National Institute for Health and Care Excellence

DIAGNOSTICS ASSESSMENT PROGRAMME

Evidence overview

Fluorouracil plasma monitoring: the My5-FU assay for guiding dose adjustment in patients receiving fluorouracil chemotherapy by continuous infusion

This overview summarises the key issues for the Diagnostics Advisory Committee's consideration. It includes a brief description of the topic, a description of the analytical structure and model, a discussion of the analytical difficulties, and a brief summary of the results. It is not a complete summary of the diagnostics assessment report, and it is assumed that the reader is familiar with that document. This overview contains sections from the scope and the diagnostics assessment report, as well as referring to specific sections of these documents.

1 Background

1.1 Introduction

The My5-FU assay (Saladax Biomedical Inc.) was selected by the Medical Technologies Advisory Committee (MTAC) for the Diagnostics Assessment Programme to develop recommendations on its use in the NHS. No other technologies were identified during the scoping phase.

The purpose of this assessment is to evaluate the clinical and cost effectiveness of the My5-FU assay for the pharmacokinetic dose adjustment of continuous infusion fluorouracil (5-FU) chemotherapy. Provisional recommendations on the use of this technology will be formulated by the Diagnostics Advisory Committee at the Committee meeting on 16 July 2014.

1.2 The Conditions

Continuous infusion 5-FU chemotherapy is commonly used in the treatment of many cancers including colorectal, head and neck, stomach and pancreatic cancer. 5-FU chemotherapy and its role in the care pathway for each of these cancer types are described in more detail in section 1.4.

Colorectal cancer

Colorectal cancer is the fourth most common cancer in the UK with around 40,000 new cases registered each year; this represents 11% of all new cancer cases in women and 14% of all new cancer cases in men (CRUK CancerStats, 2013a). Colorectal cancer accounts for 10% of all cancer deaths; in 2010, there were 15,708 deaths from bowel cancer in the UK (CRUK CancerStats, 2013b). Two-thirds of bowel cancers develop in the colon with the remaining third developing in the rectum. Around half of all people diagnosed with colorectal cancer survive for at least five years after diagnosis (CRUK CancerStats, 2012a).

Head and neck cancer

Head and neck cancer describes a variety of malignant tumours occurring in the head and neck region, mainly in the mouth and throat. Around 16,000 people in the UK are diagnosed with a head and neck cancer each year (NHS Choices, 2012). The average national incidence rates are 3.02 per 100,000 for oral cancer, 3.01 per 100,000 for laryngeal cancer and 0.39 per 100,000 for nasopharyngeal cancer (Oxford Cancer Intelligence Unit, 2010). Five year survival rates vary depending on the type of head and neck cancer; thyroid cancer has an estimated five year survival rate of 87%, whereas the five year survival rate for hypopharyngeal cancer is 26% (Oxford Cancer Intelligence Unit, 2010).

Stomach cancer

Stomach cancer is the ninth most common cancer in males in the UK and the fourteenth most common in females. There were 7,610 new cases of stomach

cancer diagnosed in 2008 (CRUK CancerStats, 2013c). The majority of cases are adenocarcinomas. Around 42% of people will survive for a year after diagnosis, although this falls to around 18% after 5 years (CRUK CancerStats, 2012b).

Pancreatic cancer

Pancreatic cancer is the tenth most common cancer in the UK and the fifth most common cause of death from cancer, accounting for 2.6% of cancer cases and 5% of all cancer deaths; around 8,500 people were diagnosed with pancreatic cancer in the UK in 2010 (CRUK CancerStats, 2013d). Pancreatic cancer has a poor survival rate because of typical late presentation and early metastases. It is estimated that less than a fifth of patients present with potentially curable tumours and the overall five-year survival rate is less than 5% (CRUK CancerStats, 2012c).

1.3 Patient issues and preferences

Fluoropyrimidine-based chemotherapy can be administered either orally (capecitabine tablets) or intravenously (bolus or infusion 5-FU), and a joint treatment decision is made between the clinician and the patient, taking into account the clinical situation and the patient's preference over the mode of administration. Although capecitabine does not require central venous access, the ability to reduce toxicity and improve the efficacy of treatment through monitoring and adjusting the dose of 5-FU administered by infusion may be an important consideration for patients.

1.4 Care pathways

Fluoropyrimidine-based chemotherapy

Fluoropyrimidine-based chemotherapy is used in the treatment of many different cancers. Fluoropyrimidine-based chemotherapy that is given as an infusion or an injection is known as 5-FU. It can be prescribed either as a single agent or in conjunction with other chemotherapy drugs, which is known

as a regimen. A summary of some of the most commonly used 5-FU infusion chemotherapy regimens is given in Table 1.

Table 1: Examples of 5-FU infusion chemotherapy regimens

Regimen	Agents			
de Gramont*	5-FU	Folinic acid		
FOLFIRI*	5-FU	Folinic acid	Irinotecan	
FOLFOXIRI	5-FU	Folinic acid	Oxaliplatin	Irinotecan
FOLFOX*	5-FU	Folinic acid	Oxaliplatin	
ECF	5-FU	Epirubicin	Cisplatin	

*see glossary for further details on the administration of these regimens

Chemotherapy is usually given as a course of treatments over 3-6 months. An average course of chemotherapy typically includes between 4-8 cycles, with each cycle including both the time when the chemotherapy is administered and a break to allow for recovery before the next cycle begins. Continuous infusions of 5-FU last for around 22-48 hours and usually require a patient to have a central venous access device such as a central line or PICC (peripherally inserted central catheter) line. Some patients are able to have their 5-FU infusion via a portable pump which can enable them to go home during treatment.

5-FU is commonly given to people with a confirmed diagnosis of: colorectal cancer, head and neck cancer, stomach cancer, or pancreatic cancer. The care pathways for each disease are summarised below.

Colorectal cancer

The care pathway for people with colorectal cancer is outlined in Colorectal cancer: The diagnosis and management of colorectal cancer (NICE clinical guideline 131 [CG131]).

Treatment for early stage colorectal cancer:

Following tumour resection, adjuvant chemotherapy may be considered for people with high-risk stage II colon cancer, and most people with stage III

colorectal cancer will be advised to have adjuvant therapy. The following regimens are recommended as options for the adjuvant treatment of patients with stage III colon cancer:

- Capecitabine monotherapy
- Oxaliplatin in combination with 5-FU and folinic acid (FOLFOX)

The choice of adjuvant treatment is decided jointly by the patient and their clinician, taking into account contraindications, the side effect profile of the drugs and the method of administration, as well as the clinical condition and preferences of the individual. Although not covered by CG131, neoadjuvant chemoradiation may also be recommended for people who have tumours which are likely to be resectable.

Treatment for advanced colorectal cancer:

The chemotherapy drugs most frequently used in the treatment of advanced colorectal cancer are 5-FU, capecitabine, raltitrexed, irinotecan, and oxaliplatin. NICE CG131 makes the following recommendations on the treatment of metastatic colorectal cancer: “When offering multiple chemotherapy drugs to patients with advanced and metastatic colorectal cancer, consider one of the following sequences of chemotherapy unless they are contraindicated:

- FOLFOX (folinic acid plus fluorouracil plus oxaliplatin) as first-line treatment then single agent irinotecan as second-line treatment or;
- FOLFOX as first-line treatment then FOLFIRI (folinic acid plus fluorouracil plus irinotecan) as second-line treatment or;
- XELOX (capecitabine plus oxaliplatin) as first-line treatment then FOLFIRI (folinic acid plus fluorouracil plus irinotecan) as second-line treatment.”

Raltitrexed may be considered as an alternative for patients who are intolerant to 5-FU and folinic acid or for whom these drugs are not suitable, for example patients who develop cardiotoxicity.

Oral therapy with fluoropyrimidines is recommended as an option for first line treatment of metastatic colorectal cancer. NICE technology appraisal 61 (TA61) recommends both capecitabine and tegafur with uracil, as alternatives to intravenous 5-FU. When making a choice between oral and intravenous fluoropyrimidines clinicians should take into account contraindications and side effect profiles, the clinical condition and patient preferences. NICE Technology Appraisal 176 (TA176) also recommends cetuximab in combination with FOLFOX or FOLFIRI chemotherapy for the first line treatment of metastatic colorectal cancer in people with KRAS wild-type tumours in whom:

- The primary 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.

Head and neck cancer

Localised head and neck cancers which have not spread to nearby lymph nodes are usually treated with surgery or radiotherapy, whilst cancers which are locally advanced and have spread to nearby lymph nodes are usually treated with chemotherapy and/or radiotherapy. Chemotherapy drugs which may be used to treat head and neck cancers include carboplatin, docetaxel, gemcitabine and 5-FU. The chemotherapy drugs prescribed vary depending on the location of the cancer:

- Nasal and sinus cancer: cisplatin, 5-FU, carboplatin, docetaxel, paclitaxel and gemcitabine.
- Nasopharyngeal cancer: cisplatin, 5-FU, docetaxel, paclitaxel and gemcitabine.
- Mouth and oropharyngeal cancer: cisplatin, 5-FU, carboplatin, bleomycin, methotrexate and docetaxel.

- Laryngeal cancer: cisplatin, 5-FU, carboplatin, taxol, capecitabine, and gemcitabine.
- Oesophageal cancer: epirubicin, 5-FU, capecitabine, cisplatin, oxaliplatin, taxol, irinotecan and vinorelbine.
- Salivary gland cancer: cisplatin, carboplatin, cyclophosphamide, doxorubicin, methotrexate and paclitaxel.

For people in whom platinum-based chemotherapy is contraindicated, NICE Technology Appraisal 145 (TA 145) Cetuximab for the treatment of locally advanced squamous cell cancer of the head and neck (2008) makes the following recommendation: “Cetuximab in combination with radiotherapy is recommended as a treatment option only for patients with locally advanced squamous cell cancer of the head and neck whose Karnofsky performance status score is 90% or greater and for whom all forms of platinum-based chemotherapy treatment are contraindicated”.

Stomach cancer

Treatment for early stage stomach cancer:

Early stage stomach cancer is usually treated with surgery, with neo-adjuvant or adjuvant chemotherapy being offered where appropriate. Chemotherapy drugs used in the treatment of stomach cancer include cisplatin, epirubicin and 5-FU.

Treatment for advanced stomach cancer:

Advanced stomach cancer is treated with chemotherapy. NICE Technology Appraisal 191 (TA191) capecitabine for the treatment of advanced gastric cancer (2010) recommends capecitabine in conjunction with a platinum-based regimen for the treatment of inoperable advanced gastric cancer. Capecitabine and platinum based regimens include epirubicin, cisplatin and capecitabine (ECX), epirubicin, oxaliplatin and capecitabine (EOX) and capecitabine and cisplatin (CX). 5-FU remains an alternative for people in

whom capecitabine is contraindicated or otherwise unsuitable. This may include patients who are unable to tolerate oral administration, because of difficulty swallowing or nausea. NICE Technology Appraisal 208 (TA208) HER2 positive gastric cancer trastuzumab (2010) recommends trastuzumab in combination with cisplatin and capecitabine or 5-FU as an option for the treatment of HER2 positive metastatic adenocarcinoma of the stomach or gastro-oesophageal junction in people who have not received prior treatment for their metastatic disease and have tumours expressing high levels of HER2.

Pancreatic cancer

Chemotherapy drugs that may be used to treat pancreatic cancer are 5-FU, capecitabine, and gemcitabine. If surgery is possible, adjuvant treatment with 5-FU can reduce the risk of recurrence; gemcitabine can also be used as it has a lower side effect profile than 5-FU.

NICE Technology Appraisal 25 (TA 25) Guidance in the use of gemcitabine for the treatment of pancreatic cancer (2001) recommends that gemcitabine may be considered as a treatment option for patients with advanced or metastatic adenocarcinoma of the pancreas and a Karnofsky performance score of 50 or more, where first line chemotherapy is to be used. Gemcitabine is not recommended for patients who are suitable for potentially curative surgery, or patients with a Karnofsky performance score of less than 50. The guidance also states that there was insufficient evidence to support the use of gemcitabine as a second line treatment in patients with pancreatic adenocarcinoma.

1.5 The population

The population covered in this assessment is people receiving 5-FU chemotherapy by continuous infusion. Where evidence permits, this will include people with colorectal cancer, head and neck cancer, stomach cancer or pancreatic cancer.

2 The technologies

2.1 My5-FU

The My5-FU assay (previously known as OnDose) is a CE-marked in vitro diagnostic test designed to measure the levels of fluorouracil (5-FU) chemotherapy in plasma samples. The assay is intended for use in patients who are receiving 5-FU chemotherapy by continuous infusion, to facilitate pharmacokinetic dose adjustment and therapeutic drug monitoring with the aim of achieving an optimal plasma level of the drug. 5-FU is amenable to therapeutic drug monitoring because it has a narrow therapeutic index, that is doses below the therapeutic window potentially reduce treatment efficacy and doses above the window are more likely to cause side effects and toxicity. Commonly reported side effects of 5-FU chemotherapy include diarrhoea, oral and gastrointestinal mucositis, anaemia, fatigue, nausea and vomiting and palmar-plantar erythrodysesthesia (hand-foot syndrome), all of which when severe can indicate the need to limit the dose. The consequences of 5-FU toxicity can include neuropathy (damage to nerve cells), severe damage to organs, cardiotoxicity, neutropenia, sepsis and septic shock (Hale et al, 2002). In addition, people with dihydropyrimidine dehydrogenase deficiency (DPD deficiency) have a reduced ability to metabolise 5-FU and can develop serious toxicity following treatment with 5-FU.

My5-FU is a homogenous two-reagent nanoparticle agglutination assay that can be adapted for use on a range of clinical chemistry analysers. It is based upon the measurement of changes in scattered light which is dependent on the level of agglutination of nanoparticles; agglutination is partially inhibited when 5-FU is present in the sample and results in less scattering of light. The assay requires a peripheral venous blood sample (not from the infusion port) which is taken towards the end of each 5-FU infusion cycle using an EDTA or heparin tube. Turnaround time is dependent on the analyser used but is

around 10–15 minutes to the first result, with subsequent results following in less than a minute.

Results are reported in nanograms 5-FU/millilitre and are converted to an area under the concentration curve (AUC) value in the laboratory, by multiplying the concentration of 5-FU in a steady state by the time of the infusion (in hours). This is then compared with a pre-defined optimal therapeutic range and the results, reported as mg*h/L (milligram hours per litre), are used to guide the dose of 5-FU given in subsequent chemotherapy cycles. It is advised that AUC values of greater than 50 mg*h/L (milligram hours per litre) should be disregarded as this may signify that the blood sample has been taken too close to the infusion port. The assay has a limit of detection of 52 nanograms/millilitre and a lower limit of quantitation of 85 nanograms/millilitre. The My5-FU assay has been validated against liquid chromatography mass spectrometry (Beumer et al, 2009) and high performance liquid chromatography, laboratory techniques commonly used in pharmacokinetic studies.

When using the My5-FU assay in clinical practice, the initial dose of 5-FU is calculated according to the patient's body surface area and a sample of the patient's blood is taken towards the end of the infusion cycle, at least 18 hours after the start of the infusion. For example, during a 46 hour infusion it is recommended that a blood sample is taken 24 hours after the start of the infusion (with a sample collection window between hours 18 and 44), whilst the pump is infusing at a steady rate. Blood samples may be taken in the patient's home by a district nurse or in the oncology outpatient clinic, depending on local arrangements. The sample is stabilised and then sent to the hospital laboratory for analysis, with the results made available to clinicians in advance of the next chemotherapy cycle. Subsequent doses of 5-FU are then calculated using the AUC result from the My5-FU assay, in accordance with a pre-determined dose adjustment algorithm. A published dose adjustment algorithm for patients with colorectal cancer treated with

FOLFOX (Kaldate et al, 2012) recommends an optimal therapeutic range of 20–30 mg*h/L with adjustments of no more than 30% of the dose for each infusion (see table 2). Patients typically require 3–4 adjustments to reach an optimal therapeutic range. Once the optimal range is achieved, or if the patient's 5-FU plasma level is already within the optimal range, the dose is maintained and plasma levels are retested at every 6th infusion cycle to ensure sustained optimal drug levels.

Table 2: 5-FU dose adjustment algorithm for colorectal cancer patients

AUC from previous cycle (mg·h/L)	Change in Dose (mg/m^2)
≥40	↓ 30%
37-39	↓ 25%
34-36	↓ 20%
31-33	↓ 10%
20-30	NO CHANGE NEEDED
17-19	↑ 10%
14-16	↑ 20%
8-13	↑ 25%
<8	Repeat previous dose, to eliminate chance of test error If AUC of <8 is repeated, then increase dose by ↑ 30%

Source: Kaldate et al. (2012)

2.2 The comparator

The comparator used in this assessment is body surface area dose adjustment. Current NHS practice for calculating the dose of 5-FU a patient will receive is body surface area dosing. Body surface area is calculated by formulae which use the patient's height and weight (see Appendix B), and is said to correlate with blood volume, cardiac output and renal function, all of which influence drug elimination (Drug and Therapeutics Bulletin, 2010).

Usually the dose is calculated in accordance with the patient's actual bodyweight unless obesity, oedema or some other form of abnormal fluid retention such as ascites is present. In this case, ideal weight is used as the basis for the calculation (Drug and Therapeutics Bulletin, 2010). The dose may be adjusted to take into account a patient's liver and kidney function, both of which may impact upon how 5-FU is metabolised and excreted. A 5-FU dose may also be adjusted according to the severity of any side effects that a patient experiences.

For the purposes of assessing the accuracy of the My5-FU assay for measuring 5-FU plasma levels, high performance liquid chromatography and liquid chromatography mass spectrometry were considered to be the reference standard.

3 The evidence

This section summarises data from the diagnostics assessment report compiled by the External Assessment Group (EAG).

3.1 Clinical Effectiveness

The EAG conducted a systematic review of the evidence on the clinical effectiveness of 5-FU plasma monitoring to guide pharmacokinetic dose adjustment in patients receiving 5-FU chemotherapy by continuous infusion. Details of the systematic review can be found starting on page 55 of the diagnostics assessment report. Studies were included if they appeared to contain data on the following:

- Accuracy of the My5-FU assay compared with the reference standards (high performance liquid chromatography or liquid chromatography-mass spectrometry);
- Dose adjustment algorithms based on 5-FU plasma measurements;

- Pharmacokinetic dose adjustment of continuous infusion 5-FU using the My5-FU assay, high-performance liquid chromatography or liquid chromatography mass spectrometry;
- Body surface area dosing of continuous infusion 5-FU.

All included studies were appraised using either a QUADAS2 checklist which was adapted for the review, or the Downs and Black (1998) checklist. In summary, the EAG included the following:

- Three published studies and validation data from the manufacturer which compared the accuracy of the My5-FU assay with high-performance liquid chromatography or liquid chromatography-mass spectrometry;
- Twenty four single arm studies of pharmacokinetic dose adjustment or body surface area dosing in patients receiving continuous infusion 5-FU;
- Five comparative studies of pharmacokinetic dose adjustment and body surface area dosing in patients receiving continuous infusion 5-FU;
- One systematic review (containing seven relevant studies) and one randomised controlled trial containing information on 5-FU continuous infusion regimens administered using body surface area dosing.

Accuracy of the My5-FU assay compared with high performance liquid chromatography or liquid chromatography mass-spectrometry

Three studies which compared the accuracy of the My5-FU assay with that of liquid chromatography-mass spectrometry were identified from the systematic review. Unpublished validation data provided by the manufacturer were also included. These compared the accuracy of the My5-FU assay with the accuracy of both liquid chromatography mass-spectrometry and high performance liquid chromatography.

My5-FU compared with liquid chromatography-mass spectrometry:

One study, Buchel et al (2013), reported results of 197 plasma samples from 32 patients with gastrointestinal cancer which were supplemented by 50

plasma samples provided by the manufacturer. The characteristics or the number of patients who provided the supplementary samples were not reported and the EAG noted a high risk of bias for patient selection. This study compared the accuracy of the My5-FU assay (run on a Cobas Integra 800 analyser [Roche]) with that of liquid chromatography mass-spectrometry. The study reported a strong correlation between My5-FU and liquid chromatography mass-spectrometry (R^2 = 0.99) with a trend towards higher measurements with My5-FU. In addition, the Bland-Altman plot showed a 7% bias (95%CI 5.5 to 8.5%) indicating that measurements using the My5-FU assay may be higher than those obtained using liquid chromatography-mass spectrometry; upper and lower limits of agreement were around -18% to +30% suggesting that the results of the My5-FU assay may underestimate or overestimate 5-FU plasma measurements by 18% and 30% respectively. The Bland and Altman plot from this study can be found on page 69 of the diagnostics assessment report. The EAG noted that the 5-FU plasma levels reported in the study were substantially greater than the levels that would be reported in current practice.

A second study, Beumer et al (2009), reported results of 156 plasma samples provided by patients with head and neck and colorectal cancer. The EAG noted that there was a high risk of bias for patient selection. This study compared the accuracy of the My5-FU assay (run on an AU400 analyser) [Olympus]) with liquid chromatography-mass spectrometry. The study reported a strong correlation between the results of the My5-FU assay and liquid chromatography-mass spectrometry (R^2 = 0.97) and a trend towards higher measurements when using the My5-FU assay. The confidence intervals, mean bias and limits of agreements were not reported and therefore, the significance of these findings are not known.

A third study, Makihara et al (2012), was reported as an abstract only, and therefore, provided limited data. This study compared the accuracy of the My5-FU assay with that of liquid chromatography-mass spectrometry, using

plasma samples from 50 patients with colorectal cancer. The study reported a strong agreement between My5-FU and liquid chromatography mass-spectrometry (R^2 = 0.8471) but the R^2 was lower than that reported in the two other included studies.

Validation data supplied by the manufacturer reported a comparison of the accuracy between the My5-FU assay run on an AU400 analyser (Olympus) and that of liquid chromatography-mass spectrometry. Details on patient selection and methods were not available and the EAG noted that risk of bias and applicability concerns were unclear. The validation data reports the results of 75 samples, although the EAG noted that the methods section describes 56 samples. The characteristics of patients from whom the samples were obtained were not reported. The results show a Deming regression gradient of 1.005 (95%CI 0.94 to 1.07), suggesting that there is no significant difference between the methods. However, the EAG determined that the reported Bland-Altman plots showed a mean bias of +24.5ng/mL with outliers ranging from -285ng/mL to +171ng/mL (approximately -25% to +70%).

My5-FU compared with high performance liquid chromatography:

No published studies were found which compared the accuracy of My5-FU with that of high performance liquid chromatography. Validation data supplied by the manufacturer reported a comparison between the accuracy of the My5-FU assay (run on an AU400 analyser [Olympus]) and that of high performance liquid chromatography. The validation data showed a mean bias of +1.84ng/mL with outliers ranging from -80ng/mL to +137 ng/mL (approximately -30% to +35%).

Dose adjustment algorithms based on 5-FU plasma measurements

Four studies which reported the development of dose adjustment algorithms based on 5-FU plasma measurements were identified from the systematic review. Of the four studies, three reported algorithms for patients with colorectal cancer and one reported an algorithm for patients with head and

neck cancer. Each algorithm was developed for a different chemotherapy regimen.

Dose adjustment algorithms for patients with colorectal cancer:

One study, Gamelin et al (1996), reported a dose adjustment algorithm that was developed using 5-FU plasma measurements (measured with high performance liquid chromatography) from a case series of 40 patients with advanced colorectal cancer who were receiving an 8 hour infusion of 5-FU plus folinic acid (8hr 5-FU+FA). The dose of 5-FU administered to the patients increased in increments of 250mg/m^2 every 3 to 4 weeks until a maximum dose of 2000mg/m^2 was reached or toxicity was experienced. The algorithm was then developed using a regression analysis of the relationship between dose and plasma levels in patients who had a complete or partial response compared to patients who had a minimal response, stable disease or progressive disease. The algorithm established that patients with a 5-FU plasma concentration of 2000-3000µg/L (or AUC of 16 to 24 milligram hours per litre) do not require a dose adjustment (see page 72 in the diagnostics assessment report for more details).

A second study, Kaldate et al (2012), reported a dose adjustment algorithm developed using a retrospective analysis of pharmacokinetic data obtained from the database of a commercial laboratory. The algorithm was developed for use with a FOLFOX6 regimen either with or without bevacizumab. Data were analysed from 187 patients with advanced or metastatic colorectal cancer who had 5-FU plasma measurements (measured with My5-FU) recorded from two consecutive infusion cycles which included a dose adjustment: this resulted in 307 paired observations. Regression analysis was used to model the change in area under the concentration curve recorded for the 5-FU plasma measurements compared to the recorded dose adjustments. The resulting dose adjustment algorithm is based upon area under the concentration curve measurements (reported as mg*h/L) and established that patients with a 5-FU plasma concentration of 20-30mg*h/L do not require a

dose adjustment (see page 73 in the diagnostics assessment report for more details).

A third study, Ychou et al (1999), reported a dose adjustment algorithm developed in a prospective cohort study of 38 patients with advanced colorectal cancer receiving treatment with 5-FU+FA using a de Gramont regimen with a 22 hour 5-FU infusion. Consecutive participants were placed into one of two groups (A or B). Group A received a progressive increase of 5-FU of between 25-50% each cycle, resulting in a maximum increase of 150% by cycle 6 in the absence of grade 3 or worse toxicities. 5-FU plasma levels were measured using high performance liquid chromatography. Data from group A were used to develop a dose adjustment algorithm which was used to treat group B. Group B then received a dose increase at cycle 2, depending on the 5-FU plasma measurement recorded during cycle 1 and the absence of grade 3 or worse toxicities. The algorithm established that patients with an AUC value of greater than 20mg*h/L*m^2 did not require a dose increase (see page 74 of the diagnostics assessment report for more details).

Dose adjustment algorithm for patients with head and neck cancer

One study, Santini et al (1989), reported a dose adjustment algorithm developed from a retrospective analysis of 89 patients receiving treatment with a 5 day infusion of 5-FU plus cisplatin. Plasma 5-FU was measured on day 3 and the results were used to establish a threshold AUC value that is predictive of toxicity. An AUC threshold for day 3 was established as 15,000 ng/mL*h, and was validated in a prospective study of 81 patients where it was determined whether dose reduction would be needed in the second half of the 5 day cycle. The results of the prospective study indicated that a dose reduction would be needed for patients with an AUC of 15,000 – 30,000 ng/mL*h on day 3, and treatment should be stopped in patients with an AUC of greater than 30,000 ng/mL*h (see pages 74 and 75 of the diagnostics assessment report for further details).

Pharmacokinetic dose adjustment of continuous infusion 5-FU compared with body surface area dosing

The systematic review identified 24 single arm studies, 11 of which reported dose adjustment of continuous infusion 5-FU using My5-FU, high performance liquid chromatography or liquid chromatography-mass spectrometry and 13 reported body surface area dosing only. These studies were reported in a narrative synthesis; 18 included patients with colorectal cancer, three included patients with head and neck cancer, one included patients with gastric cancer and two included a mixed population. No evidence was found which was specific to patients with pancreatic cancer. Four of the 11 pharmacokinetic dose adjustment studies described dose adjustment using My-5FU, with the remainder predominantly reporting dose adjustment using high performance liquid chromatography (see pages 76 – 88 in the diagnostics assessment report for further details).

The 24 single arm studies were of poor quality; they only included small sample sizes and were likely to be subject to selection bias. The data reported in the single arm studies showed a general trend that higher levels of plasma 5-FU (in range of 5-FU infusion chemotherapy regimens) are related to improved treatment response, progression free survival and overall survival. However, the reported treatment response rates showed wide variation and median overall survival estimates were heterogeneous. Also, the positive relationship between increased exposure to 5-FU and outcomes was stronger for adverse events and toxicity than for treatment response and survival. Two of these single arm studies (Capitain et al [2008] and Gamelin et al [1998]) reported Kaplan Meier curves for survival which were used to inform both the pharmacokinetic dose adjustment effect estimates and the cost effectiveness analysis, and are reported in more detail below.

In addition to the 24 single arm studies, the EAG identified three comparative studies which included patients with colorectal cancer (Gamelin et al [2008], Capitain et al [2012] and Kline et al [2013]), and two comparative studies

which included patients with head and neck cancer (Fety et al [1998] and Santini et al [1989]). All three comparative colorectal cancer studies were used to inform the effect estimates and the cost effectiveness analysis, and are reported in more detail below. Neither of the head and neck cancer studies reported progression free survival data, but data on toxicity were extracted from Fety et al (1998) and included in the exploratory cost effectiveness analysis of head and neck cancer (see below).

Colorectal cancer clinical outcome data:

The EAG identified five studies that provided data on the following clinical outcomes: progression free survival, overall survival, treatment response rates, toxicity and side effects, and incidences of over and under-dosing. Insufficient data were available for the subgroups included in the scope; people with DPD deficiency, people with impaired renal function, people with impaired liver function, people whose body surface area is outside the standard range for dosing 5-FU and people with a less favourable performance status.

One study, Capitain et al (2008), reported results from a case series of 76 patients (median age 71 years) with advanced colorectal cancer. The study included two regimens, FUFOL with a weekly 4 hour 5-FU infusion and modified de Gramont, and pharmacokinetic dose adjustment was performed using high performance liquid chromatography with the dose adjustment algorithm reported in Gamelin et al (1996) (see above). The median length of follow up was 3.5 years. The EAG noted that patient selection methods were not reported which may limit the generalisability of the findings (see pages 92-96 in the diagnostics assessment report for further details).

A second study, Gamelin et al (1998), reported results from a prospective case series of 152 patients (mean age 62 years) from nine centres with metastatic colorectal cancer. The study used a weekly 5FU+FA regimen and pharmacokinetic dose adjustment was performed using liquid chromatography

with the dose adjustment algorithm reported in Gamelin et al (1996) (see above). The median length of follow up was 3 years. The EAG noted several concerns with the study design which limit the generalisability of the findings including the use of an obsolete 8 hour 5FU+FA regimen, an apparent error in the reported progression free survival estimates and not using an intention to treat analysis (see pages 92 to 96 in the diagnostics assessment report for further details).

A third study, Gamelin et al (2008), reported results from a phase 3 randomised controlled trial conducted in 5 centres in France which included 208 patients. All patients were receiving 5-FU+FA chemotherapy for colorectal cancer (stage not specified) and were randomised to 2 arms. One hundred and four patients (mean age 71.5) received pharmacokinetic dose adjustment with high performance liquid chromatograpy and an adjustment algorithm with a target AUC of 20-24 (adapted from Gamelin et al 1996) and 104 patients (mean age 71.2) received body surface area dosing. The median follow up was three years. The EAG noted several concerns with study design which limit the generalisability of the findings including the use of an obsolete 8 hour 5FU+FA regimen, providing insufficient details on randomisation and allocation concealment and not reporting progression free survival data estimates.

A fourth study Capitain et al (2012), reported results from a retrospective proof of concept study which included 157 patients receiving FOLFOX 6 chemotherapy for colorectal cancer (stage not specified). The study included 2 groups: 118 patients (median age 65) drawn from 8 centres received pharmacokinetic dose adjustment by high performance liquid chromatography using a commercially available algorithm (which is likely to have included additional parameters in conjunction with 5-FU plasma levels), and 39 patients (median age 63) drawn from 2 further centres who received body surface area dosing. The median follow up was 3.9 years for patients in the pharmacokinetic dose adjustment group, and was not specified for the body

surface area dosing group. The EAG noted several concerns with the study design which limit the generalisibility of the findings including incomplete reporting of patient selection methods, a non-randomised design including historical controls and limiting results to median survival only for the control arm.

A fifth study, Kline et al (2013), reported results from a retrospective analysis of stage 2/3 and stage 4 colorectal cancer patients receiving either FOLFOX6 or FOLFIRI chemotherapy. Patients selected whether they wished to receive pharmacokinetic dose adjustment (n=38) or body surface area dosing (n=46). Median follow up was 17 months for stage 4 pharmacokinetic dose adjustment patients, 14 months for stage 4 body surface area dosing patients, 16 months for stage 2/3 pharmacokinetic dose adjustment patients and 23 months for stage 2/3 body surface are dosing patients. My5-FU was used to measure 5-FU plasma levels. The EAG noted several concerns with the study design, mainly relating to patients being able to choose whether they received pharmacokinetic dose adjustment which increases the risk of allocation bias and limits the generalisability of the results.

To assess whether the results reported in the body surface area dosing arms of Gamelin et al (2008) and Capitain et al (2012) were generalisable, the EAG compared survival estimates with data extracted from seven body surface area dosing studies included in the NICE CG131 systematic review, supplemented with data from the COIN study (Adams et al, 2012). The EAG concluded that the survival estimates for body surface area dosing reported in Gamelin et al (2008) and Capitain et al (2102) were sufficiently similar to the published literature to suggest that their pharmacokinetic dose adjustment comparison was not biased by non-representative control arms.

Progression free survival

All five studies reported data on progression free survival and where possible the EAG used the reported data to reconstruct Kaplan Meier survival curves.

In the two single arm pharmacokinetic dose adjustment studies, data from Capitain et al (2008) reported a median progression free survival of 3.3 months whilst data from Gamelin et al (1998) suggested a median progression free survival of 11 months. The EAG were able to reconstruct a Kaplan Meier curve for Gamelin et al (1998).

The EAG estimated Weibull and lognormal progression free survival curves for Gamelin et al (2008) using mean duration of response data reported for both arms which, using two scenarios, appeared to show a mean time to progression of either 7.5 or 14.28 months for pharmacokinetic dose adjustment, and of either 6.0 or 12.48 months for body surface area dosing. Capitain et al (2012) reported a median progression free survival of 16 months for pharmacokinetic dose adjustment and 10 months for body surface area dosing. The EAG reconstructed a Kaplan Meier curve for the pharmacokinetic dose adjustment arm and median survival was 16 months (95%CI 12 to 20 months). As no Kaplan-Meier curves were presented for body surface area dosing, the EAG estimated a survival curve for body surface area dosing using the median survival estimate and a Weibull distribution which assumed a proportional hazard of 0.4817 between pharmacokinetic dose adjustment and body surface area dosing. Kline et al (2013) reported Kaplan-Meier curves for both stage 2/3 patients and stage 4 patients and the EAG used a log rank test to determine equivalence between the pharmacokinetic dose adjustment and body surface area dosing; for stage 4 patients median progression free survival was 14 months for pharmacokinetic dose adjustment and 10 months for body surface area dosing (P=0.16), for stage 3 patients the log rank test result was p=0.0429 which the EAG determined suggested delayed progression in the pharmacokinetic dose adjustment group.

The EAG were unable to pool results for progression free survival because of heterogeneity in the data reported for this outcome, which comprised response rates in Gamelin et al (2008), median estimates only in Capitain et

al (2008) and estimates from a mixed treatment group (FOLFOX and FOLFIRI) in Kline et al (2013).

Overall survival

Four studies reported data on overall survival and where possible the EAG used the reported data to reconstruct Kaplan Meier survival curves. In the two single-arm pharmacokinetic dose adjustment studies the EAG were able to reconstruct Kaplan Meier plots for Capitain et al (2008) which estimated a median overall survival of 20 months, and also for Gamelin et al (1998) which estimated a median overall survival of 19 months.

Gamelin et al (2008) reported a median overall survival of 22 months for pharmacokinetic dose adjustment and 16 months for body surface area dosing (p=0.18) and the EAG were able to reconstruct Kaplan Meier plots. The EAG estimated a hazard ratio of 0.82618 (95%CI 0.6198087 to 1.101265) between pharmacokinetic dose adjustment and body surface area dosing using Cox proportional hazards regression and a hazard ratio of 0.829255 using a Weibull model assuming proportional hazards. Capitain et al (2012) reported median overall survival of 28 months for pharmacokinetic dose adjustment and 22 months for body surface area dosing. The EAG were able to reconstruct a Kaplan Meier plot for pharmacokinetic dose adjustment and used a Weibull distribution which assumed proportional hazards to estimate a hazard ratio of 0.586 between pharmacokinetic dose adjustment and body surface area dosing to construct a survival curve for body surface area dosing.

The EAG combined reconstructed Kaplan Meier plots from single arms of the studies which reported overall survival with reconstructed Kaplan Meier plots from body surface area dosing studies included in the NICE CG131 systematic review, and from the COIN study (Adams et al, 2011), to compare pharmacokinetic adjusted dosing with body surface area dosing. Pooled data from studies reporting 5FU+FA regimens resulted in an estimated median

overall survival of 19.6 months (95%CI 17.0 to 21.0; three studies) for pharmacokinetic dose adjustment and 14.6 months (95%CI 14.1 to 15.3; five studies) for body surface area dosing. Pooled data from studies reporting FOLFOX6 regimens resulted in an estimated median overall survival of 27.4 months (95%CI 23.2 to 38.8; one study) for pharmacokinetic dose adjustment and 20.6 months (95%CI 18.4 to 22.9; three studies) for body surface area dosing, (see page 211 in the diagnostics assessment report for further details).

Treatment response rates

Four studies reported data on treatment response rates. Of the single arm pharmacokinetic dose adjustment studies Capitain et al (2008) reported an objective response rate of 32.9%, with 6.6% of patients reported as having complete responses, and Gamelin et al (1998) reported that the overall response rate in patients with measureable disease was 56.4% of whom 15.4% had complete response.

Gamelin et al (2008) used response rates as the primary outcome measure and provided sufficient data for the EAG to calculate relative risks for response types. From their analysis the EAG concluded that although a greater number of patients who received pharmacokinetic dose adjustment achieved complete response and partial response compared to those who received body surface area dosing the differences did not appear to be significant; complete response RR 6.00 (0.74 to 48.97) and partial response RR 1.71 (1.00 to 2.91). Capitain et al (2012) reported response rates at 3 months for both pharmacokinetic dose adjustment and body surface area dosing and at 6 months for pharmacokinetic dose adjustment only. The EAG were able to calculate relative risks for the 3 month data which appeared to favour the pharmacokinetic dose adjustment for both partial (RR 1.56 95%CI 1.07 to 2.27) and overall response (RR 1.52 95%CI 1.06 to 2.18).

Toxicity and side effects

All five studies reported data on toxicity and side effects. Of the single arm pharmacokinetic dose adjustment studies Capitain et al (2008) reported that the most commonly experienced toxicities were diarrhoea (22%), hand-foot syndrome (18%) and mucositis (7.5%) whilst Gamelin et al (1998) reported that majority of side effects observed were diarrhoea (39%) and hand-foot syndrome.

Gamelin et al (2008) reported the percentage of patients who experienced a number of side effects; each reported side effect was categorised according to severity using four WHO grades. The EAG used these data to calculate the relative risk of side effects between the pharmacokinetic dose adjustment arm and the body surface area dosing arm and concluded that the risk of diarrhoea and possibly leukopenia was reduced in pharmacokinetic dose adjustment, whilst the risk of hand and foot syndrome and conjunctivitis was raised. Capitain et al (2012) reported the number of patients who experienced grade 3 or 4 diarrhoea, mucositis, thrombocytopenia or neutropenia (described as categorised according to the “Cancer Institute’s Common Terminology Criteria Scale”). The EAG used these data to calculate the relative risk of each side effect between the pharmacokinetic dose adjustment and body surface area dosing arms and concluded that this analysis appeared to show that the risk of diarrhoea and mucositis may be reduced for pharmacokinetic dose adjustment. Kline et al (2013) reported the number of patients who experienced side effects that were either categorised as grade 3 according to the Cancer Institute’s common cancer terminology scale or necessitated dose adjustment. The EAG concluded that these data appeared to show that grade 3 toxicity occurred equally in 37% of patients with stage 4 disease, whilst in patients with stage 2/3 disease grade 3 toxicity was more common for body surface area dosing than for pharmacokinetic dose adjustment (69% versus 32%; p=0.0437). The EAG also concluded that the

number of treatment doses given before toxicity occurred was greater for pharmacokinetic dose adjustment.

Incidence of over- and under-dosing and proportion of 5-FU plasma levels in target range

Four of the included studies reported data on 5-FU plasma levels. Of the two single arm pharmacokinetic dose adjustment studies Gamelin et al (1998) reported that only 4% of patients had 5-FU plasma levels in the target range after one cycle, whilst under-dosing occurred in 82% of patients and over-dosing in 9% of patients. The target range was achieved in 94.1% of patients after dose adjustment.

Gamelin et al (2008) reported that target 5-FU plasma levels were reached in 94% of patients who received pharmacokinetic dose adjustment after a mean of 4 treatment cycles, and noted that the dose received when in target range varied greatly. In addition, 49 patients who received body surface area dosing had their 5-FU plasma levels measured, 4 of whom were in the target range. Capitain et al (2012) reported that at 3 months 91% of patients receiving pharmacokinetic dose adjustment were receiving an adjusted dose. Additionally, around two thirds of patients who received pharmacokinetic dose adjustment had their starting dose increased and about 20% had their starting dose decreased. Kline et al (2013) reported the distribution of doses at each successive cycle; the median dose remained the same for pharmacokinetic dose adjustment and body surface area dosing but around 25-30% of patients with stage 4 disease who received pharmacokinetic dose adjustment had their dose increased by cycles 3 and 4, and some patients received dose reductions.

Head and neck cancer clinical outcome data:

Fety et al (1998) reported a randomised prospective study which included 122 patients with advanced head and neck cancer treated with cisplatin and a 96 hour 5-FU infusion. The study used high performance liquid chromatography

to measure plasma 5-FU. The EAG noted that the reported results did not correspond with the study's methods and were unable to assess the study's internal validity. The EAG also noted that 4 patients in the body surface area dosing arm and 12 patients in the pharmacokinetic dose adjustment arm were not included in the analysis of toxicity. The study reported that grade 2 and 4 neutropenia and thrombopenia were reduced in the pharmacokinetic dose adjustment arm (7.6% versus 17.5%, p=0.013) and that grade 2 and 4 mucositis was only reported in the body surface area dosing arm (5.1%)

3.2 Costs and cost effectiveness

The EAG conducted a search to identify existing studies investigating the cost effectiveness of pharmacokinetic dose adjustment of 5-FU compared with body surface area dosing. The EAG also constructed a de novo economic model to assess the cost effectiveness of the My-5FU assay in patients receiving continuous infusion 5-FU chemotherapy for metastatic colorectal cancer, and undertook an exploratory cost effectiveness analysis for patients with advanced head and neck cancer.

Systematic review of cost effectiveness evidence

The EAG conducted a search for studies reporting the cost effectiveness of pharmacokinetic dose adjustment of continuous infusion 5-FU compared with body surface area dosing, using the search strategies developed for the clinical effectiveness review. The search identified an abstract (Becker et al, 2013) which reported the results of a cost utility analysis of My5-FU compared with body surface area dosing in patients with metastatic colorectal cancer in the UK. The abstract reported ICERs per QALY gained for the following regimens: 5-FU+FA (£28,862), FOLFOX4 (£3467), FOLFOX6 (£3594), FOLFIRI (£23,428), FOLFOX6 + bevacizumab (£3508) and FOLFIRI + bevacizumab (£21,874). The EAG received a copy of the model which is considered to be academic in confidence at this time (for further details see pages 149-152 in the diagnostics assessment report).

Additional cost searches were also conducted for quality of life estimates, resource use estimates and adverse events associated with chemotherapy (see pages 143 -157 in the diagnostics assessment report for further details).

Metastatic colorectal cancer economic analysis

The EAG developed a de novo economic model designed to assess the cost effectiveness of using the My5-FU assay for the pharmacokinetic dose adjustment of continuous infusion 5-FU chemotherapy in people with metastatic colorectal cancer.

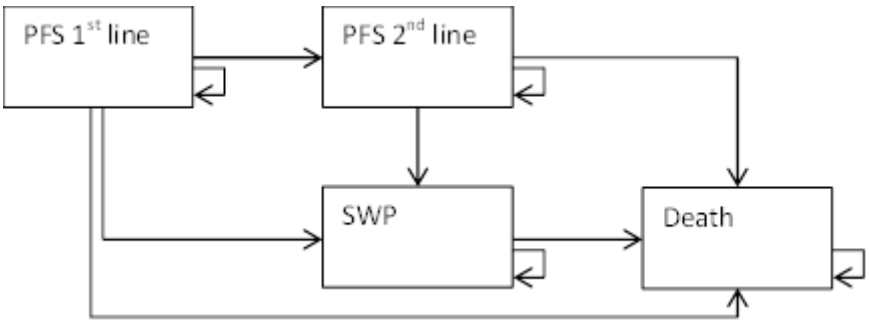
Model structure

The model was based upon a cohort distributed between four health states over a twenty year time horizon. The following health states were included in the model:

- progression free survival with first line therapy (PFS 1st line),
- progression free survival with second line therapy (PFS 2nd line),
- survival with progression (SWP)
- death.

The cycle length was two weeks, which was chosen to reflect the length of a FOLFOX6 chemotherapy cycle, and a half cycle correction was applied. The model structure is shown in Figure 1.

Figure 1 metastatic colorectal cancer model structure



The distribution of the cohort amongst the four health states was determined by the underlying survival curves, which were constructed using evidence from the clinical effectiveness section (see model inputs). The model took the perspective of the health and personal social services.

Model inputs

The EAG populated the model using data derived from the clinical effectiveness review, published literature and routine sources of cost data. Where published data were unavailable the EAG used expert opinion to derive estimates to populate the model. A discount rate of 3.5% was applied to both costs and effects. Survival data derived from the clinical effectiveness were supplemented with survival data for body surface area dosing obtained from seven studies included in NICE CG131 and the COIN study (Adams et al, 2011).

Costs

The cost of the My5-FU assay was provided by the manufacturer and the EAG consulted experts to obtain estimates of annual laboratory throughput and additional laboratory costs associated with running the My5-FU assay. From this, the EAG calculated a cost per completed by My5-FU assay of £61.03 which includes £25.53 for laboratory costs (assays, consumables and staff costs) and £35.50 for a community health visitor to take a blood sample. This cost assumes an annual laboratory throughput of 300 My5-FU assays

with weekly batching and 100 assays per kit. In addition, based on expert advice, a cost of 10 minutes of consultant time per dose adjustment is also applied to the My5-FU arm of the model. The EAG also estimated that the average number of My5-FU assays required per patient for each course of treatment would be 3.23: however this estimate is dependent on numerous factors including the size of dose adjustments, the number of cycles taken to achieve the optimal target range and whether or not the patient experiences toxicity (see pages 170 to 174 in the diagnostics assessment report for further details).

Chemotherapy costs were obtained from the CMU EMIT database, published literature and expert advice; a cost of £584.54 per cycle was applied for FOLFOX and £595.44 per cycle for FOLFIRI. In addition an ongoing monthly cost of £128 for secondary/tertiary care consultations, £103 for imaging and laboratory tests and £17 primary care costs was applied (see pages 176 to 177 in the diagnostics assessment report for further details).

To derive estimates of the resource use associated with adverse events the EAG undertook a systematic review (see appendix 21 in the diagnostics assessment report) and the results of this were combined with NHS reference costs for non-elective hospitalisations. Medication costs only were applied for adverse events which did not require hospitalisation (see pages 177-179 in the diagnostics assessment report for further details).

Health related quality of life and QALY decrements

Data on quality of life associated with progression free survival and survival with progression were drawn from the literature (see page 166 in the diagnostics assessment report for further details); quality of life values of 0.820 for progression free survival and 0.643 for survival with progression were applied in the base case.

To derive estimates of quality of life decrements associated with adverse events, that is diarrhoea, nausea and vomiting, hand and foot syndrome, mucositis, neutropenia, thrombocytopenia, and leukopenia, the EAG undertook a systematic review (see appendix 22 in the diagnostics assessment report for further details). The results of the review were supplemented by expert advice, and the quality of life decrements included in the base case are shown in Table 50 on page 169 in the diagnostics assessment report. In summary, QALY decrements ranged from -0.013 to -0.053 for grade 1 and 2 adverse events and from -0.038 to -0.103 for grade 3 and 4 adverse events.

Estimates of the duration of quality of life decrements were drawn from expert advice and ranged from 12 to 18 days for grade 1 and 2 adverse effects and from 3 to 7 days for grade 3 and 4 side effects (see page 170 in the diagnostics assessment report for further details).

Base case analyses

Overall and progression free survival curves were extrapolated from Gamelin et al (2008) and Gamelin et al (1998) (5-FU+FA), and Capitain et al (2012) (FOLFOX 6). The EAG noted that Gamelin et al (2008) provided the most robust estimate of overall survival for both pharmacokinetic dose adjustment and body surface area dosing, but the applicability of the results is uncertain as 5FU+FA regimens may no longer be used to treat metastatic colorectal cancer in the UK. As the overall survival curves differed substantially between the two studies, the EAG constructed two base case analyses:

- FOLFOX6 base case: survival data drawn from Capitain et al (2012) supplemented with FOLFOX6 body surface area dosing studies
- 5FU+FA base case: survival data drawn from Gamelin et al (2008) and Gamelin et al (1998) supplemented with 5FU+FA body surface area dosing studies, combined with drug costs for FOLFOX6 (to represent UK practice).

For the purposes of decision making, the ICERs per QALY gained or lost will be considered. The following assumptions were common to both base case analyses:

- First line treatment is 12 cycles of FOLFOX6, and second line treatment is 12 cycles of FOLFIRI (whilst patients remain in progression free survival).
- By default, patients moved from progression free survival into survival with progression and then to death. Moving directly from progression free survival to death only applied when there was an adding up constraint determined by the Weibull survival curves, that is where the incident number of deaths in a cycle is greater than the proportion of the cohort in the survival with progression health state.
- A constant proportion (60%) of the cohort progress from first line therapy to second line therapy.
- Estimates of survival and toxicity obtained from studies which used HPLC to measure plasma 5-FU are applicable to the My5-FU assay.
- The duration, effect and cost of second line therapy is independent of the duration, effect and cost of first line therapy.
- Neutropenia, thromobocytopenia and leukopenia have no impact upon quality of life.
- An annual laboratory throughput of 300 My5-FU assays, with weekly batching and 100 assays per kit (£61.03 per completed My5-FU assay).
- 3.23 My5-FU assays per patient are required over the course of treatment.
- The blood sample required for the My5-FU assay was taken in the community by a health visitor.
- Ten minutes of consultant time are required for each dose adjustment in the My5-FU arm.
- No end of life costs are applied

FOLFOX 6 base-case results

The FOLFOX 6 base case applied the Weibull survival curves from the pharmacokinetic dose adjustment arm in Capitain et al (2012) to the My5-FU arm, and the parameterised Weibull survival curves constructed from medians reported for the body surface area dosing arm in Capitain et al (2012) to the body surface area dosing arm. The following additional assumption was specific to the FOLFOX6 base case:

- The Weibull survival curves applied to the body surface area dosing arm (estimated from median survival only) have the same shape parameter as the Weibull survival curves applied to the My5-FU arm

The EAG undertook a deterministic analysis of the FOLFOX6 base case which produced an ICER of £4148 per QALY gained for My5-FU, based on an estimated gain of 0.599 QALYs and an incremental cost of £2483. The EAG also undertook a probabilistic sensitivity analysis (PSA), based on 10,000 iterations which also produced an ICER of £4148 per QALY gained for My-5FU. The results of the PSA were presented as both a cost effectiveness plane scatter plot and cost effectiveness acceptability curve (see page 182 in the diagnostics assessment report). At a maximum acceptable ICER threshold of £20,000 per QALY gained, the probability that dose adjustment using My5-FU is cost effective compared to body surface area dosing is 100%.

FOLFOX6 scenario analyses

The EAG undertook 5 scenario analyses for the FOLFOX6 base case, which applied different progression free and overall survival estimates to the body surface area dosing arm only (see pages 160-162 in the diagnostics assessment report for further details). The scenario analyses resulted in ICERs ranging from £3514 to £3950 per QALY gained, and the EAG concluded that applying alternative overall and progression free survival curves to the body surface area dosing arm had minimal impact upon the

estimated cost effectiveness of My5-FU (see pages 183 to 184 in the diagnostics assessment report for further details).

FOLFOX6 sensitivity analyses

The EAG conducted a number of univariate sensitivity analysis:

- Assumptions relating to throughput and batching of the My5-FU assay, the number of assays that are obtained from each kit, the number of assays that are required per patient were changed, and the impact of including ongoing monitoring with My5-FU after initial stabilisation was investigated.
- It was assumed that a proportion (40%) of patients who remain in progression free survival after one year opt to have a second course of FOLFOX; this is equivalent to 10% of the patients who started the first course of FOLFOX.
- Second line treatment with FOLFIRI was excluded.
- An end of life cost of £3000 was applied to each incident death.
- It was assumed that blood samples were taken in an oncology outpatient setting.
- Alternative quality of life estimates were applied.
- Adverse event estimates from Gamelin et al (2008) were applied.
- Overall and progression free survival were excluded.

The results of the univariate sensitivity analysis are shown in Table 3.

Table 3 FOLFOX 6 base case univariate sensitivity analyses

Sensitivity analysis	Δ QALY	Δ Cost	ICER
Base case	0.599	£2,483	£4,148
500 throughput, 100 per kit	0.599	£2,466	£4,120
1,000 throughput, 100 per kit	0.599	£2,454	£4,100
300 throughput, 200 per kit	0.599	£2,454	£4,100
500 throughput, 200 per kit	0.599	£2,443	£4,082
1,000 throughput, 200 per kit	0.599	£2,436	£4,069
Daily My5-FU batches	0.599	£2,586	£4,320
10% 2nd course FOLFOX6	0.599	£3,156	£5,272
No 2nd line FOLFIRI	0.600	£2,618	£4,363
£3,000 End of life cost	0.599	£2,410	£4,026
Quality of life: TA176	0.589	£2,483	£4,214
Quality of life: Best et al (2010)	0.413	£2,483	£6,016
[redacted]	[redacted]	[redacted]	[redacted]
4.4 My5-FU assays	0.599	£2,554	£4,267
Single adjustment/extra assay	0.599	£2,465	£4,118
Ongoing 1/3rd My5-FU assays used	0.599	£2,610	£4,361
OP visit for blood test	0.599	£2,697	£4,506
AEs from Gamelin et al (2008)	0.599	£2,562	£4,277
Same OS and PFS	0.000	£104	£435,819

The EAG concluded that the sensitivity analyses which assumed a proportion of patients received a second course of FOLFOX6, applied alternative quality of life estimates, or assumed that blood samples were taken in an oncology outpatient setting had a noticeable impact on cost effectiveness of My5-FU and resulted in slightly higher ICERs than that reported for the deterministic base case analysis. Most noticeably, when overall and progression free survival were excluded, the ICER rose to £435,819 per QALY gained, suggesting that the cost effectiveness of My5-FU is largely dependent upon improved progression free and overall survival being achieved.

5FU+FA base-case results

The 5FU+FA base case applied the Weibull overall survival curves for pharmacokinetic dose adjustment and body surface area dosing from Gamelin et al (2008) to the My5-FU and body surface area dosing arms respectively,

and applied the Weibull progression free survival curve which was estimated by pooling results from 3 body surface area dosing studies which were included in NICE CG131 to both the My5-FU and body surface area dosing arms (Kohne et al 2003, Kohne et al 2005 and Cunningham et al, 2009). The following additional assumptions were specific to the 5FU+FA base case:

- Progression free survival is equivalent in the My5-FU and body surface area dosing arms.
- Drug costs are for FOLFOX6.

The EAG undertook a deterministic analysis of the 5FU+FA base case which produced an ICER of £5853 per QALY gained for My5-FU. The EAG also undertook a PSA, based on 10,000 iterations which produced an ICER of £5852 per QALY gained for My-5FU. The results of PSA were presented as both a cost effectiveness plane scatter plot and cost effectiveness acceptability curve (see page 186 in the diagnostics assessment report). At a maximum acceptable ICER threshold of £20,000 per QALY gained, the probability that dose adjustment using My5-FU is cost effective compared to body surface area dosing is 90%. Both the cost effectiveness plane scatter plot and the cost effectiveness acceptability curve suggest that there is greater uncertainty in the 5-FU+FA base case than the FOLFOX6 base case.

5FU+FA scenario analyses

The EAG undertook 6 scenario analyses for the 5FU+FA base case, each of which used a different combination of progression free and overall survival estimates for both My5-FU and body surface area dosing (see pages 162 – 163 in the diagnostics assessment report for further details). The scenario analyses resulted in ICERs ranging from £3989 to £8615 per QALY gained, and the EAG concluded that, in two of the six scenario analyses, the ICER was sensitive to changes in progression free survival which impact upon the number of patients receiving ongoing first line FOLFOX6 treatment resulting in

ICERs of £6965 and £8615 per QALY gained (see pages 187 to 188 in the diagnostics assessment report for further detail).

5-FU+FA sensitivity analyses

The EAG repeated the univariate sensitivity analyses of the FOLFOX6 base case for the 5FU+FA base case, the only difference being that adverse event estimates from Capitain et al 2012 were applied in one analysis. The results of the univariate sensitivity analyses are shown in Table 4.

Table 4 5FU+FA univariate sensitivity analyses

Sensitivity analysis	Δ QALY	Δ Cost	ICER
Base case	0.151	£883	£5,853
500 throughput, 100 per kit	0.151	£866	£5,743
1,000 throughput, 100 per kit	0.151	£854	£5,663
300 throughput, 200 per kit	0.151	£854	£5,662
500 throughput, 200 per kit	0.151	£844	£5,593
1,000 throughput, 200 per kit	0.151	£836	£5,540
Daily My5-FU batches	0.151	£986	£6,535
10% 2nd course FOLFOX6	0.151	£883	£5,853
No 2nd line FOLFIRI	0.151	£878	£5,820
£3,000 End of life cost	0.151	£859	£5,693
Quality of life: TA176	0.141	£883	£6,270
Quality of life: Best et al. (2010)[0]	0.051	£883	£17,485
[redacted]	[redacted]	[redacted]	[redacted]
4.4 My5-FU assays	0.151	£954	£6,324
Single adjustment/extra assay	0.151	£865	£5,736
Ongoing 1/3rd My5-FU assays used	0.151	£990	£6,559
OP visit for blood test	0.15	£1,098	£7,274
AEs from Capitain et al. (2012)	0.150	£804	£5,344
Same OS and PFS	0.000	£104	£435,804

As for the FOLFOX 6 sensitivity analyses, the EAG concluded that using alternative quality of life estimates or assuming that blood samples were taken in an oncology outpatient setting had a noticeable impact on cost effectiveness and resulted in slightly higher ICERs. Again, when overall and progression free survival were excluded the ICER rose to £435,804 per QALY gained.

Economic analysis of head and neck cancer

As outcome data were limited to adverse event and treatment response rates the EAG undertook an exploratory analysis of the cost effectiveness of My5-FU in people with locally advanced head and neck cancer. The aim of the analysis was to combine the adverse events and response rates from Fety et al (1998) (reported in the clinical effectiveness review), with the following inputs which were derived from published literature and supplemented with expert advice: progression free and overall survival data for TPF (docetaxel, cisplatin and 5-FU) induction chemotherapy, costs of induction chemotherapy and subsequent chemo-radiotherapy, the costs and quality of life impacts of adverse events and the costs associated with ongoing monitoring. The resulting data were used to estimate the overall and progression free survival hazard ratios that would be required for My5-FU to be considered cost effective at a maximum acceptable ICER threshold of £20,000 per QALY. The EAG noted that the adverse event data for pharmacokinetic dose adjustment and body surface area dosing reported by Fety et al (1998) were based on a cisplatin and 5-FU regimen which is not used in current practice.

The analysis estimated that a hazard ratio of 0.966 for progression free survival would result an ICER of £20,586 per QALY gained, and a hazard ratio of 0.990 for overall survival would result in an ICER of £20,601 per QALY gained. Sensitivity analyses around the proportion of patients receiving subsequent chemo-radiotherapy suggest that a hazard ratio of 0.980 for progression free survival or 0.995 for overall survival would be sufficient to justify the additional costs of My5-FU. The EAG concluded that given the low incremental costs associated with My5-FU testing (£137 to £335) and the relatively long survival among patients with locally advanced head and neck cancer it is likely that only small increases in progression free and overall survival are required for the My5-FU assay to be considered cost effective (see pages 191 to 204 in the diagnostics assessment report for further details).

4 Issues for consideration

Clinical effectiveness

- It is not certain whether the accuracy of the My5-FU assay can be considered comparable to the reference standards (high performance liquid chromatograpy and liquid chromatography mass-spectrometry). Only limited data were available for this comparison which showed a high correlation between My5-FU and the reference standards. However, there was considerable variability between the methods: 95% of measurements were between -18% to +30% compared with liquid chromatography-mass spectrometry; and similar plots were seen with high performance liquid chromatography. The data suggest that the variability in 5-FU plasma measurements may be random but it is important to note that any systematic variability in the measurements from the My5-FU assay could result in patients receiving sub-therapeutic doses of 5-FU or being exposed to greater toxicities. Variability in My5-FU measurements may also occur between different clinical chemistry platforms and it is not known whether validated platform specific protocols were used in published studies. Additionally, as high performance liquid chromatography and liquid chromatography-mass spectrometry are not currently used to measure 5-FU plasma levels in clinical practice, the accuracy of the reference standard is not certain.
- It is not clear whether the target ranges and suggested adjustments recommended in each of the included dose adjustment algorithms are transferable between chemotherapy regimens. Older algorithms were developed for use with chemotherapy regimens which are thought to have resulted in greater toxicity than regimens currently used in UK clinical practice such as FOLFOX and FOLFIRI. One dose adjustment algorithm (Kaldate et al, 2012) is available for a FOLFOX 6 regimen and may be applicable to UK clinical practice, but this has not yet been trialled in a prospective study. It is also uncertain which algorithms would be suitable

for use in patients receiving treatment for head and neck cancer, stomach cancer or pancreatic cancer.

- It is not certain whether pharmacokinetic dose adjustment is associated with increased progression free and overall survival when compared to body surface area dosing in people receiving continuous infusion 5-FU for colorectal cancer. Although the comparative studies included in the clinical effectiveness review appeared to have included a representative sample in their control arms, the reporting of survival data, particularly progression free survival, was often incomplete and studies were mostly of poor quality. The results of the pooled analysis suggested that pharmacokinetic dose adjustment is associated with increased overall survival compared to body surface area dosing, but the significance of this increase is not known, and data were drawn from single arms of heterogeneous studies.
- It is uncertain whether the observed increases in progression free and overall survival can be generalised to UK practice. Only one comparative study included in the clinical effectiveness review reported survival data for a FOLFOX6 regimen (Capitain et al, 2012), however, this study reported median survival data only for the non-randomised control arm. The most robust survival estimates came from the one randomised study (Gamelin et al 2008), but the applicability of this study's findings are limited by its use of an outdated regimen (8 hour 5FU+FA).
- Data included in the clinical effectiveness review suggested that pharmacokinetic dose adjustment may be associated with a reduction in some toxicities, particularly diarrhoea. However, toxicity data were often selectively reported in studies and the use of different classification systems made comparison difficult. Where the EAG were able to calculate relative risks for toxicities, confidence intervals often crossed unity, suggesting that any observed reductions in toxicities were not statistically significant. However, the evidence in Capitain et al (2012) indicated a statistically significant reduced risk of diarrhoea with pharmacokinetic dose adjustment of the FOLFOX6 regimen.

- There were insufficient clinical outcome data available on the use of pharmacokinetic dose adjustment in people receiving treatment for head and neck cancer, stomach cancer and pancreatic cancer. No studies reported survival or toxicity data for either stomach or pancreatic cancer and one randomised study (Fety et al, 1998) reported toxicity data for people with head and neck cancer. The results suggested that pharmacokinetic dose adjustment was associated with reduced toxicity, however the study used a regimen which is no longer used and therefore, the applicability of the results to current practice is uncertain.

Cost effectiveness

- There were sufficient clinical effectiveness data to construct a cost effectiveness model for metastatic colorectal cancer only. Exploratory analyses were carried out for head and neck cancer. The model assumes that the accuracy of the My-5FU assay is comparable to high performance liquid chromatography and liquid chromatography-mass spectrometry for measuring 5-FU plasma levels. As high performance liquid chromatography and liquid chromatography-mass spectrometry are not currently used to measure 5-FU plasma levels in clinical practice, there is uncertainty in their accuracy.
- The base case analyses reflect UK clinical practice and assume that FOLFOX6 is the first line treatment. The survival estimates available for FOLFOX6 were limited to one non randomised study and consequently the effect estimates underpinning the FOLFOX6 base case may not be robust. The survival data obtained from the randomised 5FU+FA study (Gamelin et al, 2008) were considered to be more robust and were applied to FOLFOX6 treatment costs in a second base case analysis. It is not certain whether effect estimates obtained from a 5FU+FA regimen would be equivalent to those expected for FOLFOX6 as the base case analyses suggest that 5FU+FA results in smaller incremental QALY gains than FOLFOX6 (0.15 versus 0.60 QALYs).

- The cost effectiveness of the My5-FU assay is driven by progression free and overall survival. The ICERs were relatively robust to the scenario analyses in which different survival estimates were assumed. However, when progression free and overall survival are assumed to be equivalent for the My5-FU assay and body surface area dosing, the incremental impact on toxicity was not sufficient to justify the costs associated with My5-FU (£435,819 and £435,804 per QALY gained for FOLFOX6 and 5FU+FA respectively).
- The base case analyses assume that a health visitor would be responsible for taking the blood sample required for the My5-FU assay. If taking the blood sample requires an outpatient appointment, sensitivity analysis showed that the cost of the My5-FU assay would double. Additionally, the base case analyses assume that up to 12 cycles of FOLFOX are given as first line treatment to reflect current UK practice where up to 12 FOLFOX cycles are given before a break in treatment. A patient may then choose to start a second cycle of FOLFOX; sensitivity analyses showed that the FOLFOX6 ICERs were sensitive to the addition of a second course of FOLFOX for 10% of patients (£5,272 per QALY gained).
- Various quality of life decrements for both adverse events and the health states included in the model are reported in the literature. The QALYs, and consequently the ICERs, are sensitive to the quality of life weights applied to survival. When QALY estimates which place less value on additional survival are applied the ICERs rise to £6,016 and £17,485 per QALY gained in the FOLFOX6 and 5FU+FA analyses respectively.
- Current practice often includes administering chemotherapy orally (capecitabine tablets) instead of continuous intravenous infusion of 5-FU, which reduces the requirement for patients to attend chemotherapy clinics. The ability to reduce toxicity and improve the efficacy of treatment through monitoring and adjusting the dose of 5-FU could lead to an increase in patient preference for continuous infusion of 5-FU. The impact of increased demand for continuous infusion 5-FU which requires patients to attend

chemotherapy clinics has not been considered in the cost-effectiveness analysis.

- The cost effectiveness of using the My5-FU assay to monitor the dose of 5-FU in the treatment of locally advanced head and neck cancer was assessed in an exploratory analysis. In this analysis, it was assumed that the effect estimates of pharmacokinetic dose adjustment derived from a cisplatin and 5-FU induction regimen are generalisable to current practice, that is, an induction regimen of docetaxel or paclitaxel with cisplatin and 5-FU. The results of this analysis are therefore uncertain.

5 Equality considerations

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others.

All people with cancer are covered by the disability provision of the equality act from the point of diagnosis. People who may be at greatest risk of 5-FU toxicity include people with impaired liver function, people with impaired renal function, people whose body surface area is outside the standard range for dosing 5-FU, and those who have a less favourable performance status (including older people) prior to commencing chemotherapy. These groups of people may gain the greatest benefit from reduced 5-FU toxicity, which could enable them to have treatment that may not otherwise be suitable for them. My5-FU may also be of particular benefit to people who are receiving 5-FU by continuous infusion for the treatment of metastatic disease, in whom a greater emphasis is placed on maintaining quality of life.

6 Implementation

Use of the My5-FU assay may require changes to local protocols to ensure that blood samples are taken towards of the end of the 5-FU infusion, and results are available to guide dose adjustment when the next chemotherapy

cycle begins. There may also be an increased requirement for services to deliver 5-FU as an infusion, particularly for patients who would otherwise have opted to receive capecitabine.

7 Authors

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Appendix A: Sources of evidence considered in the preparation of the overview

A. The diagnostics assessment report for this assessment was prepared by Warwick Evidence:

Freeman K, Connock M, Cummins E, Gurung T, Taylor-Phillips S, Court R, Saunders M, Clarke A and Sutcliffe P. Fluorouracil plasma monitoring: the My5-FU assay for guiding dose adjustment in patients receiving fluorouracil chemotherapy by continuous infusion. A Diagnostic Assessment Report. Warwick Evidence, June 2014.

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

Manufacturer(s) of technologies included in the final scope:

- Saladax Biomedial Inc

Other commercial organisations:

- ODPM - Onco Drug Personalised Medicine

Professional groups and patient/carer groups:

- Association for Clinical Biochemistry and Laboratory Medicine
- Bowel Cancer UK
- Pancreatic Cancer UK
- Royal College of Nursing
- Royal College of Physicians

Research groups:

None

Associated guideline groups:

None

Others:

- Department of Health
- Healthcare Improvement Scotland
- NHS England
- Welsh Government

Appendix B: Glossary of terms

Area under the plasma drug concentration-time curve

The curve shows the plot of the plasma concentration level (mg/L) against time (hours [h]). The area under the curve represents the body's actual exposure to the drug after drug has been administered and is dependent upon both the dose administered and the rate of elimination of the drug from the body. Results of area under the drug concentration time curve are expressed in mg·h/L. Using the area under the plasma concentration-time curve to adjust drug dosing is a method of pharmacokinetic dose adjustment.

Body surface area dosing

A method of calculating the dose of a drug using body surface area in m^2. Body surface area is calculated by formulae using the patient's height and weight. Body surface area is said to correlate with blood volume, cardiac output and renal function which influence drug elimination, but does not take into account other important factors such as coexisting illness, genetic variations, nutritional status, renal and hepatic function and previous response to chemotherapy (Drug and Therapeutics Bulletin, 2010).

de Gramont or modified de Gramont

A de Gramont or modified de Gramont cycle lasts for 14 days.

- de Gramont: on day 1 an infusion of folinic acid and injection of 5-FU are given followed by a 22 hour infusion of 5-FU. On day 2 a second infusion of folinic acid and injection of 5-FU are given, followed by a second 22 hour infusion of 5-FU.
- modified de Gramont: on day 1 an infusion of folinic acid and injection of 5-FU are given, followed by a 46 hour infusion of 5-FU.

FOLFIRI

A FOLFIRI cycle lasts 14 days. On day one of the cycle an infusion of irinotecan followed by an infusion of folinic acid is given prior to the

administration of 5-FU. FOLFIRI schedules then vary depending on the administration of 5-FU:

- On day 1, after the infusions of irinotecan and folinic acid, an injection of 5-FU is given, followed by a 20 hour infusion of 5-FU. On day 2 an infusion of folinic acid and injection of 5-FU are given, followed by a second 20 hour infusion of 5-FU.

Or

- On day 1, after the infusions of irinotecan and folinic acid, an injection of 5-FU is given followed by a 46 hour infusion of 5-FU.

FOLFOX

A FOLFOX cycle lasts 14 days. On day 1 of the cycle concurrent infusions of folinic acid and oxaliplatin are given prior to the administration of 5-FU. There are two commonly used FOLFOX schedules depending on the administration of 5-FU:

- FOLFOX4 – On day 1, after the administration of folinic acid and oxaliplatin, an injection of 5-FU is given, followed by a 22 hour infusion of 5-FU. On day two there is a second infusion of folinic acid and injection of 5-FU, followed by a second 22 hour infusion of 5-FU.
- FOLFOX6 – On day 1, after the administration of folinic acid and oxaliplatin, an injection of 5-FU is given followed by a 46 hour infusion of 5-FU.

Induction chemotherapy

A course of chemotherapy which is given to people with locally advanced head and neck cancer with the aim of shrinking the primary tumour in advance of surgery or concurrent chemoradiotherapy.

Performance status

Performance status is used to assess a person's general health, and may be used to determine whether a course of treatment is appropriate. Commonly used scales for assessing performance status are the World Health Organisation (WHO) performance scale, ECOG performance status and the Karnofsky performance status scale. The scales differ, but range from fully active with no evidence of disease to very ill with a high level of care required, or death.

Pharmacokinetics

The study of the actions of the body on a drug and their impact on drug uptake rates. Considerations in pharmacokinetics include the mechanisms of drug absorption, distribution, metabolism and excretion.

Side effects

Side effects of chemotherapy are commonly graded according to systems such as the National Cancer Institute's Common Terminology for Adverse Events system, with grade one side effects being mild and grade five representing toxicity resulting in death.

Therapeutic range

The range from the lowest dose to the maximum tolerated dose.

Appendix C: Abbreviations

BSA	Body surface area
5-FU	Fluorouracil
DHD	Dihydropyrimdine dehydrogenase
EDTA	Ethylenediaminetetraacetic acid (anticoagulant)
HPLC	High performance liquid chromatography
ICER	Incremental cost-effectiveness ratio
LC-MS	Liquid chromatography mass spectrometry
QALY	Quality adjusted life year

Appendix D: References

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