Diagnostic Assessment Report commissioned by the NIHR HTA Programme on behalf of the National Institute for Health and Clinical Excellence – Protocol

Title of project

KRAS mutation testing in tumours for adults with metastatic colorectal cancer.

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1 Plain English Summary

Bowel cancer is the third most common cancer in the UK, accounting for 13% of new cancer cases and around 10% of all cancer deaths. The likelihood of surviving 1 year after diagnosis is around 73%, and the likelihood of surviving 5 years after diagnosis is lower at around 55% and continues to fall after 5 years.

Bowel cancer occurs when uncontrolled cell growth begins in the bowel. Rather than growing into normal healthy bowel cells the abnormal cells form lumps or masses of tissue called tumours which may interfere with normal bowel function; early symptoms of bowel cancer often include altered bowel habit and/or blood in the stool. Around three quarters of bowel cancers are initially treated with surgery, but around 1 in 6 will go on to spread to the liver. When this happens the cancer in the liver can sometimes be treated by further surgery, or, when surgery is not initially possible, chemotherapy may be used with the aim of shrinking the tumour to make surgery possible.

Certain mutations within tumour cells can make them more or less receptive to specific types of chemotherapy. KRAS mutations make some tumours less responsive to treatment with biological therapies, such as cetuximab. Before deciding on which treatment to offer patients with bowel cancer that has spread to the liver patients are therefore tested to see if their tumour has a mutation in the KRAS gene. There are a variety of tests available to detect these specific mutations but it is not known which test is the best test to use. The different tests vary in the specific mutations which they attempt to detect, the amount of mutation they are able to detect, the amount of tumour cells needed for the test to work, the time that it takes to give a result, the error rate of the test, and the cost of the test.

This projects aims to evaluate KRAS mutation tests to determine which should be the recommended test or tests for use in the NHS in England and Wales. The assessment will consider both clinical effectiveness (improvement in patients' symptoms associated with the test) and cost effectiveness (cost of different testing strategies).

2 Decision problem

2.1 Population

The indication for this assessment is the detection of mutations in the KRAS oncogene in adults with metastatic colorectal cancer (CRC), where metastases are confined to the liver and are un-resectable. The presence or absence of KRAS (Kirsten rat sarcoma viral oncogene homolog) mutations can affect the choice of first-line chemotherapy in these patients and mutation testing is used to direct the treatment pathway.[1]

The 2010 cancer registration data from the Office for National Statistics, London showed that CRC was the third most common cancer in both men and women, accounting for approximately 13% of all new cancer cases. The 2010 age-standardised incidence rate for CRC in England was 56.5 per 100,000 in men and 36.1 per 100,000 in women and this has remained constant, for both sexes, over the last ten years.[2] In 2009 there were approximately 36,000 new cases of CRC recorded in England and Wales,[3] and in 2010 there were 14,691 recorded deaths from CRC in England and Wales, accounting for around 10% of all cancer deaths.[4] Age-standardised five year survival rates for CRC in England (2005-2009) were 54.2% for men and 55.6% for women.[5] Approximately two thirds of CRC cases (64% in 2009) are cancers of the colon and one third (36%) are rectal (including the anus). Most (60%) rectal cancer cases occur in men and colon cancer cases are evenly distributed between the sexes.[3] CRC incidence is strongly related to age, with incidence rates increasing from age 50 and peaking in the over 80s; in the UK (2007-2009) 72% of new cases were diagnosed in people over 65 years.[3] There is some evidence of an association between incidence of CRC and deprivation in UK males; 2000-2004 data show incidence rates approximately 11% higher for men living in more deprived areas compared with the least deprived.[6] The National Bowel Cancer Audit (NBCA) data for 2011 included 28,260 new cases for England and Wales, of which 21,306 (75.4%) were surgically treated and 3,425 (16.1%) of these had confirmed liver metastases.[7] Reported estimates of the prevalence of KRAS mutations in codons 12 and 13 in the tumours of patients with metastatic CRC range from 35% to 42%,[8-10] and are similar (approximately 36%) when samples taken from metastases are considered separately.[8, 9] The three most common mutations, G12D, G12V and G13D, account for approximately 75% of all KRAS mutations.[8] Because not all patients whose tumours are wild-type for KRAS codons 12 and 13 respond to treatment with epidermal growth factor inhibiting monoclonal antibodies, the potential effects of mutations in codons 61 and 146 of KRAS have also been investigated. A US study, which found KRAS codon 12 or 13 mutations in 900/2121 (42.4%) of CRC patients, conducted further analysis of the 513 wild-type samples and found 19 additional mutations at KRAS codon 61 and 17 at KRAS codon 146; these additional mutations represent <2% of the total study population.[11]

2.2 Intervention technologies

There are a variety of tests available for KRAS mutation testing (Table 1) in NHS reference laboratories currently providing testing (laboratories participating in the UK National External Quality Assurance Scheme (NEQAS)). The tests used can be broadly grouped into two subgroups: mutation screening and targeted mutation detection. Mutation screening tests screen samples for all KRAS mutations (known and novel) whilst targeted tests analyse samples for specific known mutations. Successful mutation analysis is dependent on adequate sample quality and a sufficient quantity of tumour tissue in the sample. The sample requirements vary between test methods, with some (e.g. Sanger sequencing) requiring up to 25% tumour cells. The limit of detection (the percentage of mutation detectable in a tumour sample against a background of wild-type DNA) may also vary between different test methods, with some studies reporting mutation detection at as little as 1% against a background of wild-type DNA (Table 1). This is an important issue, as it is unclear whether detecting diminishingly small proportions of mutation is clinically useful; should patients with very low proportions of mutation be treated as mutation positive or wild-type. There is some evidence that the results of KRAS mutation testing in plasma samples correlate well with those obtained from tumour tissue.[12, 13] However, tissue samples remain the gold standard. Clinical opinion, provided by specialist advisors during scoping, suggested that plasma testing is currently a 'research only' application which should not be included in this assessment.

Targeted mutation detection tests

All targeted tests are commercial kits and these look for different numbers of mutations within specific codons of the KRAS gene and have differing limits of detection. They may therefore differ in their ability to accurately differentiate patients who are likely to benefit from treatment with cetuximab in combination with standard chemotherapy from those who should receive standard chemotherapy alone.

The Therascreen® KRAS RGQ PCR Kit is a CE marked real-time PCR assay for the qualitative detection of seven mutations in codons 12 and 13 of the KRAS gene. It has been approved by the US Food and Drug Administration (FDA) for the application covered by this assessment, i.e. the selection of patients with metastatic colorectal cancer for treatment with cetuximab. The Therascreen® KRAS RGQ PCR Kit uses two technologies for the detection of mutations: ARMS (Amplification Refractory Mutation System) for mutation specific DNA amplification and Scorpions for detection of amplified regions. Scorpions are bi-functional molecules containing a polymerase chain reaction (PCR) primer covalently linked to a fluorescently labelled probe. A real-time PCR instrument (Rotor-Gene Q 5-Plex HRM for consistency with CE-marking) is used to perform the amplification and to measure fluorescence.[14] There is an earlier version of the Therascreen® KRAS PCR Kit which also uses ARMS and Scorpions for the detection of KRAS mutations and is designed to detect the

same KRAS mutations as the current, re-formulated and re-validated version. Evidence for both versions will be included in this assessment.

The Therascreen® KRAS Pyro Kit is a CE marked test for the quantitative measurement of twelve mutations in codons 12, 13 and 61 of the KRAS gene. The kit is based on pyrosequencing technology and consists of two assays: one for detecting mutations in codons 12 and 13, and a second for detecting mutations in codon 61. The two regions are amplified separately by PCR, then amplified DNA is immobilised on Steptavidin Sepharose High Performance beads. Single-stranded DNA is prepared and sequencing primers added. The samples are then analysed on the PyroMark Q24 System. The KRAS Plug-in Report is recommended by the manufacturer for the analysis of results, however, the analysis tool within the pyrosequencer can also be used.[15]

The cobas KRAS Mutation Test (Roche Molecular Systems) is a CE marked TaqMelt real-time PCR assay intended for the detection of 19 mutations in codons 12, 13 and 61 of the KRAS gene. The assay uses DNA extracted from formalin-fixed paraffin-embedded tissue and is validated for use with the cobas 4800 System.

The KRAS LightMix Kit (TIB MolBiol) is a CE marked test designed for the detection and identification of mutations in codons 12 and 13 of the KRAS gene. The first part of the test involves PCR amplification of the KRAS gene. In order to reduce amplification of the wild-type KRAS gene and therefore enrich the mutant KRAS gene, a wild-type specific competitor molecule is added to the reaction mix. This is called clamped mutation analysis. The second part of the test procedure involves melting curve analysis with hybridisation probes. The melting temperature is dependent on the number of mismatches between the amplification product and the probe, and allows the detection and identification of a mutation within the sample. The test is run on the LightCycler Instrument (Roche).[16]

The KRAS StripAssay (ViennaLab) is a CE marked test for the detection of mutations in the KRAS gene. The test procedure involves three steps: the DNA is first isolated from the specimen; PCR amplification is then performed; the amplification product is then hybridised to a test strip containing allele-specific probes immobilised as an array of parallel lines. Colour substrates are used to detect bound sequences which can then be identified with the naked eye or by using a scanner and software.[17] There are two versions of the KRAS StripAssay: one is designed to detect 10 mutations in codons 12 and 13 of the KRAS gene; a second is designed to detect the same 10 mutations in codons 12 and 13 plus 3 mutations in codon 61 of the KRAS gene.

Mutation screening tests

'In-house' laboratory-based tests are designed to detect all mutations within specific codons of the KRAS gene.

Pyrosequencing assays are the most commonly used method of KRAS mutation testing in UK laboratories (Table 1). The process involves first extracting DNA from the sample and amplifying it using PCR. The PCR product is then cleaned up before the pyrosequencing reaction. The reaction involves the sequential addition of nucleotides to the mixture. A series of enzymes incorporate nucleotides into the complementary DNA strand, generate light proportional to the number of nucleotides added and degrade unincorporated nucleotides. The DNA sequence is determined from the resulting pyrogram trace.[18]

Sanger sequencing is a commonly used method (Table 1); however, there is much variation in the detail of how the method is carried out. In general, after DNA is extracted from the sample it is amplified using PCR. The PCR product is then cleaned up and sequenced in both forward and reverse directions. The sequencing reaction uses dideoxynucleotides labelled with coloured dyes which randomly terminate DNA synthesis creating DNA fragments of various lengths. The sequencing reaction product is then cleaned up and analysed using capillary electrophoresis. The raw data are analysed using analysis software to generate the DNA sequence. All steps are performed at least in duplicate to increase confidence that an identified mutation is real. It should be noted that sequencing only works well when viable tumour cells constitute at least 25% or more of the sample.[19] Sanger sequencing will be treated as the comparator for the cost-effectiveness analysis component of this assessment.

NICE contact with laboratories (October/November 2012) suggested that several laboratories were planning to convert to next generation sequencing in the coming year. As with Sanger sequencing, there is much variation in the methodology used to perform next generation sequencing. The concept is similar to Sanger sequencing, however the sample DNA is first fragmented into a library of small segments that can be sequenced in parallel reactions.[20]

High resolution melt (HRM) analysis assays are also commonly used by laboratories participating in the UK NEQAS scheme (Table 1). For this technique, the DNA is first extracted from the sample and amplified using PCR. The HRM reaction is then performed. This involves a precise warming of the DNA during which the two strands of DNA 'melt' apart. Fluorescent dye which only binds to double stranded DNA is used to monitor the process. A region of DNA with a mutation will 'melt' at a different temperature to the same region of DNA without a mutation. These changes are documented as melt curves and the presence or absence of a mutation can be reported.[21]

MALDI-TOF (Matrix Assisted Laser Desorption Ionization Time-of-Flight) mass spectrometry is currently used by one laboratory participating in the UK NEQAS scheme. This technique involves extracting DNA and amplifying it using PCR. The PCR products are then cleaved and fragments separated based on mass by the MALDI-TOF mass spectrometer. This generates a 'fingerprint' of the DNA where each fragment is represented as a peak with a certain mass. The 'fingerprint' of the test sample is compared to the 'fingerprint' of the wild-type DNA. A mutation would appear as a peak shift due to a change in the mass of a fragment caused by a base change.[22] MALDI-TOF can be used to identify all mutations within selected codons in the KRAS oncogene and has a limit of detection of approximately 10% tumour DNA in a background of wild-type DNA.[23]

Table 1: Overview of KRAS mutation tests

Sequencing method	**Targeted (Mutations targeted)/ Screening test**	**Limits of detection (% mutation)**	**Number of laboratories using the method**	
			NEQAS report*	**Lab contact†**
Commercial tests				
Therascreen® KRAS Kit (PCR) (Qiagen)	Targeted (7 mutations: 6 codon 12 and 1 codon 13)	0.77-6.43%	3	1
Therascreen® KRAS Kit (Pyro) (Qiagen)	Targeted (12mutations: 6 codon 12, 1 codon 13 and 5 codon 61)	1.0-3.5%		2
cobas® KRAS mutation test (Roche Molecular Systems)	Targeted (19 mutations: 6 codon 12, 6 codon 13 and7 codon 61)	1.6-6.3% depending on mutation	4	4
KRAS LightMix kit (TIB MolBiol)	Targeted (9 mutations: 7 codon 12, 2 codon 13)	unclear	0	0
KRAS StripAssay (ViennaLab)	Targeted (13 mutations: 8 codon 12, 2 codon 13 and 3 codon 61)	unclear	0	0
In house tests				
Sanger sequencing	All mutations within specific codons of the KRAS gene	unclear	6	1
Pyrosequencing	All mutations within specific codons of the KRAS	5-10%†	15	8

Sequencing method	Targeted (Mutations targeted)/ Screening test	Limits of detection (% mutation)	Number of laboratories using the method	
			NEQAS report*	Lab contact†
	gene			
Real Time PCR	Targeted (details unclear)	unclear	2	0
High resolution melt analysis	All mutations within specific codons of the KRAS gene	~5%†	2	2
Next generation sequencing	All mutations within specific codons of the KRAS gene	~5%†	0	0
MALDI-TOF (Matrix Assisted Laser Desorption Ionization Time-of-Flight) Mass spectrometry	All mutations within selected codons in the KRAS oncogene	~10%	1	0

* NEQAS pilot scheme 2012-2013, run 2.[24] Thirty UK based laboratories participated in the scheme; some laboratories used more than one method

† NICE contact with laboratories October/November 2012. Fifteen laboratories provided information on methodologies used. Laboratories using pryosequencing frequently stated that the cobas KRAS mutation test was used as an alternative for samples with low tumour content.

Subgroup analyses of patients tested for KRAS mutation status, from randomised controlled trials, have shown that treatment with the epidermal growth factor inhibiting monoclonal antibody cetuximab in combination with standard chemotherapy can increase progression-free survival (PFS) and tumour response in patients with KRAS wild-type tumours, compared to standard chemotherapy alone.[25, 26] Whereas patients whose tumours were positive for KRAS mutations had reduced (PFS) and tumour response when treated with cetuximab in combination with standard chemotherapy compared to standard chemotherapy alone.[25, 26] These two trials formed the basis of NICE Technology Appraisal 176, which recommends cetuximab in combination with standard chemotherapy for the first-line treatment of metastatic colorectal cancer in patients whose tumours are KRAS wild-type and whose metastases are confined to the liver and are un-resectable.[1] However, both of these trials used a pre-CE marked version of the LightMix KRAS Kit (TIB MolBiol), which is not currently in use by any laboratory participating in the UK NEQAS scheme.

2.3 Care pathway

NICE guidance on the diagnosis and management of colorectal cancer was updated in 2012.[27]

Diagnosis of CRC

This guideline states that patients referred to secondary care for suspected colorectal cancer should be assessed using colonoscopy, flexible sigmoidoscopy followed by barium enema, or computed tomography (CT), dependent upon comorbidities and local expertise and test availability. Where a lesion suspicious of cancer is detected a biopsy should be performed to confirm the diagnosis.[27]

All patients with histologically confirmed CRC should be offered contrast-enhanced CT of the chest, abdomen and pelvis to estimate the stage of the disease. Further imaging (e.g. contrast-enhanced MRI or PET-CT) may be considered if the CT scan shows metastatic disease only in the liver.[27] The aim of further imaging is to identify those patients who have resectable metastases, or metastases which may become resectable following response to chemotherapy. For the second group of patients, European Society for Medical Oncology clinical practice guidelines for the treatment of advanced colorectal cancer (2010) recommend establishing KRAS mutation status in order to determine the best treatment regimen. These guidelines do not stipulate which specific mutations should be analysed, or which test method should be used.[28] The KRAS status of a patient's tumour is identified through analysis of a biopsy sample, or more frequently, a section of resected tumour tissue. The tissue is fixed in formalin and embedded in a block of paraffin (FFPE) for storage by the pathologist who also examines the histology and evaluates the tumour content of the sample. Macrodissection may be performed before DNA is extracted and mutation analysis is carried out to determine the KRAS status of the tumour.

To minimise turnaround time, guidance from the Royal College of Pathologists recommends that mutation testing should be ordered by the pathologist reporting on the cellular make-up of the tumour.[29] However, this is not currently universal practice and often the decision to perform a KRAS mutation test is often taken at the multidisciplinary team meeting. If a sample is stored as a formalin fixed and paraffin embedded (FFPE) specimen for a long time this can lead to DNA degradation which can result in a higher chance of failure when testing for KRAS mutations. The timing of the KRAS test varies between patients, with some clinicians preferring to test at diagnosis, potentially before the disease becomes metastatic, and other clinicians waiting until the cancer has progressed to metastatic disease. If the KRAS status is tested early, then the result is then referred to if metastatic disease develops. It has been suggested that analysing multiple resection or biopsy samples from the same patient increases the chances of identifying a KRAS mutation due to potential heterogeneity between tumour sites. The evidence on this is conflicting, with studies reporting that testing a single site only will potentially misclassify between 2% and 10% of tumours as KRAS wild-type.[30, 31]

Treatment of CRC

In patients with unresectable liver metastases, whose primary tumour has been resected or is potentially operable, and who are fit enough to undergo liver surgery, the aim of chemotherapy is to induce tumour response such that resection becomes possible. The KRAS mutation status of a patient's tumour is used to determine the optimal chemotherapy regimen for this purpose. Evidence suggests that patients with KRAS wild-type tumours are more likely to benefit from treatment with an epidermal growth factor receptor inhibiting monoclonal antibody (cetuximab) in combination with standard chemotherapy. However, patients whose tumours are positive for KRAS mutations are more likely to benefit from standard chemotherapy alone. In addition, the overall health and the preferences of the patient should be taken into consideration when selecting treatment.

The choice of standard chemotherapy is covered by NICE clinical guideline 131,[27] which recommends that one of the following sequences of chemotherapy is considered:

- Oxaliplatin in combination with infusional fluorouracil plus folinic acid (FOLFOX) as first line treatment then single agent irinotecan as second-line treatment.
- FOLFOX as first-line treatment then irinotecan in combination with infusional fluorouracil plus folinic acid (FOLFIRI) as second-line treatment.
- Oxaliplatin and capecitabine (XELOX) as first-line treatment then FOLFIRI as second-line treatment.

The guideline further states that raltitrexed should only be considered for patients who are intolerant to fluorouracil and folinic acid, or for whom these drugs are not suitable.[27] NICE technology appraisal 61 suggests that oral therapy with either capecitabine or tegafur with uracil (in combination with folinic acid) can also be considered as an option for the first-line treatment of metastatic colorectal cancer.[32]

With respect to the use of biological agents (epidermal growth factor receptor inhibitors), NICE technology appraisal guidance 176 recommends cetuximab in combination with FOLFOX or FOLFIRI, within its licensed indication, for the first-line treatment of metastatic colorectal cancer in whom:

- The primary colorectal tumour has been resected or is potentially operable.
- The metastatic disease is confined to the liver and is unresectable.
- The patient is fit enough to undergo surgery to respect the primary colorectal tumour and to undergo liver surgery if the metastases become resectable after treatment with cetuximab.[1]

The European Medicines Agency marketing authorisation for cetuximab states that it is 'indicated for the treatment of patients with EGFR-expressing, KRAS wild-type metastatic colorectal cancer'.[33] Therefore KRAS mutation testing is an important component of the care pathway. Cetuximab (monotherapy or combination therapy) and bevacizumab (in combination with non-oxaliplatin chemotherapy) for the treatment of metastatic colorectal

cancer after first-line chemotherapy are not recommended in NICE technology appraisal 242.[34] However, these treatments may be given to some patients through the Cancer Drugs Fund. If cetuximab is considered in the third-line setting, KRAS status is often not retested, but a decision will be made based on the result of the KRAS test performed earlier in the care pathway. No other biological agents are currently recommended by NICE for the first-line treatment of patients with unresectable live metastases from CRC.

NICE guideline 131 stipulates that all patients with primary colorectal cancer undergoing treatment with curative intent should have follow-up at a clinic visit 4-6 weeks after the potentially curative treatment. They should then have regular surveillance including:

- A minimum of two CT's of the chest, abdomen and pelvis in the first 3 years and
- Regular serum carcinoembryonic antigen tests (at least every 6 months in the first 3 years).

They should also have a surveillance colonoscopy at 1 year after initial treatment and, if the result is normal, further colonoscopic follow-up after five years, and thereafter as determined by cancer networks.[27]

3 Objectives

The overall objective of this project is to summarise the evidence on the clinical- and cost-effectiveness of KRAS mutation tests (commercial or in-house) to differentiate adults with metastatic CRC, whose metastases are confined to the liver and are un-resectable, and who may benefit from first-line treatment with cetuximab in combination with standard chemotherapy from those who should receive standard chemotherapy alone, as recommended in NICE Technology Appraisal TA176.[1] In order to address the clinical-effectiveness we would ideally like data on the analytical validity of the different KRAS mutation tests (sensitivity/specificity for detection mutations known to be linked to be treatment effectiveness). However, there is no gold standard for KRAS mutation testing and the exact mutations, and level of mutation, linked to the effectiveness of different treatment options is not known. We therefore defined the following research questions to address the review objectives:

- What is the technical performance of the different KRAS mutation tests (e.g. proportion tumour cells needed, limit of detection (minimum percentage mutation detectable against a background of wild-type DNA), failures, costs, turnaround time)?

- What is the accuracy (clinical validity) of KRAS mutation testing, using any test, for predicting response to treatment with cetuximab in combination with standard chemotherapy?

- How do clinical outcomes from treatment with cetuximab in combination with standard chemotherapy and, where reported, from treatment with standard chemotherapy vary according to which test is used to select patients for treatment?

- What is the cost-effectiveness of the use of the different KRAS mutation tests to decide between standard chemotherapy or cetuximab in combination with standard chemotherapy?

4 Methods for assessing clinical effectiveness

Systematic review methods will follow the principles outlined in the Centre for Reviews and Dissemination (CRD) guidance for undertaking reviews in health care[35] and NICE Diagnostic Assessment Programme manual.[36] In addition to the effectiveness review additional data will be obtained by contacting those reference laboratories in England and Wales known to perform KRAS mutation testing.

4.1 Inclusion and exclusion criteria

Separate inclusion criteria were developed for each of the three clinical effectiveness questions. These are summarised in Table 2.

Table 2: Inclusion criteria

Question	What is the technical performance of the different KRAS mutation tests?	What is the accuracy of KRAS mutation testing, using any test, for predicting response to treatment with cetuximab in combination with standard chemotherapy?	How do outcomes from treatment with cetuximab in combination with standard chemotherapy and, where reported, from treatment with standard chemotherapy vary according to which test is used to select patients for treatment?
Participants:	Adult patients (≥18 years) with metastatic CRC and a resected or resectable primary tumour, whose metastases are confined to the liver and are un-resectable but may become resectable after response to chemotherapy.	Adult patients (≥18 years) with metastatic CRC and a resected or resectable primary tumour, whose metastases are confined to the liver and are un-resectable but may become resectable after response to chemotherapy.	Adult patients (≥18 years) with metastatic CRC and a resected or resectable primary tumour, whose metastases are confined to the liver and are un-resectable but may become resectable after response to chemotherapy. Patients who have been tested for KRAS mutation status.
Setting:		Secondary or tertiary care	
Interventions (index test):	Any commercial or in-house KRAS mutation test listed in Table 1	Any commercial or in-house KRAS mutation test listed in Table 1	First-line chemotherapy with cetuximab in combination with standard chemotherapy
Comparators:	Not applicable	Not applicable	Standard chemotherapy
Reference standard:	Not applicable	Response to treatment with cetuximab in combination with standard chemotherapy (e.g. progression free survival, objective response rate, disease control rate)	Not applicable
Outcomes:	Proportion tumour cells needed, failures, limit of detection, turnaround time, costs, expertise/logistics of test	Overall survival or progression free survival in patients whose tumours are KRAS mutation positive versus wild-type. Test accuracy – the number of true positive, false negative, false positive and true negative.	Progression free survival, overall survival, objective response rate, disease control rate
Study design:	To be addressed by survey; see below Publications from UK laboratories	RCTs (CCTs and cohort studies will be considered if no RCTs are identified)	RCTs (CCTs will be considered if no RCTs are identified)

4.2 Questionnaire

To address the research question on the technical performance of the different KRAS mutation tests, we will need to collect data from sources other than the systematic review. This section provides a brief description of these data and will be expanded as necessary to inform the economic model. A web-based questionnaire will be developed to gather information from laboratories in England and Wales offering KRAS testing that participate in the UK NEQAS scheme. Questions will cover, but will not be limited to:

1. Assay method used
2. Is the method targeted or screening?
3. If targeted method, mutations targeted
4. In your institution is KRAS mutation testing performed on initial diagnosis of CRC or later in the point of disease?
5. If later, at what timepoint is the test carried out?
6. If screening, which codons are screened?
7. Limit of detection (minimum % mutation)
8. Sample requirements (minimum % tumour cells required to run the test)
9. Definition and proportion of inadequate sample
10. Definition and proportion of failed tests (for reasons other than inadequate sample)
11. Number of samples processed
12. Batching size – do you wait until you have certain number of samples before running the test
13. Costs of the test (fixed and variable costs, i.e. what is cost of a full batch and what is the cost of e.g. 50% full batch if partial batches are routinely run)
14. Turnaround time, including definition
15. Any logistic / other issues related to the use of the test?

Information obtained from this survey will be used to provide information on tests that have not been evaluated in studies included in the systematic review. If any published reports on technical performance, from NHS laboratories in England and Wales, are identified by the systematic review searches, these will be summarised alongside the survey data.

4.3 Search strategy

Search strategies will be based on target condition and intervention, as recommended in the Centre for Reviews and Dissemination (CRD) guidance for undertaking reviews in health care and the Cochrane Handbook for Diagnostic Test Accuracy Reviews.[35] Additional supplementary searches will be carried out as necessary. Searches for studies for cost and quality of life will be developed separately.

Candidate search terms will be identified from target references, browsing database thesauri (e.g. Medline MeSH and Embase Emtree), existing reviews identified during the rapid appraisal process and initial scoping searches. These scoping searches will be used to generate test sets of target references, which will inform text mining analysis of high-frequency subject indexing terms using Endnote reference management software. Strategy development will involve an iterative approach testing candidate text and indexing terms across a sample of bibliographic databases, aiming to reach a satisfactory balance of sensitivity and specificity.

The following databases will be searched for relevant studies from 2000 to the present:

- MEDLINE (OvidSP)
- MEDLINE In-Process Citations and Daily Update (OvidSP)
- EMBASE (OvidSP)
- Cochrane Database of Systematic Reviews (CDSR) (Internet)
- Cochrane Central Register of Controlled Trials (CENTRAL) (Internet)
- Database of Abstracts of Reviews of Effects (DARE) (Internet)
- Health Technology Assessment Database (HTA) (Internet)
- Science Citation Index (SCI) (Web of Science)
- LILACS (Latin American and Caribbean Health Sciences Literature) (Internet) http://regional.bvsalud.org/php/index.php?lang=en
- Biosis Previews (Web of Science)
- NIHR Health Technology Assessment Programme (Internet)
- PROSPERO (International Prospective Register of Systematic Reviews) (Internet) http://www.crd.york.ac.uk/prospero/

Completed and ongoing trials will be identified by searches of the following resources (2000-present):

- NIH ClinicalTrials.gov (http://www.clinicaltrials.gov/)
- Current Controlled Trials (http://www.controlled-trials.com/)
- WHO International Clinical Trials Registry Platform (ICTRP) (http://www.who.int/ictrp/en/)

Key conference proceedings, to be identified in consultation with clinical experts, will be screened for the last five years. References in retrieved articles and relevant systematic reviews will be checked. Search strategies will be developed specifically for each database and the keywords associated with colorectal cancer will be adapted according to the configuration of each database.

No restrictions on language or publication status will be applied. Searches will take into account generic and other product names for the intervention. Examples of the search strategies to be used are presented in Appendix 1; these will be adapted as necessary

following consultation with clinical experts. The main Embase strategy for each search will be independently peer reviewed by a second Information Specialist, using the PRESS-EBC checklist.[37] Identified references will be downloaded in Endnote X4 software for further assessment and handling. References in retrieved articles will be checked for additional studies. The final list of included papers will also checked on PubMed for retractions and errata.[38-40]

4.4 Review strategy

Two reviewers will independently screen titles and abstracts of all reports identified by the searches and discrepancies will be discussed. Full copies of all studies deemed potentially relevant, after discussion, will be obtained and two reviewers will independently assess these for inclusion; any disagreements will be resolved by consensus or discussion with a third reviewer.

Where available, data will be extracted on the following: study design/details, participants, KRAS mutation test(s), clinical outcomes, and test performance outcome measures (against treatment response as reference standard), test failure rates, limit of detection. Data will be extracted by one reviewer, using a piloted, standard data extraction form. A second reviewer will check data extraction and any disagreements will be resolved by consensus or discussion with a third reviewer.

4.5 Quality assessment strategy

The methodological quality of included RCTs will be assessed using the Cochrane Risk of Bias Tool.[41] Diagnostic accuracy studies will be assessed using QUADAS-2. [42] The results of the quality assessment will be used for descriptive purposes to provide an evaluation of the overall quality of the included studies and to provide a transparent method of recommendation for design of any future studies. Quality assessment will be undertaken by one reviewer and checked by a second reviewer, any disagreements will be resolved by consensus or discussion with a third reviewer.

4.6 Methods of analysis/synthesis

If sufficient data are available summary estimates of the sensitivity and specificity together with 95% confidence intervals (CIs) and prediction regions of each mutation test for the prediction of response to treatment will be calculated. We will use the bivariate/hierarchical summary receiver operating characteristic (HSROC) random effects model to generate summary estimates and an SROC curve.[43-45] If more than one RCT evaluates treatment effect in patients who were tested with the same KRAS mutation test, then data will be pooled on treatment effect (e.g. hazard ratios, odds ratio, relative risks) within the test positive and,

where available test negative arms. The DerSimonian and Laird random effects model will be used to generate summary estimates together with 95% CIs.

Where meta-analysis is considered unsuitable for some or all of the data identified (e.g. due to the heterogeneity and/or small numbers of studies), we will employ a narrative synthesis. Typically, this will involve the use of text and tables to summarise data. These will allow the reader to consider any outcomes in the light of differences in study designs and potential sources of bias for each of the studies being reviewed. Studies will be organised by research question addressed and by KRAS mutation test. A detailed commentary on the major methodological problems or biases that affected the studies will also be included, together with a description of how this may have affected the individual study results. Recommendations for further research will be made based on any gaps in the evidence or methodological flaws.

5 Methods for synthesising evidence of cost-effectiveness

5.1 Identifying and reviewing published cost-effectiveness studies

Exploration of the literature will be focused on published economic evaluations, utility studies and cost studies relevant to the use of KRAS mutation tests (commercial or in-house) to differentiate adults with metastatic CRC, whose metastases are confined to the liver and are un-resectable, and who may benefit from first-line treatment with cetuximab in combination with standard chemoptherapy from those who should receive standard chemotherapy alone. The literature search will be performed in the literature databases listed above. In addition, specific health economic databases will be searched (e.g. NHSEED (NHS Economic Evaluation Database), and HEED (Health Economic Evaluation Database). Searches will focus on original papers that report on cost, cost-accuracy, cost-effectiveness or cost-utility analyses.

The results and the methodological quality of the studies selected will be summarised. Assessment of methodological quality will follow the criteria for economic evaluations in health care as described in the NICE methodological guidance.[36, 46] Data extraction will focus on technologies compared, indicated population, main results in terms of costs and consequences of the alternatives compared, and the incremental cost-effectiveness, but also on methods of modelling used (if applicable), analytical methods and robustness of the study findings.

5.2 Evaluation of costs, quality of life and cost-effectiveness

Decision analytic modelling will be undertaken to determine the cost-effectiveness of different KRAS mutation tests to decide between standard chemotherapy or standard chemotherapy plus cetuximab in adults with metastatic colorectal cancer and a resected or resectable primary tumour, whose metastases are confined to the liver and are un-

resectable but may become resectable after response to chemotherapy. Standard chemotherapy regimens considered include FOLFOX and FOLFIRI.[1]

Diagnosis and treatment strategies

The analysis will consider the long term consequences of technical performance, clinical validity and prognostic value (i.e. prediction of relative response to treatment with cetuximab in combination with standard chemotherapy and from treatment with standard chemotherapy alone) of the different tests.

For tests for which technical performance, clinical validity and/or prognostic value is unclear, when feasible, assumptions will be made to provide some indication of the (range) of cost-effectiveness outcomes.

Model structure

Published studies that report on the value of KRAS mutation testing from initial diagnosis through to intermediate (curative resection rate) and final (progression free and overall survival) health outcomes are likely to be very scarce. During the scoping phase, one end-to-end study of the therascreen KRAS RGQ PCR kit was identified,[47] but since this study only included patients that had failed previous chemotherapy it is not directly relevant to the population included in the scope. There are two studies using the LightMix KRAS assay,[25, 26] but the LightMix test is currently not in use in laboratories in the UK. The COIN study, finally, uses both pyrosequencing and MADLI-TOF mass array.[48] In order to be able to report on tests listed in the scope for which no data on relative effectiveness (curative resection rate, progression free and overall survival) is available, an alternative scenario analysis will be performed assuming equal prognostic value of the tests. Necessary choices and definitions regarding the structure of the model will depend on the findings from the literature review and consultation with clinical experts.

In order to be consistent with earlier related assessments, the economic model used in STA 176 for Cetuximab in KRAS wild type patients[1] will be used as starting point to model treatment pathways. First, consistency with STA176 will be ensured by replicating the outcomes with the de novo model. Next, the model will be expanded with the test phase and non KRAS wild type patients. In addition, the existence/availability of any other electronic models that reflect the cost-effectiveness of diagnosis and treatment pathways for these patients, and are representative of current care within the NHS, will be determined.

Issues relevant to analyses:

- Longer term costs and consequences will be discounted using the UK discount rates of 3.5% of both costs and effects.

- One way sensitivity analyses will be performed for all key parameters, especially for parameters in the models which are based on expert opinion.
- Probabilistic sensitivity analyses will be performed using parameter distributions instead of fixed values.
- Decision uncertainty regarding mutually exclusive alternatives will be reflected using cost-effectiveness planes and cost-effectiveness acceptability curves.

A simple draft model structure is presented (Appendix 3); this may be developed/expanded as indicated and as available data allow.

The potential impact of KRAS mutation testing on initial presentation with CRC, rather than testing of stored samples following diagnosis of un-resectable liver metastases (as recommended in NICE Technology Appraisal TA176[1]), will not be formally investigated in the cost-effectiveness analyses. A summary of the arguments for and against testing on presentation will be indluded in the discussion section of the Diagnostic Assessment Report.

Health outcomes

Utility values, based on literature or other sources, will be incorporated in the economic model. QALYs will be calculated from the economic modelling.

Costs

Resource utilisation will be estimated for the diagnostic tests and treatments. Data for the cost analyses will be drawn from routine NHS sources (e.g. NHS reference costs, Personal Social Services Research Unit (PSSRU), British National Formulary (BNF)), discussions with individual hospitals and with the manufacturers of the comparators, and the online survey.

6 Handling of information from the companies

All data submitted by the manufacturers/sponsors will be considered if received by the EAG no later than 09/04/2013. Data arriving after this date will not be considered. If the data meet the inclusion criteria for the review they will be extracted and quality assessed in accordance with the procedures outlined in this protocol.

Any 'commercial in confidence' data provided by manufacturers, and specified as such, will be highlighted in blue and underlined in the assessment report (followed by company name in parentheses). Any 'academic in confidence' data provided by manufacturers, and specified as such, will be highlighted in yellow and underlined in the assessment report. Any confidential data used in the cost-effectiveness models will also be highlighted.

7 Competing interests of authors

None

8 Timetable/milestones

Milestones	Completion data
Draft protocol	10/12/2012
Final protocol	09/01/2013
Progress report	09/04/2013
Draft assessment report	06/06/2013
Final assessment report	04/07/2013

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Appendix 1: Clinical effectiveness search

Embase (OvidSP): 2000-2012/wk 48
Searched 4.12.12

(Colorectal Cancer + KRAS) Limits = 2000-2012

1 exp colon cancer/ or exp rectum cancer/ (150551)

2 ((colorect$ or rectal$ or rectum$ or colon$ or sigma$ or sigmo$ or rectosigm$ or bowel$ or anal or anus) adj3 (cancer$ or neoplas$ or oncolog$ or malignan$ or tumo?r$ or carcinoma$ or adenocarcinoma$ or metasta$ or meta-sta$ or sarcoma$ or adenom$ or lesion$)).ti,ab,ot,hw. (243311)

3 CRC.ti,ab,ot. (13754)

4 ((cecum or cecal or caecum or caecal or il?eoc?ecal or il?eoc?ecum) adj3 (cancer$ or neoplas$ or oncolog$ or malignan$ or tumo?r$ or carcinoma$ or adenocarcinoma$ or metasta$ or meta-sta$)).ti,ab,ot. (1631)

5 (large intestin$ adj3 (cancer$ or neoplas$ or oncolog$ or malignan$ or tumo?r$ or carcinoma$ or adenocarcinoma$ or metasta$ or meta-sta$)).ti,ab,ot. (1625)

6 (lower intestin$ adj3 (cancer$ or neoplas$ or oncolog$ or malignan$ or tumo?r$ or carcinoma$ or adenocarcinoma$ or metasta$ or meta-sta$)).ti,ab,ot. (17)

7 or/1-6 (246582)

8 k ras oncogene/ (4844)

9 (k ras or kras or V-Ki-ras$ or V-K-ras or V-Ki-ras or v ki ras or c-ki-ras or c-k-ras or ki-ras or ki ras).af. (15425)

10 (Kirsten adj3 (murine or rat) adj3 sarcoma$).ti,ab,ot. (391)

11 (thera?screen$ or therascreen$).af. (57)

12 (Cobas adj3 (k ras or kras or V-Ki-ras$ or V-K-ras or c-ki-ras or c-k-ras or ki-ras or ki ras)).af. (8)

13 (sanger sequencing adj3 (k ras or kras or V-Ki-ras$ or V-K-ras or c-ki-ras or c-k-ras or ki-ras or ki ras)).af. (14)

14 (pyrosequencing adj3 (k ras or kras or V-Ki-ras$ or V-K-ras or c-ki-ras or c-k-ras or ki-ras or ki ras)).af. (25)

15 ((HRM or HRMA) adj3 (k ras or kras or V-Ki-ras$ or V-K-ras or c-ki-ras or c-k-ras or ki-ras or ki ras)).af. (13)

16 (high resolution adj3 melt$ adj3 (k ras or kras or V-Ki-ras$ or V-K-ras or c-ki-ras or c-k-ras or ki-ras or ki ras)).af. (8)

17 (SNapShot adj3 (k ras or kras or V-Ki-ras$ or V-K-ras or V-Ki-ras or v ki ras or c-ki-ras or c-k-ras or ki-ras or ki ras)).af. (5)

18 (Next generation sequencing adj3 (k ras or kras or V-Ki-ras$ or V-K-ras or c-ki-ras or c-k-ras or ki-ras or ki ras)).af. (1)

19 high resolution melting analysis/ (632)

20 19 and (8 or 9 or 10) (57)

21 or/8-18,20 (15677)

22 7 and 21 (5546)

23 limit 22 to yr="2000 -Current" (4874)

24 limit 23 to embase (4388)

25 remove duplicates from 24 (4385)

Appendix 2: Related NICE guidance

Cancer service guidance

- Improving outcomes in colorectal cancer. Cancer service guidance (2004). Available from: http://guidance.nice.org.uk/CSGCC

Clinical guideline

- Colorectal cancer: the diagnosis and management of colorectal cancer. NICE clinical guideline CG131 (2011). Available from http://guidance.nice.org.uk/CG131 Date of review: TBC. CG131 updates and replaces TA93 Irinotecan, oxaliplatin and raltitrexed for advanced colorectal cancer, and incorporates TA100 Capecitabine and oxaliplatin in the adjuvant treatment of stage III (Dukes' C) colon cancer and TA105 Laparoscopic surgery for the treatment of colorectal cancer and TA61 Capecitabine and tegafur uracil for metastatic colorectal cancer

Technology appraisals

- Colorectal cancer (metastatic) 2nd line: cetuximab, bevacizumab and panitumumab (review). NICE technology appraisal guidance TA242 (2012). Available from: http://guidance.nice.org.uk/TA242. Date for review: January 2015. Replaces TA150 Colorectal cancer (metastatic) - cetuximab (terminated appraisal) and partially updates TA118 Colorectal cancer (metastatic) - bevacizumab and cetuximab
- Bevacizumab in combination with oxaliplatin and either fluorouracil plus folinic acid or capecitabine for the treatment of metastatic colorectal cancer. NICE technology appraisal guidance TA212 (2010). Available from: http://guidance.nice.org.uk/TA212. Date for review: TBC.
- Cetuximab for the first line treatment of metastatic colorectal cancer. NICE technology appraisal guidance TA176 (2009). Available from: http://guidance.nice.org.uk/TA176. The last review decision was in June 2011, when it was agreed that TA176 would be cross referenced with CG131. The reason given for not incorporating TA176 into CG131 was "…as the results of the further subgroup analyses of the COIN study could potentially lead to the need to update the recommendations in the future."

NICE pathways

- NICE Pathway (November 2011) Colorectal cancer. Available from: http://pathways.nice.org.uk/pathways/colorectal-cancer

Quality standards

- Colorectal cancer. NICE quality standard QS20 (August 2012). Available from: http://guidance.nice.org.uk/QS20

Under development

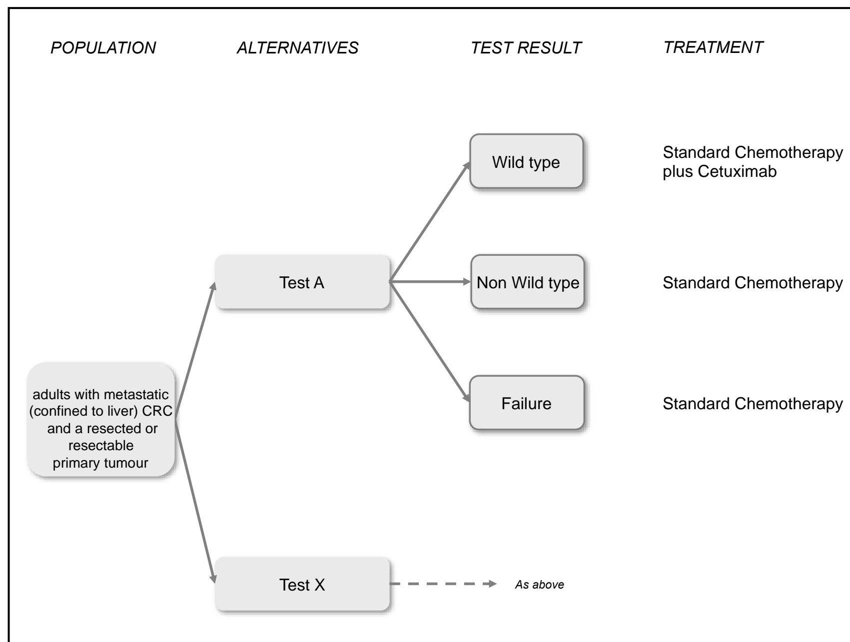
- Aflibercept for the treatment of metastatic colorectal cancer which has progressed following prior oxaliplatin-based chemotherapy. NICE technology appraisal (publication expected October 2013). http://guidance.nice.org.uk/TA/Wave0/617

Terminated

- Panitumumab in combination with chemotherapy for the treatment of metastatic colorectal cancer (terminated NICE technology appraisal TA240). "NICE is unable to recommend the use in the NHS of panitumumab in combination with chemotherapy for the treatment of metastatic colorectal cancer because no evidence submission was received from the manufacturer or sponsor of the technology." (December 2011). http://guidance.nice.org.uk/TA240

Appendix 3: Draft model structure

Decision tree modelling test phase



Model structure as used in TA 176: [49]