 2-year time horizon. Resource use was taken from the clinical trials and costs were based on the Ontario health Insurance plan. The cost-effectiveness ratio of combined testing compared with Pap test alone was Can $4456 per additional case of CIN 2/3 detected. Taking account of future costs of missed CIN2/3 cases with Pap test alone, this ratio decreased to $1837. It was concluded that repeating Pap smear alone is not convenient since almost one third of cases remained undetected, while the addition of HPV test might be cost-effective especially when considering future costs of cancer treatment.

Key messages

- In the UK, referral to colposcopy after one mild result during cervical screening rather than after two consecutive mild results appears a cost-effective option.
- Published studies suggest that the addition of HPV triage to standard repeat of Pap smear for women with ASC-US might provide good value for money. However, expert opinion confirms that HPV triage has subsequently been introduced into the NHS cervical screening programme.

4.2.2 Referral studies on colorectal cancer

Two studies assessed the cost-effectiveness of diagnostic options for patients with suspected colorectal cancer.[4, 12]

Beggs et al (2011)[12] analysed the cost-effectiveness of a strategy of immediate colonoscopy (within 2

weeks) versus a traditional system of “waiting list” for colonoscopy in patients presenting to their GP with lower gastrointestinal symptoms (e.g. rectal bleeding etc.). The study was based on a retrospective audit of 317 patients who had received immediate colonoscopy in a British hospital. The number of cancers detected was the primary outcome measure. No model was used and a 1-year time-horizon was considered. Only the costs of colonoscopy and outpatient consultations were considered from the perspective of the NHS. It was found that the use of straight-to-test colonoscopy led to cost savings of £26,176 (£82.57/patient) in this group compared to standard practice. It was concluded that the use of colonoscopy as ‘straight-to-test’ tool is feasible, safe and cost effective as it allows early detection of cancers.

Allen et al (2005),[4] in a study conducted in the US, compared several diagnostic strategies for patients aged 40 years or more presenting at primary care with rectal bleeding: watchful waiting, flexible sigmoidoscopy, flexible sigmoidoscopy followed by air contrast barium enema and colonoscopy. They developed a Markov model that followed-up these patients over lifetime from the perspective of the society (but excluding indirect costs). HRQoL was estimated from published studies. Diagnostic accuracy was obtained from a review of published studies, but no evidence synthesis appears to have been made. The ICER for colonoscopy compared with flexible sigmoidoscopy was $5,480 per QALY. Watchful waiting and flexible sigmoidoscopy followed by air contrast barium enema were generally more expensive and less effective than colonoscopy. Colonoscopy remained the most cost-effective option in most sensitivity analyses and it was more cost-effective in younger patients.

Key messages:

- Colonoscopy might be the most cost-effective strategy in patients presenting to their GP with rectal bleeding compared to other diagnostic options such as sigmoidoscopy or watchful waiting. This is a clinically appropriate response in some higher risk patients
- Immediate colonoscopy (within 2 weeks) is likely to lead to cost savings compared to a traditional system of “waiting list” for colonoscopy. However, future studies with longer time horizon and more valid design are required to corroborate these findings.
- Expert opinion focussed on follow-up rather than referral, though a general comment that papers that papers become dated very quickly in this field.

4.2.3 Referral studies on breast cancer

Two studies focused on the cost-effectiveness of diagnostic strategies for women with palpable breast masses.[10, 19]

Morris et al (2003),[10] in a US analysis, compared the use of a triple test score (TTS), including physical examination, mammography, and fine needle aspiration with a traditional evaluation including physical examination, mammography and ultrasound. They used a standard decision tree to compare costs and cases detected with these two options. Diagnostic accuracy of traditional evaluation was taken from published studies identified by means of a systematic literature review. Data for TTS were taken from a sample of 484 women evaluated by US practitioners. The perspective of the payer was adopted. The average cost per mass evaluated and cost per malignancy diagnosed ($1,793 vs. $925 and $5,670 vs. $2,925) favored TTS, due to substantially reduced open biopsy.

Flobbe et al[19] evaluated the cost-effectiveness of immediate fine-needle aspiration cytology (FNAC) after clinical examination and mammography compared to three different experimental strategies of preceding ultrasonography[1]. A sample of 492 Dutch women with palpable breast masses was analysed in a prospective diagnostic study. A decision tree was used to estimate costs and life-year gained for the compared strategies over lifetime. A healthcare perspective was adopted and long-term costs of cancer care in addition to diagnostic and consultation costs were considered. All strategies reported a similar life expectancy of 31.0 years. The least expensive strategy consisted of using ultrasound for lesions without suspicion of breast cancer based on mammography and clinical examination, and immediate FNAC of suspicious lesions.

Key messages:

- Immediate FNAC appears a cost-effective option for patients with suspicious lesions identified with mammography and clinical examination, though this has been implemented in many centres.
- Ultrasound might be preferred for those patients without suspicion of breast cancer based on mammography and clinical examination. The most important role for ultrasound is the differentiation between solid and cyst masses, though clinical input suggests that this would add little.

[1] In experimental strategy 1, ultrasound (US) was performed in all patients, and a cut-off point between benign and probably benign imaging diagnosis was used for further referral for additional FNAC. Patients were discharged when no abnormality was found; palpable cysts were aspirated under US guidance; solid benign structures, such as fibroadenoma, were removed by simple surgical excision; and all suspicious findings on US were excised surgically. In experimental strategy 2, the effect of shifting the cut-off point for referral for FNAC to normal and benign imaging diagnosis was studied. Assumptions were similar to those in experimental strategy 1. In experimental strategy 3, US was only performed in patients with normal or benign results on mammography and clinical examination, whereas immediate FNAC was performed in patients with suspicious lesions.

- Expert opinion confirmed that FNAC is routinely used in many centres, though core biopsy may have overtaken this procedure in some centres.

4.2.4 Referral studies on cancer-related low pack pain

Two US studies were identified on diagnostic/referral strategies for patients presenting in primary care with low back pain that might be related to cancer.[7, 9]

Hollingworth et al[7] compared lumbar X-ray versus magnetic resonance imaging (MRI) for the diagnosis of patients with low-back pain presenting in primary care. They developed a Markov model that followed hypothetical patients over their lifetimes. Evidence on diagnostic accuracy and disease progression was taken from selected published studies and cohorts of US patients. Published studies were also used to obtain HRQoL weights. A payer (Medicare) viewpoint was applied, and both short-term and long-term costs (e.g. cancer treatment) were considered. The cost per QALY for MRI compared to lumbar X-ray was $296,176. The sensitivity analysis showed that very high prevalence of cancer (up to 5%) and high sensitivity of MRI is needed for MRI to be cost-effective. In addition, there are likely to be limited resources to conduct all these MRIs in general practise. The authors stated that studies that only measure cost per case detected are likely to overvalue the importance of imaging because of the short life expectancy and high morbidity of patients with cancer-related back pain.

Joines and colleagues[9] compared several diagnostic strategies based on different use of clinical findings, erythrocyte sedimentation rate (ESR), and plain x-rays prior to imaging and biopsy. They used a decision tree to compare costs and cancer cases detected over a short time-horizon and from the payer perspective populated by studies selected from the literature (not pooled). The cost-effectiveness analysis indicated a set of diagnostic strategies that are dominant in terms of incremental cost-effectiveness, but did not provide a criterion for choosing a single best strategy from this set of strategies. The choice of strategy involves a trade-off between sensitivity, specificity, and cost. In general, the use of a higher ESR cut-off point (50 mm/hr) improved specificity and cost effectiveness. The authors recommended strategy of imaging patients who have a clinical finding (history of cancer, age more 50 years, weight loss, or failure to improve with conservative therapy) in combination with either an elevated ESR (>50 mm/hr) or a positive x-ray. Cancer prevalence was an important determinant of cost-effectiveness, but again, the feasibility of conducting these investigations in UK primary care is limited.

Key messages:

- MRI might not be a cost-effective option for patients with low-back pain potentially related to cancer, unless highly sensitive.
- Cancer prevalence is a key parameter to establish the cost-effectiveness of diagnostic option in this patient population. Imaging could be recommended in patients at higher risk of cancer.
- Expert input suggested that primary care was unlikely to have capacity to conduct all the MRI required in these papers.

4.2.5 Referral studies on gastro-oesophageal cancer

Two studies investigated the cost-effectiveness of diagnostic options for patients suspected of gastro-oesophageal cancer.[6, 11] Both were conducted in the US.

Vakil et al (2007)[11] assessed the cost-effectiveness of undertaking endoscopy in a prospective diagnostic study of 2,741 primary-care outpatients aged 18 to 70 years with dyspepsia. The cost per cancer case detected with endoscopy was estimated. Only the cost of endoscopy was considered and future costs associated to cancer were not included. On the basis of the sample of patients analysed, it was found that, if the age threshold for endoscopy was set at 50 years (at a cost of $300/endoscopy), it would cost $49,740 (95%CI: $21,429-$150k) to detect each case of cancer. The authors concluded that the prevalence of upper gastro-intestinal malignancy is low in dyspeptic patients presenting without alarm symptoms. Performing early endoscopy in all patients presenting with dyspepsia would lead to very large costs per malignancy detected. An age cut-off of 50 years offers a reasonable compromise between cost and the risk of a missed lesion (US guidelines recommended endoscopy for patients aged 55 years or more at the time of this study).

Di Giulio et al (2009)[6] assessed the cost-effectiveness of referring patients aged 60-year or more to endoscopy following the American Society for Gastrointestinal Endoscopy (ASGE) or the European Panel on the Appropriateness of Gastrointestinal Endoscopy guidelines (EPAGE). These guidelines provide criteria to select patients “appropriate” or “inappropriate” for undertaking endoscopy. Using a decision tree model, the authors estimated the cost-effectiveness of endoscopy in appropriate or inappropriate patients (on the basis of the above guidelines) compared to no endoscopy. Data to populate the model were obtained from a review of the literature and published estimates were pooled when possible. A societal perspective was adopted and both direct and productivity costs were included. The incremental cost-effectiveness ratios of appropriate and inappropriate upper endoscopy as compared to a policy of not referring patients for endoscopy were $16,577 and $301,203, respectively, per life-year gained. Cancer prevalence represented the main model driver.

Key messages:

- Endoscopy appears a cost-effective option only in a selected subgroup of patients, namely those considered "appropriate" on the basis of ASGE or EPAGE guidelines.
- Performing early endoscopy in all patients presenting with dyspepsia would lead to very large costs per malignancy detected.
- Expert opinion suggested that the capacity of UK endoscopy systems to cope with increased demand for these investigations is limited and this leads to delays and late presentation of cancers.

4.2.6 Referral studies on other cancer types

The remaining four studies focused on the value for money of diagnostic/referral strategies for skin, lung, hepatocellular and endometrial cancer (one study per cancer type).

Wilson et al (2013)[16] assessed the cost-effectiveness of using the MoleMate system for the diagnosis and management of adults with a pigmented skin lesion in the UK. The MoleMate system represents a novel diagnostic aid comprising a handheld SIAscopy scanner incorporating an algorithm developed for use in primary care. The authors developed a decision tree model followed by a Markov chain to estimate lifetime costs and life-year gained of a cohort of patients entering the model with the characteristics of 1,297 adults that were randomised in the MoleMate trial. Resource use data were mainly taken from the trial and the perspective of the NHS was used. Over a lifetime horizon, the MoleMate system was expected to cost an extra £18 over best practice alone and yielded an extra 0.01 QALYs per patient examined. The incremental cost-effectiveness ratio was £1,896 per QALY gained. The probabilistic sensitivity analysis showed that at a cost-effectiveness threshold of £30,000 per QALY gained, there is a 66.1% probability that the MoleMate system is cost-effective compared with best practice. High uncertainty was found around mean cost-effectiveness results given the little difference between the two compared strategies both in terms of costs and benefits. However, input from an expert clinician suggests that Molemate identifies a large number of false positives and that its' usefulness is very limited.

Bechtel et al (2005),[5] in a US analysis, assessed the cost-effectiveness of three diagnostic procedures (chest posteroanterior radiographs, thoracic CT scans, sputum cytology) in patients at high risk of lung cancer (smoking, family history of aerodigestive tract cancer, or occupational exposures) with spirometric abnormalities. A sample of 126 patients was considered in a prospective cohort study. Cost per case detected was assessed from a payer perspective over a short-term time horizon. The combination of the three diagnostic strategies yielded a cost per case detected of $11,925. Chest CT scan was the most

sensitive test to identify lung cancer while standard chest radiographs added little additional information.

Thompson et al (2007)[15] in a conference abstract evaluated different diagnostic tests for surveillance of cirrhosis for hepatocellular carcinoma in the UK context. Periodic serum alpha-fetoprotein (AFP) testing and liver ultrasound examination were compared in patients with cirrhosis (alcoholic liver disease (ALD)-, hepatitis B (HBV)- and C virus (HCV)-related). A cost-effectiveness analysis was conducted and a decision-analytic model developed. A systematic review was conducted to identify relevant studies to populate the model, but no study was found and model parameters appear to have been based on experts' opinions. The perspective of the analysis was not clearly reported. Model results showed that, in people with HBV-related cirrhosis, the optimal surveillance strategy (at a cost-effectiveness threshold of €30,000 per QALY), would be 6-monthly surveillance with the combination of AFP testing and ultrasound. In contrast, for those with ALD-related cirrhosis, annual screening with AFP as a triage test is the only surveillance strategy that is likely to be considered cost-effective at this threshold. Finally, for people with HCV-related cirrhosis, the most cost-effective strategy would be surveillance with a 6-monthly AFP triage strategy.

Finally, Clark et al (2006),[13] in a UK analysis, investigated several diagnostic options for women with postmenopausal bleeding aged 45 years or more: endometrial biopsy (EB) devices, ultrasonography (USS), outpatient hysteroscopy (OPH), no initial investigation. Different cut-off points were considered. A standard decision tree model was used to assess costs and life-year gained over a lifetime time horizon and from the NHS perspective. Diagnostic probability estimates were derived from systematic quantitative reviews, and clinical outcomes came from published literature. All strategies were cost-effective compared to no investigation (using a threshold of £30,000 per LYG). A strategy based on initial diagnosis with USS using a 5-mm cut-off was the least expensive (£11 470/LYG). Initial investigation with EB or USS using a 4-mm cut-off was comparably cost-effective (less than £30 000/LYG versus USS with a 5-mm cut-off). The strategies involving initial evaluation with test combinations or hysteroscopy alone were not cost-effective compared to single tests. The sensitivity analysis showed that only at higher disease prevalence (10%), a strategy based on initial testing with EB was potentially more cost-effective than strategies based on USS.

Key messages:

- The MoleMate system (siascope) appears a cost-effective option for the diagnosis and management of adults with a pigmented skin lesion in the UK context, though clinical opinion suggests this is an optimistic assessment
- The most cost-effective diagnostic tests in patients with cirrhosis that might lead to hepatocellular cancer depends on whether this is alcoholic liver disease (ALD)-, hepatitis B (HBV)- and C virus (HCV)-related.

- Expert opinion suggests that the cost-effectiveness of diagnostic test also an area of clinical interest, but that siascope is not.

4.3 Quality assessment of referral studies

Twelve of the 16 studies included in the analysis were based on a decision model. Of these, ten studies undertook a review of the literature (4 systematic reviews) to identify model parameters. However, only one study pooled the published evidence to obtain model parameters. The other 2 economic evaluations based on a decision model represented extrapolation on a longer-term of a single study. The remaining 4 analyses were based on a single study (RCT, prospective cohort study, retrospective audit).

Five of the 16 studies used QALYs as main benefit measure and utility weights were taken from previously published studies in 3 cases. Little description of these published studies was generally provided since the values used for utility weights were reported but no description of the instrument used to elicit these values was given. In one study (Thompson et al, 2007) no information on sources of utility weights was provided (but this was available only in abstract format). Finally, Hollingworth et al (2008) stated that no published study was available with utility weights for the patient population of interest and assigned subjectively quality of life scores to the Markov state of their model, on the basis of the Quality of Well-Being scale.

Half of the studies identified (8/16) used a lifetime horizon, while the remaining studies adopted a relatively short time-horizon (2 years or less) which appears not adequate to follow patients in the case of cancer detection.

An incremental analysis was conducted in the majority of studies (12/16), two studies only estimated average cost-effectiveness ratios, while the remaining 2 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 3 studies, respectively. The other analyses reported ratio with limited value for decision-making as, for example, incremental or average cost per case detected.

Finally, 2 studies adopted a probabilistic sensitivity analysis and 8 studies conducted deterministic sensitivity analysis on several parameters or considered several alternative scenarios. The other analyses did not perform any sensitivity analysis (3/16) or only on few parameters (3/16).

Comparator(s) • is there a full range of comparators, limited set or just one comparator? • how appropriate are comparator(s)?	**In general comparators were appropriate for the setting and date of the studies, but many are now used in routine practise.**
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	**10 based on published studies (4 with systematic reviews). Only 1 study appears to have conducted data synthesis pooling the studies identified** **6 based on a single study.**
Outcome measure • where QALYs assessed as main outcome measure? • how measurement of health-related quality of life (HRQoL) was conducted?	**5/16 studies used QALYs** **HRQoL weights were taken from published studies in 3 cases.**
Time horizon • was an appropriate time horizon considered?	**8/16 lifetime** **8/16 short-term (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 12/16 studies** **Only ACERs calculated in 2 studies** **2 cost-minimisation analyses** **6 Cost per cases detected** **5 Cost per QALY** **3 Cost per LYG** **In 2 studies ratios not calculated (CMAs)**
Presentation of uncertainty • was a probabilistic sensitivity analysis conducted? • were appropriate deterministic sensitivity analyses on relevant parameters made?	**2/16 PSA (and deterministic)** **3/16 SA not performed** **3/16 very few univariate** **8/16 univariate on several parameters and/or multivariate and/or scenario analyses**

4.2 Relevance to the UK setting

There were five studies conducted in the UK. 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. Of these five studies, three considered interventions that were shown to be cost-effective and have subsequently been implemented (Hadwin et al, Beggs et al, Clark et al),[12-14] one had questionable conclusions based on a single trial,[16] while a further study[15] used appropriate comparators but only presented an abstract. In short, none of the full UK studies could be considered to suggest alternatives that may enhance efficient diagnosis and referral in the UK NHS.

Of the other studies, several suggested that earlier referral and investigation may be cost-effective. This needs to be considered alongside the capacity of systems to deal with any increase in demand for tests/investigations. Several other countries have a higher "baseline" level of tests/investigations than that in the UK, but general consensus was that these additional tests were of little use in detecting additional cases.

5. DISCUSSION

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 conclusions should be treated cautiously. While this study identified some good quality papers (in particular, studies concluded that speedier referral for suspected cancers) it appears that interventions that were demonstrably cost-effective have been implemented in the UK NHS.

In general, studies were of reasonable quality, though few conducted evidence synthesis and only half used an appropriate time horizon. To be useful for decision making purposes, economic analyses should aim to include all relevant evidence on appropriate comparators over a reasonable time horizon. This would normally extend beyond the time period of the trial. Consultation with experts in the relevant fields suggested that, in general, there were few relevant comparators that were omitted.

A notable finding was that there are differing "baseline" levels of tests and investigations conducted across countries in some cancer types. These differences tend to be based on limited evidence of effectiveness.

One encouraging finding of this review is that interventions that have been shown to be cost-effective are generally implemented within the NHS. A possible exception to this would be the early referral for some tests (such as endoscopy), though the capacity of the NHS to provide these services would have to be considered.

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6. Appendix 1

Draft Medline keyword strategies

Draft diagnosis and referral 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:

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1 exp Neoplasms/ (2536685)

2 cancer.tw. (1019562)

3 1 or 2 (2740302)

4 di.fs. (1960888)

5 diagnosis.tw. (1034500)

6 detect$.tw. (1602760)

7 "Referral and Consultation"/ (50612)

8 referral.tw. (58003)

9 decision support techniques/ (11806)

10 exp Decision Support Systems, Clinical/ (4664)

11 decision protocol.tw. (23)

12 (decision adj (tool or strategy or protocol or system or support or policy)).tw. (7721)

13 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 (3893678)

14 exp General Practice/ (63280)

15 Primary Health Care/ (52930)

16 general practic$.tw. (32125)

17 primary care.tw. (69473)

18 14 or 15 or 16 or 17 (159767)

19 3 and 13 and 18 (4992)

20 Economics/ (26517)

21 exp "Costs and Cost Analysis"/ (178226)

22 Economics, Dental/ (1863)

23 exp Economics, Hospital/ (19240)

24 Economics, Medical/ (8601)

25 Economics, Nursing/ (3889)

26 Economics, Pharmaceutical/ (2508)

27 (economic$ or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic$).tw. (455515)

28 (expenditure$ not energy).tw. (18159)

29 value for money.tw. (952)

30 budget.tw. (12996)

31 or/20-30 (577497)

32 ((energy or oxygen) adj cost).tw. (2857)
33 (metabolic adj cost).ti,ab. (824)
34 ((energy or oxygen) adj expenditure).tw. (16725)
35 or/32-34 (19678)
36 31 not 35 (573038)
37 letter.pt. (829768)
38 editorial.pt. (349068)
39 historical article.pt. (299167)
40 or/37-39 (1463433)
41 36 not 40 (544873)
42 Animals/ (5245752)
43 Humans/ (13264077)
44 23 not (23 and 24) {No Related Terms} (9140)
45 41 not 44 (544545)
46 "Value of Life"/ec [Economics] (228)
47 quality-adjusted life years/ (6766)
48 exp models, economic/ (9935)
49 46 or 47 or 48 (15637)
50 45 or 49 (547636)
51 19 and 50 (479)

7. APPENDIX 2.

Table 1a. Details of referral studies

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
E. Allen, C. Nicolaidis and M. Helfand	2005	US	Colorectal	patients aged 40 years or more presenting at primary care with rectal bleeding	Watchful waiting, flexible sigmoidoscopy, flexible sigmoidoscopy followed by air contrast barium enema, colonoscopy.	CUA	Markov	3% costs and benefits	lifetime	Review of diagnostic studies	QALYs	Modified societal	All direct costs, no indirect costs. Main source: Medicare	ICER for colonoscopy compared with flexible sigmoidoscopy $5,480 per QALY. Watchful waiting and FS1ACBE were generally more expensive and less effective than colonoscopy.	Univariate and multivariate deterministic	Colonoscopy remained the most cost-effective options in most SAs. It was more cost-effective in younger patients.
J. J. Bechtel, W. A. Kelley, T. A. Coons, M. G. Klein, D. D. Slagel and T. L. Petty	2005	US	Lung	patients at high risk of lung cancer (smoking, family history of aerodigestive tract cancer, or occupational exposures) with spirometric abnormalities (n=126)	Chest posteroanterior radiographs, thoracic CT scans, sputum cytology	CEA	No model used	not applied	1 yr	Prospective cohort study	Cancer cases detected	Payer	Visits, screening and diagnostic tests	Costs per cancer found were $11,925 per patient	Not performed	Not performed
A. D. Beggs, R. D. Bhate, S. Irukulla, M. Achiek and A. M. Abulafi	2011	UK	Colorectal	Patients (n=317) presenting to their GP with lower gastrointestinal symptoms (e.g. rectal bleeding etc)	Immediate colonoscopy versus waiting list for colonoscopy	CEA	No model used	not relevant	1 yr	Retrospective audit	Cancer cases detected	NHS	Diagnostic tests	The use of straight-to-test colonoscopy lead to cost savings of £26,176 (£82.57/patient) in this group compared to standard practice	Not performed	Not performed
T. J. Clark, P. M. Barton, A. Coomarasamy, J. K. Gupta and K. S. Khan	2006	UK	Endometrial	Women with postmenopausal bleeding (45 years or more)	endometrial biopsy (EB) devices, ultrasonography (USS) and outpatient hysteroscopy (OPH), no initial investigation. Different cut-off were considered	CEA	Decision tree	outcomes 1.5%; costs 0%	lifetime	Systematic reviews of diagnostic studies	LYG	NHS	all direct medical costs (from standard local and national sources)	All strategies were cost-effective compared to no investigation (using a threshold of £30,000 per LYG) and a strategy based on initial diagnosis with USS using a 5-mm cutoff was the least expensive (£11 470/LYG). Initial investigation with EB or USS using a 4-mm cutoff was comparably cost-effective (less than £30 000/LYG versus USS with a 5-mm cutoff). The strategies involving initial evaluation with test combinations or hysteroscopy alone were not cost-effective compared to single tests	Univariate and scenario analyses	At higher disease prevalence (10%), a strategy based on initial testing with EB was potentially more cost-effective than strategies based on USS. In contrast, at cancer prevalence of 5% assumed in the base case analysis, USS strategies were more favourable on cost-effectiveness grounds
K. Flobbe, A. G. Kessels, J. L. Severens, G. L. Beets, H. J. de Koning, M. F. von Meyenfeldt and J. M. van Engelshoven	2004	Netherlands	Breast	Women with palpable breast masses (522 breasts in 492 patients)	immediate fine-needle aspiration cytology after clinical examination and mammography, and three different experimental strategies of preceding ultrasonography	CEA	Decision tree	not applied	lifetime	Prospective diagnostic study	LYG	Health-care	Diagnostic tests, surgeries, long-term costs of cancer (Dutch standard sources)	All strategies reported a similar life expectancy of 31.0 years. Two US strategies were preferred because they were less expensive than the conventional FNAC strategy (€ 3,047 and € 3,013 versus € 3,087, respectively). The conventional FNAC strategy was preferred to experimental 1 of the three US strategies (€ 3,512 versus € 3,089).	Univariate (all parameters)	Most important influential variables included the proportion of suspicious and benign FNAC results and the proportion of false-negative US results

E. D. Giulio, C. Hassan, P. J. Pickhardt, A. Zullo, A. Laghi, D. H. Kim and F. Iafrate	2009	US	Gastro-oesophageal	60-year old patients referred to EGD	ASGE and EPAGE guidelines in selecting patients referred for upper endoscopy, no referral to upper endoscopy	CEA	Decision tree	not applied	lifetime	Review of published studies subsequently pooled	LYG	Societal	Direct (Medicare) and indirect costs	The incremental cost-effectiveness ratios of appropriate and inappropriate EGDs as compared to a policy of not referring patients for endoscopy were $16,577 and $301,203, respectively, per life-year gained.	Univariate (several parameters)	Cancer prevalence appears the key parameter
R. Hadwin, S. Eggington, A. Brennan, P. Walker, J. Patnick and H. Pilgrim	2008	UK	Cervical	women with mild dyskaryosis	new guidelines recommending referral to colposcopy after one mild result during cervical screening rather than after two consecutive mild results	CUA	Markov	Applied but rate not reported (probably 3.5% costs and benefits)	90 years	Systematic literature review	QALY	NHS	Screening, diagnostic tests, cancer therapies	The cost per LYG as a result of the new mild referral policy ranges from £10,031 to £35,126 according to the screening interval. The cost per QALY of the impact of the change to mild referral guidelines for an age-related screening is £13,477, while for 3-year and 5-year screening, it is £21,893 and £6,244, respectively	Some alternative scenarios considered	New referral strategies generally cost-effective at £30,000 per QALY threshold
W. Hollingworth, D. T. Gray, B. I. Martin, S. D. Sullivan, R. A. Deyo and J. G. Jarvik	2003	US	cancer-related low back pain	patients with low-back pain	lumbar X-ray versus MRI	CUA	Markov	3% costs and benefits	lifetime	Several published studies selected by authors	QALY	Payer	Diagnostic tests and cancer treatment (Medicare and publisehd studies)	Cost per QALY for MRI vs lumbar X-ray $296,176	Univariate	Very high prevalence of cancer (up to 5%) and high sensitivity of MRI is needed for MRI to be cost-effective
A. A. Hughes, J. Glazner, P. Barton and J. C. Shlay	2005	US	cervical	women with atypical squamous cells of undetermined significance (ASC-US)	1) immediate colposcopy, (2) repeat cytology after an ASC-US Pap smear result, (3) conventional Pap with reflex human papillomavirus (HPV) testing, and (4) liquid-based cytology with reflex HPV testing.	CEA	Unclear	not relevant	1 yr	Systematic literature review	Cancer cases detected	Payer	Tests and procedures (Medicare)	For the repeat Pap smear strategy, the incremental cost per true positive result was $331 when compared with colposcopy. Comparing liquid-based cytology with conventional cytology resulted in an additional cost of $306 to detect each additional true positive result using liquid-based cytology. The immediate colposcopy strategy was more costly and less effective than liquid-based cytology with reflex HPV testing.	subgroup analyses by age	All incremental CE ratios were higher with increasing age for all four strategies
J. D. Joines, R. A. McNutt, T. S. Carey, R. A. Deyo and R. Rouhani	2001	US	cancer-related low back pain	patients with low-back pain	11 diagnostic strategies based on different in their use of clinical findings, erythrocyte sedimentation rate (ESR), and plain x-rays prior to imaging and biopsy.	CEA	Decision tree	not relevant	short term	Several published studies selected by authors	Cancer cases detected	Payer	Diagnostic tests (Medicare)	Use of a higher ESR cutoff point (50 mm/hr) improved specificity and cost effectiveness for most strategies	Several univariate	Cancer prevalence was an important determinant of cost effectiveness.

A. Lytwyn, J. W. Sellors, J. B. Mahony, D. Daya, W. Chapman, M. Howard, P. Roth, A. T. Lorincz, A. Gafni and S. D. Walter	2003	Canada	Cervical	women low-grade squamous intraepithelial lesions (LSILs) or atypical squamous cells of undetermined significance (ASCUS) (n=257)	repeated Papanicolaou (Pap) test and oncogenic HPV testing	CEA	No model used	not applied	2 yrs	RCT	histologicall y confirmed cervical intraepitheli al neoplasia 2 or 3	Ministry of health	Tests, procedures and treatments (Ontario health Insurance plan)	The cost-effectiveness ratio of combined testing compared with Pap test alone was Can $4456 per additional case of CIN 2/3 detected. Taking account of future costs of missed CIN2/3 cases with Pap test alone this ratio decreased to $1837	Not performed	Not performed
A. M. Morris, C. R. Flowers, K. T. Morris, W. A. Schmidt, R. F. Pommier and J. T. Vetto	2003	US	Breast	Women with palpable breast masses	triple test score (TTS), namely physical examination, mammography, and fine needle aspiration vs single tests	CEA	Decision tree	not relevant	short term	Systematic literature review	Cancer cases detected	Payer	Tests (Medicare)	The average cost per mass evaluated and cost per malignancy diagnosed ($1793 vs. $925 and $5670 vs. $2925) favoured TTS, due to substantially reduced open biopsy	Few Univariate	Little impact on basecase results
S. K. Sheriff, K. U. Petry, H. Ikenberg, G. Crouse, P. D. Mazonson and C. C. Santas	2004	Germany	Cervical	Women with atypical and abnormal Pap smear results	(1) repeat Pap smear, (2) triage with HPV DNA testing, or (3) immediate treatment	CEA	Decision tree	not applied	short-term	Published literature supplemented by experts' opinion	Histologic. confirmed cervical intraepitheli al neoplasia 2+	Payer	Tests and visits (standard German sources)	For patients with initial PapIIw, III, and IIId results, incremental cost effectiveness ratios for HPV triage versus repeat Pap smears are €2,232, €815, and €487 per additional case of CIN2+ detected and treated. For patients with initial PapIII and IIId results, immediate treatment of 1,000 patients detects only four and 11 additional cases of CIN2+ versus HPV triage at incremental cost effectiveness ratios of €39,684 and €10,716 per case, respectively	Univariate	HPV triage remained generally the most cost-effective option
C. J. Thompson, G. Rogers, P. Hewson, D. Wright, R. Anderson, M. Cramp, S. Jackson, S. Ryder, A. Price and K. Stein	2007	UK	Hepatocellular	patients with cirrhosis [alcoholic liver disease (ALD)-, hepatitis B (HBV)- and C virus (HCV)-related	periodic serum alpha-fetoprotein (AFP) testing and/or liver ultrasound examination,	CUA	Decision model (not specified)	not reported	probably lifetime	Systematic literature review	QALYs	not reported	not reported	In people with HBV-related cirrhosis, the optimal surveillance strategy (at a threshold of €30,000 per QALY) would be 6-monthly surveillance with the combination of AFP testing and ultrasound. In contrast, for those with ALD-related cirrhosis, annual screening with AFP as a triage test is the only surveillance strategy that is likely to be considered cost-effective at this WTP. Finally, for people with HCV-related cirrhosis, the most cost-effective surveillance strategy would be surveillance with a 6-monthly AFP triage strategy.	Deterministic and probabilistic	not reported
N. Vakil, N. Talley, S. V. van Zanten, N. Flook, T. Persson, E. Bjorck, T. Lind and E. Bolling-Sternevald	2009	US	Gastro-oesophageal	Patients (N 2471) aged 18–70 years with intermittent or continuous pain or burning centered in the upper abdomen for at least 3 months	Endoscopy	CEA	No model used	not relevant	short-term	Prospective diagnostic study	Cancer cases detected	not clear	Endoscopy (assumed)	If the age threshold for endoscopy were set at 50 years, at a cost of $300/endoscopy, it would cost $49,740 (95%CI: $21,429-$150k) to detect each case of cancer	Change in endoscopy price	At a cost of $100 for endoscopy, the cost per cancer case detected fell to $16,580, while at a cost of $500 rose at $82,900
E. C. Wilson, J. D. Emery, A. L. Kinmonth, A. T. Prevost, H. C. Morris, E. Humphrys, P. N. Hall, N. Burrows, L. Bradshaw, J. Walls, P. Norris, M. Johnson and F. M. Walter	2013	UK	Skin	Adults with a pigmented skin lesion	MoleMate system, based on SIAscopy vs best practice	CUA	Markov	3.5% costs and benefits	lifetime	RCT supplemented with experts' opinion	QALYs	NHS	Diagnostic tests, surgeries, long-term costs of cancer treatment (UK standard sources)	Over a lifetime horizon, the MoleMate system is expected to cost an extra £18 over best practice alone, and yield an extra 0.01 QALYs per patient examined. The incremental cost-effectiveness ratio is £1,896 per QALY	Probabilistic SA	At a typical willingness-to-pay value of £30,000 per QALY gained, there is a 66.1% probability that the MoleMate system is cost-effective compared with best practice