

## Diagnosics consultation document

# KRAS mutation testing of tumours in adults with metastatic colorectal cancer

The National Institute for Health and Care Excellence (NICE) is producing guidance on using KRAS mutation testing in the NHS in England. The Diagnostics Advisory Committee has considered the evidence submitted and the views of expert advisers.

**This document has been prepared for public consultation.** It summarises the evidence and views that have been considered, and sets out the draft recommendations made by the Committee. NICE invites comments from registered stakeholders, healthcare professionals and the public. This document should be read along with the evidence base (the diagnostics assessment report), which is available from <http://guidance.nice.org.uk/DT/InDevelopment>.

The Advisory Committee is interested in receiving comments on the following:

- Has all of the relevant evidence been taken into account?
- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
- Are the provisional recommendations sound, and a suitable basis for guidance to the NHS?

### Equality issues

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations:

- could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology
- could have any adverse impact on people with a particular disability or disabilities.

**Note that this document is not NICE's final guidance on KRAS mutation testing. The recommendations in section 1 may change after consultation.**

After consultation, the Committee will meet again to consider the evidence, this document and comments from the consultation. After considering these comments, the Committee will prepare its final recommendations, which will be the basis for NICE's guidance on the use of the technology in the NHS in England.

For further details, see the 'Diagnostics Assessment Programme process guide' (available at [www.nice.org.uk/aboutnice/howwework/developingnicediagnostictechnologiesguidance](http://www.nice.org.uk/aboutnice/howwework/developingnicediagnostictechnologiesguidance)).

**Key dates:**

Closing date for comments: 24 October 2013

Second Diagnostics Advisory Committee meeting: 6 November 2013

## **1 Provisional recommendations**

1.1 The tests and methods listed below are recommended as options for detecting KRAS mutations in the tumours of adults with previously untreated metastatic colorectal cancer, when used in accredited laboratories participating in an external quality assurance scheme.

- therascreen KRAS RGQ PCR Kit (CE-marked, Qiagen)
- KRAS LightMix Kit (CE-marked, TIB MolBiol)
- pyrosequencing of codons 12, 13 and 61
- MALDI-TOF (matrix-assisted laser desorption ionisation time-of-flight) mass spectrometry of codons 12, 13 and 61.

1.2 There was insufficient evidence for the Committee to make recommendations on the following tests and methods:

- therascreen KRAS Pyro Kit (CE-marked, Qiagen)
- KRAS StripAssay (CE-marked, ViennaLab)

- cobas KRAS Mutation Test (CE-marked, Roche Molecular Systems)
- high-resolution melt analysis of codons 12, 13 and 61
- next-generation sequencing of codons 12, 13 and 61.

1.3 The Committee requested further data on concordance between the tests and methods listed in 1.1 and 1.2, in order to support further consideration by the Committee of the technologies listed in 1.2.

## **2 The technologies**

2.1 Nine KRAS mutation testing methods for identifying adults with metastatic colorectal cancer who may benefit from first-line treatment with cetuximab were evaluated. Five are CE-marked tests and 4 are laboratory-developed methods. Additional details of the tests are provided in section 4.

2.2 The tests and methods in this guidance were identified during scoping as being relevant to this assessment. NICE is aware that the tests and methods are evolving, so modifications and new tests are likely to be developed in the future.

## **3 Clinical need and practice**

### ***The problem addressed***

3.1 KRAS mutation tests are used as companion diagnostics to identify patients with metastatic colorectal cancer that is likely to respond to therapy with cetuximab (an epidermal growth factor receptor-inhibiting monoclonal antibody). Patients with a KRAS wild-type tumour have been shown to benefit from treatment with cetuximab in combination with standard chemotherapy. However, KRAS mutant tumours do not respond to treatment with cetuximab, so patients with these tumours would experience the toxic side effects

of the drug unnecessarily and would benefit most from being treated with standard chemotherapy alone.

- 3.2 The purpose of this evaluation was to evaluate the clinical and cost effectiveness of the 9 tests for determining the KRAS mutation status of tumours in adults with metastatic colorectal cancer, to inform first-line treatment with cetuximab as currently recommended in [Cetuximab for the first-line treatment of metastatic colorectal cancer](#) (NICE technology appraisal guidance 176).

### ***The condition***

- 3.3 Colorectal cancer is the third most common cancer in the UK after breast and lung cancer, with approximately 40,000 new cases each year. Between 20% and 55% of people initially present with stage IV metastatic colorectal cancer. In addition, approximately 50–60% of patients who have had surgery for early-stage colorectal cancer will eventually develop advanced disease and distant metastases, most commonly in the liver and typically within 2 years of initial diagnosis. Colorectal cancer is the second most common cause of cancer death in the UK and the 5-year survival rate for metastatic colorectal cancer is less than 7%. Between 35% and 40% of patients with advanced colorectal cancer have mutations in the KRAS oncogene.

### ***The diagnostic and care pathways***

- 3.4 NICE has produced a clinical guideline on [the diagnosis and management of colorectal cancer](#) (NICE clinical guideline 131). The guideline states that diagnostic investigations for people presenting to secondary care with suspected colorectal cancer include colonoscopy, flexible sigmoidoscopy followed by barium enema, or CT colonography.

- 3.5 If a lesion suspected to be cancer is detected, a biopsy is performed to confirm the diagnosis. All patients diagnosed with colorectal cancer should be offered contrast-enhanced CT of the chest, abdomen and pelvis to estimate the stage of the disease. Further imaging may be considered if the CT scan shows metastatic disease only in the liver. The aim of further imaging is to identify patients who have metastases suitable for resection, and patients who have metastases that might become resectable after combination chemotherapy.
- 3.6 The aim of chemotherapy in patients with initially unresectable metastatic colorectal cancer is to make tumours resectable. In this group of patients, European Society for Medical Oncology clinical practice guidelines for treatment of advanced colorectal cancer recommend establishing the KRAS status of the patient's tumour in order to determine the best treatment regimen. These guidelines do not state which specific mutations should be analysed.
- 3.7 The KRAS status of a tumour is identified by analysing resected tumour tissue or biopsy tissue. The tissue is fixed in formalin and embedded in a block of paraffin (FFPE) to allow long-term storage. Tissue to be tested for KRAS mutation is first examined by a pathologist to evaluate the tumour content of the sample. Macrodissection of the tissue may be performed before DNA is extracted and mutation analysis is carried out to determine the KRAS status. If a sample is stored as a FFPE specimen for a long time, the DNA may degrade, which can result in a higher chance of failure when testing for KRAS mutations.
- 3.8 To minimise turnaround time, pathology guidelines recommend that molecular diagnostic tests such as a KRAS mutation test should normally be ordered by the pathologist reporting on the histology of the tumour. However, this is not currently universal practice, and

often the decision to perform a KRAS mutation test is taken at the multidisciplinary team meeting when considering if a patient may be a candidate for cetuximab therapy. The type of test, type of cancer and clinical situation are carefully considered when requesting molecular testing of solid cancers to guide treatment.

3.9 The timing of the KRAS mutation test can vary, with some clinicians preferring to test the KRAS status of patients' tumours at first diagnosis (reflex testing), potentially before the disease becomes metastatic, and other clinicians waiting until the cancer has progressed to metastatic disease (demand testing). Reflex testing avoids a potential delay of 2–4 weeks in starting cetuximab treatment if metastatic disease develops, which may occur with demand testing.

3.10 The KRAS status of a patient's tumour determines the best treatment regimen. Patients with a KRAS wild-type tumour will benefit most from treatment with an epidermal growth factor receptor-inhibiting monoclonal antibody in combination with standard chemotherapy. KRAS mutant tumours will not respond to an epidermal growth factor receptor-inhibiting monoclonal antibody, so patients with these tumours will benefit most from having standard chemotherapy alone and avoiding the toxic side effects of the antibody. The overall health and the preferences of the patient will also influence the choice of treatment.

3.11 For patients with advanced or metastatic colorectal cancer, [NICE clinical guideline 131](#) recommends that one of the following sequences of chemotherapy is considered:

- oxaliplatin plus an infusion of fluorouracil plus folinic acid (FOLFOX) as first-line treatment, then single-agent irinotecan as second-line treatment

- FOLFOX as first-line treatment, then irinotecan plus an infusion of fluorouracil plus folinic acid (FOLFIRI) as second-line treatment
- oxaliplatin plus capecitabine (XELOX) as first-line treatment, then FOLFIRI as second-line treatment
- raltitrexed for patients with advanced colorectal cancer who are intolerant to fluorouracil and folinic acid, or for whom these drugs are not suitable.

3.12 Oral therapy with either capecitabine or tegafur with uracil (in combination with folinic acid) is recommended as an option for the first-line treatment of metastatic colorectal cancer in line with [Guidance on the use of capecitabine and tegafur with uracil for metastatic colorectal cancer](#) (NICE technology appraisal guidance 61).

3.13 Cetuximab is a monoclonal antibody that inhibits the epidermal growth factor receptor. [NICE technology appraisal guidance 176](#) recommends cetuximab plus FOLFOX or FOLFIRI, within its licensed indication, for the first-line treatment of patients with 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 resect the primary colorectal tumour and to undergo liver surgery if the metastases become resectable after treatment with cetuximab
- the patient is unable to tolerate or has contraindications to oxaliplatin (for treatment with cetuximab plus FOLFIRI)

Patients who meet the above criteria should receive treatment with cetuximab for no more than 16 weeks.

- 3.14 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'. Therefore, patients must have a KRAS mutation test and the tumour be identified as a wild-type KRAS tumour before treatment with cetuximab can be considered.
- 3.15 Cetuximab (monotherapy or combination therapy) and bevacizumab (in combination with non-oxaliplatin chemotherapy) are not recommended for the treatment of metastatic colorectal cancer after first-line chemotherapy in [Cetuximab, bevacizumab and panitumumab for the treatment of metastatic colorectal cancer after first-line chemotherapy](#) (NICE technology appraisal guidance 242).
- 3.16 NICE clinical guideline 131 recommends that all patients with primary colorectal cancer undergoing treatment with curative intent should start follow-up at a clinic visit 4–6 weeks after the potentially curative treatment. They should then have regular surveillance including:
- a minimum of 2 CT scans 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. If the result of this test is normal, further colonoscopic follow-up after 5 years should be considered, and thereafter as determined by cancer networks.



## 4 The diagnostic tests

### *The interventions*

#### **therascreen KRAS RGQ PCR Kit (Qiagen)**

- 4.1 The therascreen KRAS RGQ PCR Kit is a CE-marked real-time polymerase chain reaction (PCR) assay for the detection of mutations in the KRAS gene. This kit has been approved by the US Food and Drug Administration (FDA) for use in identifying patients with metastatic colorectal cancer who would benefit from treatment with cetuximab. The therascreen KRAS RGQ PCR Kit uses 2 technologies for the detection of mutations: ARMS (amplification refractory mutation system) for mutation-specific DNA amplification and Scorpions (bi-functional molecules containing a PCR primer covalently linked to a probe) to detect amplified genomic regions. 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.
- 4.2 The therascreen KRAS RGQ PCR Kit is designed to detect 7 mutations in codons 12 and 13 of the KRAS gene. The limit of detection ranges from 0.77 to 6.43%, depending on the mutation. The limit of detection is defined as the lowest amount of mutant DNA in a background of wild-type DNA at which a mutant sample will provide mutation-positive results in 95% of the test results.

#### **therascreen KRAS Pyro Kit (Qiagen)**

- 4.3 The therascreen KRAS Pyro Kit is a CE-marked test for the quantitative measurement of mutations in the KRAS gene. The kit is based on pyrosequencing technology and consists of 2 assays: one for detecting mutations in codons 12 and 13, and the other for detecting mutations in codon 61. The 2 DNA regions are amplified separately by PCR, then amplified DNA is immobilised on

Streptavidin Sepharose High Performance beads. Single-stranded DNA is prepared and sequencing primers are added. The samples are then analysed on the PyroMark Q24 System. The KRAS Plug-in Report is recommended for analysing the results, but the analysis tool within the pyrosequencer can also be used. The thescreen KRAS Pyro Kit is designed to detect and quantify 12 mutations in codons 12, 13 and 61 of the KRAS gene. The limit of detection ranges from 1.0 to 3.5%, depending on the mutation.

#### **cobas KRAS Mutation Test (Roche)**

4.4 The cobas KRAS Mutation Test 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 limit of detection ranges from 1.6 to 6.3%, depending on the mutation. The assay uses DNA extracted from formalin-fixed paraffin-embedded (FFPE) tissue and is validated for use with the cobas 4800 System. Mutation detection is achieved by PCR amplification of target DNA using labelled probes, followed by melting curve analysis. Data are analysed by the cobas 4800 software and results are presented as 'mutation detected' (in codon 12 and/or 13, or codon 61, or both), or 'mutation not detected'.

#### **KRAS StripAssay (ViennaLab)**

4.5 The KRAS StripAssay is a CE-marked test for the detection of mutations in the KRAS gene. There are 2 versions of the KRAS StripAssay: one is designed to detect 10 mutations in codons 12 and 13 of the KRAS gene, and the other is designed to detect the same 10 mutations in codons 12 and 13 plus 3 mutations in codon 61 of the KRAS gene. The test procedure involves 3 steps: the DNA is first isolated from the specimen, PCR amplification is performed, and 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 by eye or by using a scanner and software.

### **KRAS LightMix Kit (TIB MolBiol)**

4.6 The KRAS LightMix Kit is a CE-marked test designed for the detection and identification of 9 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 increase the chance of detecting 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).

### **High-resolution melt analysis**

4.7 High-resolution melt analysis assays are designed to detect all mutations within specific codons of the KRAS gene. The DNA is first extracted from the sample and amplified using PCR. The high-resolution melt reaction is then performed. This involves a precise warming of the DNA during which the 2 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. The limit of detection for high-resolution melt analysis is approximately 5%.

## **Pyrosequencing**

- 4.8 Pyrosequencing is designed to detect all mutations within codons 12, 13 and 61 of the KRAS gene. The process involves extracting DNA from the sample and amplifying it using PCR. The PCR product is then cleaned. The pyrosequencing reaction then 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. Different laboratories may use slightly different primers for the amplification step, but the underlying methodology remains the same. The limit of detection for pyrosequencing is approximately 5–10%.

## **MALDI-TOF mass spectrometry**

- 4.9 MALDI-TOF (matrix-assisted laser desorption ionisation time-of-flight) mass spectrometry can be used to identify all mutations within selected codons in the KRAS gene. The process involves extracting DNA and amplifying it using PCR. An RNA intermediate is generated and then cleaved, and the fragments are separated based on mass by the MALDI-TOF mass spectrometer. This generates a 'fingerprint' of the DNA with each fragment represented as a peak with a certain mass. The 'fingerprint' of the test sample is compared with the 'fingerprint' of the wild-type DNA using analysis software. A mutation appears as a peak shift due to a change in the mass of a fragment caused by a base change. MALDI-TOF has a limit of detection of approximately 10%.

## **Next-generation sequencing**

- 4.10 This method can be used to identify all mutations within specific codons of the KRAS gene. There is much variation in the methodology used to perform next-generation sequencing. The

concept is similar to Sanger sequencing, but the sample DNA is first fragmented into a library of small segments that can be sequenced in parallel reactions. Some next-generation sequencing methods use pyrosequencing methodology rather than Sanger sequencing methodology. The limit of detection for next-generation sequencing is approximately 5%.

### ***The comparator***

- 4.11 A range of methods for KRAS mutation testing is currently used in NHS laboratories. Although not gold standard, the scope defined Sanger sequencing of codons 12, 13 and 61 as the comparator for the purpose of the economic modelling in this assessment.
- 4.12 Sanger sequencing is used to detect all mutations within specific codons of the KRAS gene. It is a commonly used but variable method. In general, after DNA is extracted from the sample it is amplified using PCR. The PCR product is then cleaned and sequenced in both forward and reverse directions. The sequencing reaction uses dideoxynucleotides labelled with coloured dyes, which randomly terminate DNA synthesis and create DNA fragments of various lengths. The sequencing reaction product is then cleaned and analysed using capillary electrophoresis. The raw data are analysed using 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 25% or more of the sample.

## 5 Outcomes

The Diagnostics Advisory Committee (section 10) considered evidence from a number of sources (section 11).

### ***How outcomes were assessed***

- 5.1 The assessment was performed by an External Assessment Group and consisted of a systematic review, a web-based survey and the development of a decision analytical model.
- 5.2 The systematic review was carried out to identify evidence on the technical performance and clinical effectiveness of the different tests to detect KRAS mutations in tumours of adults with metastatic colorectal cancer and their ability to identify adults who may benefit from first-line treatment with cetuximab plus standard chemotherapy.
- 5.3 The web-based survey was conducted to gather data on the technical performance characteristics and costs of KRAS mutation tests in use in NHS laboratories.
- 5.4 A decision analytical model and a Markov model were developed to assess the cost effectiveness of the different KRAS mutation tests in helping to decide appropriate treatment for patients with metastatic colorectal cancer. Two different approaches, described below, were used to calculate cost effectiveness.

### **'Linked evidence' analysis**

- 5.5 This analysis was used for all tests for which information on accuracy was available. The thescreen KRAS RGQ PCR Kit was compared with pyrosequencing, based on objective response rates and resection rates for patients with a KRAS wild-type test result treated with cetuximab plus chemotherapy and for patients with a KRAS mutation test result treated with chemotherapy alone.

Progression-free survival and overall survival after successful resection were assumed to be conditional on resection and independent of treatment. A major assumption underlying this analysis is that the differences in response rate and resection rate are solely because of the use of different KRAS mutation tests.

### **‘Assumption of equal prognostic value’ analysis**

5.6 This analysis was used for all tests for which information on technical performance was available from the online survey. In this analysis, the different tests were compared based on test-specific information on test failure rate only, while assuming equal prognostic value across tests. The equal prognostic value assigned was based on data for the pyrosequencing test (as this was the only test for which accuracy data were available on resection rates following treatment with chemotherapy with and without cetuximab, for patients with initially inoperable metastases confined to the liver and for both KRAS mutant and KRAS wild-type tumours). The tests included in this analysis were the cobas KRAS Mutation Test, the theascreen KRAS RGQ PCR Kit, the theascreen KRAS Pyro Kit, the KRAS LightMix kit, the KRAS StripAssay, high-resolution melt analysis, pyrosequencing, MALDI-TOF (matrix assisted laser desorption ionisation time-of-flight) mass spectrometry, next-generation sequencing, and Sanger sequencing.

### ***Technical performance***

5.7 No studies were identified from the systematic review that evaluated the technical performance of KRAS mutation tests.

5.8 There were 31 laboratories participating in the 2012–2013 United Kingdom National External Quality Assessment Service (UK NEQAS) pilot scheme for KRAS mutation testing. Of these, 15 UK laboratories provided information that was included in the analysis by the External Assessment Group.

- 5.9 Pyrosequencing, using laboratory-developed methods, was the most commonly used KRAS mutation test, with 9 laboratories using this approach. One laboratory stated that it was in the process of switching from pyrosequencing to high-resolution melt analysis because of its quicker turnaround time. The cobas KRAS Mutation Test was used by 3 laboratories, Sanger sequencing was used by 2 laboratories and 1 laboratory used the theascreen KRAS Pyro Kit. One laboratory stated that it used high-resolution melt analysis and Sanger sequencing.
- 5.10 More than half of the laboratories reported that KRAS mutation testing was performed on request (for instance from a pathologist or oncologist) and 1 laboratory reported routine testing of all colorectal cancer samples. There were no clear differences between tests in terms of batch size, turnaround time or test costs. All laboratories reported a limit of detection of less than or equal to 10%, for all tests except Sanger sequencing.
- 5.11 The proportion of samples rejected before analysis was less than 2% for all 13 laboratories that provided data on rejection rates. Reasons for rejection included insufficient number of tumour cells or amount of tissue, sample types unsuitable for analysis, and insufficient patient identifiers. The proportion of failed tests ranged from 3 to 6% for the 3 laboratories using the cobas KRAS Mutation Test kit and from 0.2 to 10% for the 8 laboratories using pyrosequencing. The laboratory using high-resolution melt analysis and one of the laboratories using Sanger sequencing reported no failed tests. The remaining laboratory using Sanger sequencing and the laboratory using the theascreen KRAS Pyro Kit did not provide information on the number of failed tests. Reasons for test failure included insufficient DNA, amplification failure, DNA degradation/quality, insufficient tumour cells, and poor fixation.



## Accuracy

- 5.12 There was limited evidence on the accuracy of KRAS mutation testing. The CELIM study (n=114) compared cetuximab in combination with oxaliplatin plus an infusion of fluorouracil plus folinic acid (FOLFOX) with cetuximab in combination with irinotecan plus an infusion of fluorouracil plus folinic acid (FOLFIRI) in patients with non-resectable colorectal liver metastases. Tumour response was reported as the primary outcome, and secondary end points included liver resection rates, progression-free survival, disease-free survival and overall survival. The KRAS wild-type analysis was carried out post hoc and reported a higher rate of resection in the KRAS wild-type population. The study reported sufficient data to allow estimation of the accuracy of the theascreen KRAS RGQ PCR kit for predicting response to treatment with cetuximab plus standard chemotherapy. This study provided information on the extent to which KRAS mutation testing is able to discriminate between patients who will benefit from the addition of cetuximab to standard chemotherapy regimens and those who will not. However, the study reported objective response and did not provide information on the value of the KRAS mutation test for predicting resection rate. The sensitivity estimate for the theascreen PCR Kit for predicting objective response (OR) was 74.6% (95% confidence interval [CI] 62.1 to 84.7%), and the specificity was 35.5% (95% CI 19.2 to 54.6%).
- 5.13 The COIN study (n=1630), compared cetuximab in combination with FOLFOX or oxaliplatin plus capecitabine (XELOX) with FOLFOX or XELOX alone in patients with colorectal liver metastases. Only the subgroup of patients with unresectable liver metastases (n=178) were included in this assessment. The KRAS wild-type testing was carried out before the clinical outcome was known and the analysis reported a higher resection rate for the

KRAS wild-type population. This study allowed estimation of the accuracy of KRAS mutation tests (pyrosequencing and MALDI-TOF combined) for predicting response to treatment with cetuximab plus FOLFOX or XELOX. Standard chemotherapy in this study did not match the inclusion criteria for the systematic review (some patients received XELOX) but the data allowed estimation of the accuracy of the KRAS mutation tests for predicting the more clinically relevant outcome of potentially curative resection. The sensitivity estimate for the combination of pyrosequencing and MALDI-TOF for predicting potentially curative resection following treatment was 52.0% (95% CI 31.3 to 72.2%) and the specificity was 45.6% (95% CI 37.0 to 54.3%).

### ***Clinical effectiveness***

- 5.14 Four randomised controlled trials (CRYSTAL, OPUS, COIN and Xu et al. (2012)) provided data on the clinical effectiveness of cetuximab plus standard chemotherapy compared with standard chemotherapy alone, in patients with colorectal liver metastases whose tumours were KRAS wild-type. The study by Xu et al. (2012) (reported as a conference abstract) included only patients with unresectable colorectal liver metastases and no other metastases, whose tumours were KRAS wild-type. CRYSTAL OPUS and COIN included patients with metastatic colorectal cancer and conducted KRAS mutation testing in a subgroup of these patients. Data were also reported for a smaller subgroup of patients whose metastases were confined to the liver, and outcome data were only reported for patients with KRAS wild-type tumours.
- 5.15 Patient characteristics varied across studies. The CRYSTAL, OPUS and COIN studies were multi-centre studies conducted in Europe, including the UK and the Republic of Ireland. The subgroup data taken from these studies for patients with colorectal metastases confined to the liver represented between 11% and

14% of the total study population. None of the studies reported separate patient characteristics for the relevant subgroup or the criteria used to define unresectable liver metastases. For the larger KRAS wild-type subgroup, patient characteristics were similar across the 3 studies.

- 5.16 Two studies (CRYSTAL and OPUS) used the LightMix KRAS kit to assess KRAS mutation status. The COIN study used pyrosequencing together with MALDI-TOF mass spectrometry (codons 12, 13 and 61), and OPUS used pyrosequencing alone (codons 12 and 13).
- 5.17 Surgical resection margins are classified according to the level of tumour clearance, in which R0 represents the complete removal of all tumours with microscopic examination of margins showing no tumour cells. All 4 studies reported data on R0 resection rates in patients with colorectal metastases limited to the liver and KRAS wild-type tumours, and 3 of the 4 studies also reported objective response rate.
- 5.18 All of the studies reported that the addition of cetuximab to standard chemotherapy was associated with an increase in the rate of R0 resections, although this increase was only statistically significant in the Xu et al. (2012) study (OR 4.57; 95% CI 1.56 to 13.34). All 3 studies that assessed objective response rate reported a statistically significant higher response rate for patients treated with cetuximab plus standard chemotherapy compared with patients treated with standard chemotherapy alone (ORs ranged from 3.00 [95% CI 1.49 to 6.03] to 4.93 [95% CI 1.42 to 17.06]). Only the COIN study reported a statistically significant improvement in progression-free survival associated with the addition of cetuximab to standard chemotherapy (hazard ratio [HR] 0.68; 95% CI 0.48 to 0.97). The Xu et al. (2012) study reported a significant

improvement in 3-year survival rates for patients treated with cetuximab plus standard chemotherapy compared with patients treated with standard chemotherapy alone (OR 2.76; 95% CI 1.12 to 6.26). Overall, there were no clear differences in treatment effect, regardless of which KRAS mutation test was used to select patients.

- 5.19 The median progression-free survival for patients with KRAS wild-type tumours who were treated with cetuximab plus standard chemotherapy was 11.8 months in the CRYSTAL study and 11.9 months in the OPUS study, and the corresponding progression-free survival values in the standard chemotherapy groups were 9.2 months and 7.9 months. The median overall survival for patients with KRAS wild-type tumours who were treated with cetuximab plus standard chemotherapy was 27.8 months in the CRYSTAL study and 26.3 months in the OPUS study, and the corresponding overall survival values in the standard chemotherapy groups were 27.7 months and 23.9 months.

### ***Cost effectiveness***

- 5.20 Four studies and 1 health technology assessment report were included in the systematic review on the cost effectiveness of KRAS mutation testing. In all of these studies, giving cetuximab to patients with KRAS wild-type tumours was a more cost-effective option than administering cetuximab to all patients. However, there was significant variation in the incremental cost-effectiveness ratio (ICER) reported for KRAS testing and treating only patients with KRAS wild-type tumours with cetuximab compared with standard chemotherapy alone for all patients, and the highest ICERs were greater than £1 million per quality-adjusted life year (QALY) gained.
- 5.21 The External Assessment Group performed an economic analysis to assess the cost effectiveness of different methods of KRAS

mutation testing and determine whether standard chemotherapy plus cetuximab or standard chemotherapy alone is the appropriate treatment for patients with unresectable metastatic colorectal cancer whose metastases are confined to the liver. Standard chemotherapy regimens included FOLFOX and FOLFIRI. Each different KRAS testing method targets a different range of mutations and has different limits of detection (lowest proportion of mutation detectable in tumour cells). The External Assessment Group stated that the exact combination of mutation type and limit of detection that will provide optimal treatment selection remains unclear. For this reason, assessment of test performance based on comparison with a conventional 'reference standard' was not possible, and the External Assessment Group took a 'no comparator' approach to the analysis with the cost effectiveness of each strategy only presented as compared with the next most cost-effective strategy.

- 5.22 Information on the accuracy of tests (either based on objective response rate or tumour resection rate) at distinguishing between KRAS wild-type tumours and KRAS mutant tumours in patients with metastases confined to the liver was only available for the theascreen KRAS RGQ PCR Kit, pyrosequencing and MALDI-TOF. The COIN study reported testing with both pyrosequencing and MALDI-TOF mass array, with a reported concordance of greater than 99%. The External Assessment Group therefore assumed that for the economic evaluation MALDI-TOF and pyrosequencing were equivalent, and all results reported for pyrosequencing also applied to MALDI-TOF. However, survey data were only available for pyrosequencing, so the External Assessment Group only reported pyrosequencing in the results tables. No accuracy data were available for the other tests, so comparisons were made based on the differences in technical performance and test costs retrieved from the online survey of NHS

laboratories in England and Wales. A prognostic value equal to pyrosequencing was assumed for all tests. This assumption was made because the External Assessment Group found no reliable evidence to model a difference in prognostic value for these tests.

- 5.23 For consistency between the modelling approach used in [NICE technology appraisal guidance 176](#) and the assessment of the cost effectiveness of different methods of KRAS mutation testing, the External Assessment Group examined the health economic model submitted by the manufacturer of cetuximab for the technology appraisal. The model calculated the expected cost effectiveness of cetuximab compared with chemotherapy for the first-line treatment of metastatic colorectal cancer in patients whose metastases are confined to the liver, are unresectable and are KRAS wild-type (as tested with a pre-CE-marked version of the LightMix KRAS Kit). The External Assessment Group took into account amendments made by the Evidence Review Group (the academic group that assessed the health economic model on behalf of NICE) during the appraisal of cetuximab. This model was used to inform the development of a de novo model in which the long-term consequences of using different KRAS mutation tests were assessed in patients with KRAS wild-type tumours, patients with KRAS mutant tumours, and patients with an unknown test result.
- 5.24 A decision tree and a Markov model were developed to consider the long-term consequences of technical performance and the accuracy of the different tests, followed by treatment with cetuximab plus standard chemotherapy or standard chemotherapy alone in patients with metastatic colorectal cancer whose metastases are confined to the liver and are unresectable. The decision tree was used to model the test result (KRAS wild-type, KRAS mutant or unknown) and the accompanying treatment decision. In the model, patients with a KRAS wild-type tumour

received cetuximab plus standard chemotherapy and patients with a KRAS mutant tumour or an unknown KRAS status received standard chemotherapy (FOLFOX).

- 5.25 The Markov model was used to estimate the long-term consequences in terms of costs and QALYs. The model had a cycle time of 1 week and a lifetime time horizon (23 years were modelled using 1200 cycles). Health states in the Markov model were numbered according to [NICE technology appraisal guidance 176](#).
- 5.26 The proportion of test failures in the laboratory for the KRAS mutation tests was based on the online survey of NHS laboratories in England and Wales. The proportions of KRAS wild-type and KRAS mutant test results were based on the estimated proportions of patients with KRAS wild-type tumours in the population (65.2%, with standard error 0.8%), the test accuracy (sensitivity and specificity, with objective response to cetuximab or resection rate as the reference standard) and the proportion of patients with an unknown test result. The proportion of patients with an unknown test result was based on the proportions of patients with unknown tumour mutation status relative to the number of patients for whom a tissue sample was available in the clinical studies. The proportion of patients with an unknown test result may be an over-estimate, as the clinical studies are unlikely to be representative of the true situation in current clinical practice. By contrast, the results of the online survey of laboratories in England and Wales are likely to provide an underestimation of the total proportion of patients with an unknown test result, as the laboratories may not know the total proportion of pre-test failures (samples considered inadequate by the pathologist and not sent to the laboratory). In the 'linked evidence' analysis, the proportion of unknowns was taken from the clinical studies. For the 'equal prognostic value' analysis, the

proportion of unknowns for all tests was assumed to be equal to the proportion of unknowns in the pyrosequencing tests used in the studies.

5.27 The Markov model incorporated 8 states:

- Progression-free first line – no previous surgery
- Progressive disease second line – no previous surgery
- Progressive disease second line – unsuccessful resection
- Survival after curative resection
- Progression-free first line – unsuccessful resection
- Progressive disease third line – no previous surgery
- Progressive disease third line – unsuccessful resection
- Dead

The states represented a patient having a tumour resection or not, and then progressing to first or subsequent treatment lines. A transition to death was possible from any of the states. For patients with KRAS wild-type tumours the resection rate after treatment with cetuximab and chemotherapy was used, and for patients with KRAS mutant tumours or unknown test results the resection rate after treatment with chemotherapy alone was used. The resection rates reported and used in [NICE technology appraisal guidance 176](#) for the chemotherapy-only strategy were calculated based on all patients (including patients with metastases not confined to the liver), and may therefore be an underestimation of the true resection rate in the population with metastases confined to the liver. However, in the equal prognostic value analysis the resection rate used was based on a study including a population with liver-only metastases. The resection failure rate was set at 5% and the probability of postoperative mortality was 2.8%. These rates were both consistent with NICE technology appraisal guidance 176.



- 5.28 For consistency with [NICE technology appraisal guidance 176](#), parametric survival models for patients who had an unsuccessful or no resection were taken from the appraisal, to estimate cycle-dependent progression-free survival in the first and second line, and overall survival in the first and third line. For patients who had a successful resection, parametric survival models were obtained from NICE technology appraisal guidance 176 to calculate cycle-dependent progression-free survival and overall survival probabilities. Progression-free and overall survival in the first line for standard chemotherapy were based on data from the OPUS and CRYSTAL studies respectively, and were estimated separately for patients treated with or without cetuximab.
- 5.29 The occurrence of adverse events was assumed to be dependent on treatment but independent of KRAS mutation status (that is, adverse events for patients with KRAS wild-type, KRAS unknown and KRAS mutant tumours were assumed to be equal among different test strategies). To be consistent with [NICE technology appraisal guidance 176](#), the occurrence of adverse events was only included in the model by incorporating the additional costs related to the adverse events based on the CRYSTAL and OPUS studies.
- 5.30 Resource use and costs were taken from [NICE technology appraisal guidance 176](#), with the exception of the KRAS test costs. These costs were based on the online survey of NHS laboratories in England and Wales. In the case of an unknown KRAS mutation status because of a pre-laboratory clinical failure, no test costs were taken into account. In the case of an unknown mutation status because of a technical failure in the laboratory, full test costs were taken into account. The proportion of each of these was calculated based on the proportion of patients with an unknown mutation status as taken from the literature, and the total proportion of

technical failures in the laboratories as reported in the online survey.

- 5.31 Because the economic evaluation took a 'no comparator' approach, ICERs for each test were calculated as compared with the next most cost-effective strategy. The 'linked evidence' analysis included 2 tests: pyrosequencing and the thescreen KRAS RGQ PCR Kit. These tests were the only tests for which evidence on test accuracy based on either resection rate or objective response was available.
- 5.32 Pyrosequencing resulted in the lowest total cost. The thescreen KRAS RGQ PCR Kit was the more expensive but also more effective strategy, with an ICER of £17,019 per QALY gained. The cost-effectiveness acceptability curve showed that for lower values of ICER acceptability, pyrosequencing was to be preferred, and that the thescreen KRAS RGQ PCR Kit was the most cost-effective option if the maximum acceptable ICER was £17,000 or higher. The results of the sensitivity analyses did not differ substantially from the base case, in that the thescreen KRAS RGQ PCR Kit was consistently more expensive and more effective than pyrosequencing, with ICERs ranging from £14,860 to £20,528 per QALY gained.
- 5.33 In the base case of the equal prognostic value analysis and in the first sensitivity analysis, the total technical failure rate (pre-laboratory plus within-laboratory technical failures) was assumed to be equal for all tests. In the base case, the average QALYs for all comparators were 1.48 (95% CI 1.33 to 1.64). The total costs associated with the various testing strategies were similar. The same applied to the first sensitivity analysis, in which costs were similar across the different testing methods, and average QALYs were equal by assumption at 1.28 (95% CI 1.12 to 1.44).

- 5.34 In the second sensitivity analysis the total technical failure rate was test specific, which affected the proportion of patients with unknown (and therefore also wild-type and mutant) tumour KRAS status. All other input parameters, such as test costs and test accuracy, were still considered equal. The probabilistic results showed that the cobas KRAS Mutation Test was the least costly and least effective strategy. High-resolution melt analysis and Sanger sequencing had equal costs and effects and their ICER compared with the cobas KRAS Mutation Test was £69,815 per QALY gained. Pyrosequencing and the thescreen KRAS RGQ PCR Kit were extendedly dominated in this analysis (that is, their ICERs were higher than that of the next, more effective option). From the cost-effectiveness acceptability curve it was apparent that the cobas KRAS Mutation Test was the preferred strategy when the maximum acceptable ICER was £60,000 per QALY gained or below.

## **6 Considerations**

- 6.1 The Diagnostics Advisory Committee reviewed the evidence available on the clinical and cost effectiveness of KRAS mutation testing to inform first-line treatment decisions in adults with metastatic colorectal cancer.
- 6.2 The Committee considered the technical performance of the different KRAS mutation tests. It heard from clinical specialists that, in their experience, the different tests generally have a similar level of accuracy in detecting the mutations they are designed to detect. It also heard from the clinical specialists that, in their opinion, test failure rate was largely dependent on sample quality and processing. The Committee discussed the survey of 15 NHS laboratories that participate in the UK National External Quality Assessment Service (NEQAS) scheme. The Committee noted the small sample size of the survey. The Committee was concerned

that the results may not be representative of general NHS practice, because many NHS laboratories that do not participate in the NEQAS scheme perform KRAS testing. The Committee also discussed the failure rate for the individual tests. It noted that the range in failure rates appeared to be large for some tests, and that no data were available for some tests. The Committee concluded that the survey had some important limitations, and that the results of the survey may not be sufficiently robust to allow direct comparison of technical performance of the tests included in this assessment.

- 6.3 The Committee considered the accuracy of the KRAS tests for predicting response to treatment. The Committee noted that there is no established gold standard for measuring the sensitivity and specificity of KRAS testing, and was aware of the fact that the tests covered different codons and different mutations within the codons. The Committee heard from the clinical specialists that the clinical significance of some of the mutations was uncertain, and consequently there was uncertainty in the sensitivity and specificity values calculated from treatment response. The Committee noted that the External Assessment Group had only been able to assess the accuracy of 3 tests (the thescreen KRAS RGQ PCR kit from the CELIM study, and the combination of pyrosequencing and MALDI-TOF from the COIN study), and that no accuracy data had been presented for the remaining tests. The Committee heard from a clinical specialist that the thescreen KRAS RGQ PCR kit had also been used in the NORDIC VII study, and that the results showed a similar accuracy to that of pyrosequencing from the COIN study. However, the clinical specialist noted that the NORDIC VII study did not report liver metastases data, and so did not meet the inclusion criteria for the systematic review by the External Assessment Group. The Committee concluded that in the absence of a gold standard, the approach taken by the External

Assessment Group, in which accuracy for predicting response to treatment was calculated using objective response as a reference standard, was a valid approach. It further concluded that the interpretation of the accuracy data was difficult in the absence of a gold standard, although it was not persuaded that the 3 tests differed in their ability to predict response to treatment based on the evidence presented in this assessment.

- 6.4 The Committee discussed whether concordance data could be used to compare the relative accuracy of the KRAS mutation tests in this assessment. The Committee noted that the accuracy data were calculated from treatment response rates rather than mutation status, and that evidence on concordance between the tests could be used to help understand whether the tests differed in their ability to classify tumours as wild type or mutated. The Committee therefore requested additional data on test concordance, to be considered at its next meeting.
- 6.5 The Committee discussed the technical performance data from the survey of the UK laboratories participating in the NEQAS pilot scheme. The Committee noted that the small sample size of the survey was a limitation of the data but concluded that, based on these data and the expertise of the clinical laboratory specialists on the Committee, there were no clear differences between the tests in terms of batch size, turnaround time, failure rates or test costs.
- 6.6 The Committee discussed the clinical significance of being able to detect low levels of mutation in tumours (that is, the presence of a mutation in only a low proportion of tumour cells). The Committee noted that there was considerable variation between the tests in the minimum percentage of tumour cells needed per sample, and also in the limits of detection. The Committee heard from the clinical specialists that the impact of detecting low levels of mutation on

clinical outcomes is unknown. The Committee concluded that it was uncertain whether an increased limit of detection would result in a better clinical outcome for a patient whose tumours had a low level of mutations.

6.7 The Committee then discussed the clinical significance of tests being able to detect rare KRAS mutations. It acknowledged that screening tests are designed to detect more mutations than the targeted tests. In addition, the targeted tests (therascreen KRAS RGQ PCR and Pyro kits; cobas KRAS Mutation Test; KRAS LightMix kit; and KRAS StripAssay) are designed to detect different sets of mutations, and vary in the number of rare forms of mutations they can detect. The Committee heard from the clinical specialists that KRAS mutations outside codons 12 and 13 were relatively uncommon and that evidence on the association of rarer mutations (often situated in codons 61 and 146) with response to cetuximab is inconclusive. The Committee acknowledged that clinical research continues to increase the understanding of the role of rare mutations, but concluded that, to date, the clinical significance of detecting rare mutations is uncertain.

6.8 The Committee discussed the clinical evidence of KRAS testing in adults with metastatic colorectal cancer. The Committee noted that all of the studies carried out retrospective analysis of KRAS status except for the large prospective COIN study, which used a different chemotherapy regime (XELOX) from that in the inclusion criteria in the systematic review. The Committee compared the COIN and CELIM studies and considered their different resection rates. The Committee noted that the CELIM study only reported objective response and did not have a 'cetuximab only' treatment arm. The Committee also noted that the CELIM and COIN studies had different definitions of unresectable liver metastases at baseline. The Committee considered these patient characteristics and other

factors that differed between the studies. The Committee concluded that it was uncertain whether the different abilities of the KRAS mutation tests to predict response to treatment were a result of the different KRAS mutation tests used, or a result of different patient characteristics and other factors between the studies.

6.9 The Committee considered the 'linked evidence' cost-effectiveness analysis performed by the External Assessment Group. It noted that a key assumption was that any differences in objective response rates or resection rates in the studies were assumed to be solely caused by the different KRAS mutation tests used. The Committee concluded that the differences in clinical effectiveness may be caused by a variety of factors, such as differences in the definition of unresectable liver metastases in patients at baseline (see section 6.8) and that therefore, this key assumption was unlikely to be true. The Committee therefore concluded that the incremental cost-effectiveness ratios (ICERs) produced in the 'linked evidence' analysis were subject to great uncertainty.

6.10 The Committee considered the equal prognostic value cost-effectiveness analysis. It noted that, although the External Assessment Group had attempted to model the cost effectiveness of KRAS mutation testing, the analyses were severely hampered by the lack of evidence and therefore, many assumptions were needed. The Committee questioned the validity of the assumption that all tests had prognostic value equal to that of pyrosequencing, in the absence of data to support this. The Committee also expressed concerns about the survey of technical failure rates, which it considered to be of limited value because of its small size. The Committee also noted that the ICERs were calculated based on very small differences in quality-adjusted life years (QALYs) between the tests, and therefore any uncertainty around the difference in failure rates would result in a large change in the

resulting ICER. The Committee concluded that the equal prognostic value analysis lacked face validity and its results were not robust. The Committee was therefore unable to judge the cost effectiveness of the tests based on this analysis.

- 6.11 The Committee noted that, for some of the tests (therascreen KRAS Pyro Kit, KRAS StripAssay, cobas KRAS Mutation Test, high-resolution melt analysis, next-generation sequencing), the equal prognostic value analysis was the only economic modelling performed, and that test accuracy and clinical effectiveness were not assessed by the External Assessment Group because data were not available. The Committee concluded that this represented a weaker evidence base than that for the therascreen KRAS RGQ mutation kit, pyrosequencing and MALDI-TOF mass spectrometry.
- 6.12 The Committee noted that the analysis in [NICE technology appraisal guidance 176](#) was primarily based on data from studies that included the therascreen KRAS RGQ PCR kit and the KRAS LightMix kit for KRAS mutation testing. The Committee acknowledged that the recommendation on cetuximab for the first-line treatment of metastatic colorectal cancer in people whose tumours test negative for KRAS mutation implied that these tests are recommended and cost effective as part of the test–treat strategy. In light of this, the Committee concluded that the therascreen KRAS RGQ PCR kit and the KRAS LightMix kit can be considered cost effective for informing first-line treatment in these patients. The Committee also concluded that, for pyrosequencing and MALDI-TOF mass spectrometry, an equivalent evidence base exists (the COIN and Xu et al. (2012) studies) and therefore, these tests could also be considered clinically and cost effective for informing the first-line treatment of metastatic colorectal cancer in people whose tumours test negative for KRAS mutation. The Committee further concluded that the evidence was insufficient to



allow any recommendations to be made on the use of the other KRAS mutation tests (see section 1.2).

- 6.13 The Committee stated that any laboratories testing for KRAS mutation status, either using a CE-marked or a non-CE-marked technique, should comply with an accredited external quality assurance scheme such as those provided by the UK National External Quality Assessment Service (NEQAS) or the European Molecular Genetics Quality Network (EMQN). Furthermore, laboratories should be accredited in the discipline of molecular diagnostics and any test used should be validated.

## 7 Implementation

NICE intends to develop tools, in association with relevant stakeholders, to help organisations put this guidance into practice.

## 8 Related NICE guidance

### Published

- [Colorectal cancer](#). NICE quality standard 20 (2012).
- [Cetuximab, bevacizumab and panitumumab for the treatment of metastatic colorectal cancer after first-line chemotherapy: Cetuximab \(monotherapy or combination chemotherapy\), bevacizumab \(in combination with non-oxaliplatin chemotherapy\) and panitumumab \(monotherapy\) for the treatment of metastatic colorectal cancer after first-line chemotherapy](#). NICE technology appraisal guidance 242 (2012).
- [Colorectal cancer](#). NICE pathway (2011).
- [Colorectal cancer: the diagnosis and management of colorectal cancer](#). NICE clinical guideline 131 (2011).
- [Bevacizumab in combination with oxaliplatin and either fluorouracil plus folinic acid or capecitabine for the treatment of metastatic colorectal cancer](#). NICE technology appraisal guidance 212 (2010).

- [Cetuximab for the first line treatment of metastatic colorectal cancer](#). NICE technology appraisal guidance 176 (2009).
- [Improving outcomes in colorectal cancer](#). Cancer service guidance (2004).

### **Under development**

NICE is developing the following guidance (details available from [the NICE website](#)):

- [Aflibercept for the treatment of metastatic colorectal cancer which has progressed following prior oxaliplatin-based chemotherapy](#). NICE technology appraisal (publication expected October 2013).

## **9 Review**

NICE updates the literature search at least every 3 years to ensure that relevant new evidence is identified. NICE will contact product sponsors and other stakeholders about issues that may affect the value of the diagnostic technology. NICE may review and update the guidance at any time if significant new evidence becomes available.

Professor Adrian Newland  
Chair, Diagnostics Advisory Committee  
October 2013

## **10      Diagnostics Advisory Committee members and NICE project team**

### ***Diagnostics Advisory Committee***

The Diagnostics Advisory Committee is an independent committee consisting of standing members and additional specialist members. A list of the Committee members who participated in this assessment appears below.

#### **Standing Committee members**

##### **Professor Ron Akehurst**

Professor in Health Economics, School of Health and Related Research (ScHARR), University of Sheffield

##### **Dr Trevor Cole**

Consultant Clinical and Cancer Geneticist, Birmingham Women's Hospital

##### **Professor Paul Collinson**

Consultant Chemical Pathologist and Professor of Cardiovascular Biomarkers, St George's Hospital

##### **Dr Sue Crawford**

General Practitioner (GP) Principal, Chillington Health Centre

##### **Professor Erika Denton**

National Clinical Director for Imaging, NHS England, Honorary Professor of Radiology, University of East Anglia and Norfolk and Norwich University Hospital

##### **Dr Steve Edwards**

Head of Health Technology Assessment, BMJ Evidence Centre

##### **David Evans**

Lay member

##### **Dr Simon Fleming**

Consultant in Clinical Biochemistry and Metabolic Medicine, Royal Cornwall Hospital

##### **Professor Chris Hyde**

Professor of Public Health and Clinical Epidemiology, Peninsula Technology Assessment Group (PenTAG)

##### **Professor Noor Kalsheker**

Professor of Clinical Chemistry, University of Nottingham

##### **Dr Mark Kroese**

Vice Chair, Diagnostics Advisory Committee and Consultant in Public Health Medicine, PHG Foundation, Cambridge and UK Genetic Testing Network

**Dr Peter Naylor**

General Practitioner (GP), Chair Wirral Health Commissioning Consortia

**Professor Adrian Newland**

Chair, Diagnostics Advisory Committee

**Dr Richard Nicholas**

Consultant Neurologist; Honorary Senior Lecturer, Heatherwood and Wexham Park Hospitals

**Dr Gail Norbury**

Consultant Clinical Scientist, Guys Hospital

**Dr Diego Ossa**

Director of Market Access Europe, Novartis Molecular Diagnostics

**Mr Stuart Saw**

Director of Finance, North East London and the City PCTs

**Dr Steve Thomas**

Consultant Vascular and Cardiac Radiologist at Sheffield Teaching Hospitals Foundation Trust

**Mr Paul Weinberger**

CEO, DiaSolve Ltd, London

**Mr Christopher Wiltsher**

Lay member

**Specialist Committee members**

**Jennie Bell**

Head of Cancer Genetics Programme, Birmingham Women's NHS Foundation Trust

**Dr Newton ACS Wong**

Consultant histopathologist, Bristol Royal Infirmary

**Dr Phil Chambers**

Genomics Facility Manager, Leeds Institute of Molecular Medicine

**Dr Mark Harrison**

Consultant oncologist, Mount Vernon Cancer Centre

**Kate Lloyd**

Lay Representative

### ***NICE project team***

Each diagnostics assessment is assigned to a team consisting of a Technical Analyst (who acts as the topic lead), a Technical Adviser and a Project Manager.

**Dr Sarah Byron**

Topic Lead

**Dr Pall Jonsson**

Technical Adviser

**Robert Fernley**

Project Manager

## **11 Sources of evidence considered by the Committee**

The diagnostics assessment report was prepared by Kleijnen Systematic Reviews Ltd.

- Westwood ME, van Asselt ADI, Ramaekers BLT et al. KRAS mutation testing in adults with metastatic colorectal cancer: a systematic review and cost-effectiveness analysis. A Diagnostic Assessment Report. Kleijnen Systematic Reviews Ltd, 2013.

### ***Registered stakeholders***

The following organisations accepted the invitation to participate in this assessment as registered stakeholders. They were invited to attend the scoping workshop and to comment on the diagnostics assessment report.

#### **Manufacturers/sponsors:**

- Qiagen Ltd
- Roche Molecular Systems, Inc.
- Randox Laboratories Ltd
- ViennaLab Diagnostics GmbH
- Merck Serono S.A.
- TIB MOLBIOL GmbH

#### **Professional/specialist and patient/carer groups:**

- All Wales Genetics Laboratory
- Association of Coloproctologists of Great Britain & Ireland (ACPGBI)
- Birmingham Women's NHS Foundation Trust
- Bladder & Bowel Foundation
- Bowel Cancer UK
- Bristol Royal Infirmary
- Cheshire & Merseyside Regional Genetics Laboratories

- Department of Health
- European Molecular Genetics Quality Network (EMQN)
- Guy's & St. Thomas NHS Foundation Trust
- Lab21 Ltd.
- Leeds Institute of Molecular Medicine
- Mount Vernon Cancer Centre
- NHS Lothian
- Nottingham University Hospitals NHS Trust
- Oxford BRC/NHS Molecular Diagnostic Centre
- Queen Elizabeth Hospital Birmingham
- Queen's University Belfast
- Royal College of Nursing
- Royal College of Pathologists
- Royal College of Physicians
- Royal Devon and Exeter NHS Foundation Trust
- Sheffield Diagnostic Genetics Service
- St. Mary's Hospital, Central Manchester University Hospitals NHS Foundation Trust
- The Royal Marsden NHS Foundation Trust
- UK NEQAS
- University Hospitals Birmingham NHS Foundation Trust
- Wessex Regional Genetics Laboratory