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NICE guidance

Fluorouracil chemotherapy: The My5-FU assay for guiding dose adjustment

HealthTech guidance

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Commissioners and providers have a responsibility to promote an environmentally sustainable health and care system and should assess and reduce the environmental impact of implementing NICE recommendations wherever possible.

Contents

This guidance replaces DG16.

1 Recommendations

1.1 The My5-FU assay is only recommended for use in research for guiding dose adjustment in people having fluorouracil chemotherapy by continuous infusion. The My5-FU assay shows promise and the development of robust evidence is recommended to demonstrate its utility in clinical practice (see section 7).

2 The technology

2.1 One technology, the My5-FU assay, was identified during scoping as being relevant to this assessment. The My5-FU assay can be used to guide pharmacokinetic dose adjustment and to monitor the levels of 5-fluorouracil (5-FU) in the blood (therapeutic drug monitoring) in people having 5-FU chemotherapy by continuous infusion. The aim is to achieve an optimal plasma level of the drug. 5-FU is suitable for therapeutic drug monitoring because it has a narrow therapeutic range, that is, drug levels below the therapeutic range potentially reduce treatment efficacy and drug levels above the therapeutic range are more likely to cause side effects and toxicity. Increasing the number of people with plasma levels within the therapeutic range may result in increased therapeutic effect without additional toxicity.

3 Clinical need and practice

The problem addressed

3.1 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 5-fluorouracil (5-FU) chemotherapy.

3.2 Pharmacokinetic dose adjustment of 5-FU may result in increased overall and progression-free survival, by increasing the number of people having an optimum therapeutic dose of 5-FU and by reducing the incidence of side effects and toxicities. 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. In severe cases, 5-FU toxicity can lead to neuropathy (damage to nerve cells), severe damage to organs, cardiotoxicity, neutropenia, sepsis and septic shock. In addition, people with DPD (dihydropyrimidine dehydrogenase) deficiency have a reduced ability to metabolise 5-FU and can develop serious toxicity following treatment.

The conditions

3.3 Continuous infusion 5-FU chemotherapy is commonly used in the treatment of many cancers including colorectal, head and neck, stomach and pancreatic cancer.

3.4 Colorectal cancer describes cancers originating in the colon or rectum, and is the fourth most common cancer in the UK with around 40,000 new cases registered each year. Around half of all people diagnosed with colorectal cancer survive for at least 5 years after diagnosis.

3.5 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. Five-year survival rates vary depending on the type of head and neck cancer; thyroid cancer has an estimated 5-year survival rate of 87%, whereas the 5-year survival rate for hypopharyngeal cancer is 26%.

3.6 Stomach cancer is the ninth most common cancer in males in the UK and the fourteenth most common in females. Around 42% of people will survive for a year after diagnosis, although this falls to around 18% after 5 years.

3.7 Pancreatic cancer is the tenth most common cancer in the UK and the fifth most common cause of death from cancer. 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 5-year survival rate is less than 5%.

The diagnostic and care pathways

5-FU-based chemotherapy

3.8 5-FU chemotherapy is used in the treatment of many different cancers and it can be given intravenously (by injection or as an infusion) or orally. 5-FU can be prescribed as a single agent or as a regimen, in conjunction with other chemotherapy drugs. 5-FU is commonly administered alongside folinic acid with either oxaliplatin (FOLFOX regimen), or irinotecan (FOLFIRI regimen). An oral version of 5-FU known as capecitabine is sometimes used instead of intravenous 5-FU and this is also often administered alongside oxaliplatin and irinotecan. Capecitabine is a prodrug of 5-FU, that is, an inactive form of 5-FU that is converted into active 5-FU in the tumour by metabolic processes. This guidance focuses on the pharmacokinetic dose adjustment of continuous infusion 5-FU only.

3.9 Chemotherapy is usually given as a course of treatments over 3 to 6 months. An average course of chemotherapy typically includes between 4 and 8 cycles. Continuous infusions of 5-FU last for around 22 to 48 hours and usually require a patient to have a central venous access device (such as a central line or

peripherally inserted central catheter). Some patients are able to have their 5-FU infusion through a portable pump that can make it possible for them to go home during treatment.

4 The diagnostic tests

The intervention

The My5-FU assay

4.1 The My5-FU assay (Saladax Biomedical Inc.), previously known as OnDose, is a CE-marked in vitro diagnostic test designed to measure the levels of 5-fluorouracil (5-FU) chemotherapy in plasma samples. The assay is intended for use in people who are having 5-FU chemotherapy by continuous infusion, to allow pharmacokinetic dose adjustment and therapeutic drug monitoring, with the aim of achieving an optimal plasma level of 5-FU.

4.2 The My5-FU assay is a homogenous 2-reagent nanoparticle agglutination assay that can be adapted for use on several different clinical chemistry analysers. The assay needs plasma from a peripheral venous blood sample, taken towards the end of each 5-FU infusion cycle using an EDTA or heparin tube. The assay is based on the principle of measuring scattered light; when higher levels of 5-FU are present in the plasma sample, less light is scattered. The assay typically takes about 10 to 15 minutes for the first results, depending on the analyser used, with subsequent results taking less than a minute. Results are reported in nanograms of 5-FU per millilitre of plasma and are converted to an area under the (concentration) curve value. Values of greater than 50 milligram hours per litre may signify that the blood sample has been taken too close to the infusion port and may need to be disregarded. The assay has a limit of detection of 52 nanograms/ml and a lower limit of quantitation of 85 nanograms/ml.

4.3 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. 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, while the pump is infusing at a steady rate. Subsequent doses of 5-FU are then calculated using the area under the curve result from the My5-FU assay, in conjunction with a validated dose adjustment algorithm. The My5-FU assay is intended as an aid for managing dose adjustment in patients

having 5-FU chemotherapy and the results of the test should be used in conjunction with clinical assessment to determine whether dose adjustment is appropriate.

The comparator: body surface area dosing

4.4 The comparator used in this assessment is body surface area dosing. Body surface area is calculated by formulae that use the patient's height and weight, and correlates with blood volume, cardiac output and renal function, all of which influence drug elimination. Usually the dose is calculated according to the patient's actual body weight, 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. The dose may be adjusted to take into account a patient's liver and kidney function, both of which may impact on 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.

5 Outcomes

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

How outcomes were assessed

5.1 The External Assessment Group conducted a systematic review of the evidence on test performance and clinical-effectiveness data for the My5-FU assay and comparator tests. Studies were included if they appeared to contain data on the following:

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

5.2 In summary, the following 32 studies, a systematic review and manufacturer validation data were included in this assessment:

- Validation data from the manufacturer and 3 published studies that 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 having continuous infusion 5-FU.
- Five comparative studies of pharmacokinetic dose adjustment and body surface area dosing in patients having continuous infusion 5-FU.

- One systematic review (containing 7 relevant studies) and 1 randomised controlled trial containing information on 5-FU continuous infusion regimens administered using body surface area dosing.

Accuracy of the My5-FU assay

5.3 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 analytical reference standard.

The My5-FU assay compared with liquid chromatography-mass spectrometry

5.4 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 demographic details of patients who provided the supplementary samples were not reported, so there is 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) with that of liquid chromatography mass-spectrometry. The study reported a strong correlation between the My5-FU assay and liquid chromatography mass-spectrometry (R^2=0.99), with a trend towards higher measurements with the My5-FU assay. In addition, the Bland–Altman plot showed a 7% bias (95% confidence interval [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 under- or overestimate 5-FU plasma measurements by 18% and 30% respectively. The 5-FU plasma levels reported in the study were substantially greater than the levels that would be reported in current practice.

5.5 A second study, Beumer et al. (2009), reported results of 156 plasma samples provided by patients with head and neck and colorectal cancer. This study compared the accuracy of the My5-FU assay (run on an AU400 analyser) 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 the significance of these findings is not known. This study did not state whether any data were excluded from the analysis and is therefore considered at high risk of bias for patient selection.

5.6 A third study, Makihara et al. (2012), was reported as an abstract only, and 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 correlation between the My5-FU assay and liquid chromatography-mass spectrometry (R^2=0.8471) but this was noticeably lower than that reported by Buchel et al. (2013) and Beumer et al. (2009).

5.7 Validation data supplied by the manufacturer reported a comparison of the accuracy between the My5-FU assay (run on an AU400 analyser) and liquid chromatography-mass spectrometry. 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 reported Bland–Altman plots showed a mean bias of +24.5 nanograms/ml with outliers ranging from -285 nanograms/ml to +171 nanograms/ml (approximately -25% to +70%) with the My5-FU assay. Details on patient selection and methods were not available for the validation data and the risk of bias could not be ascertained.

The My5-FU assay compared with high-performance liquid chromatography

5.8 No published studies were found that compared the accuracy of the My5-FU assay 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) and that of high-performance liquid chromatography. The validation data showed a mean bias of +1.84 nanograms/ml with outliers ranging from -80 nanograms/ml to

+137 nanograms/ml (approximately -30% to +35%) with the My5-FU assay.

Dose adjustment algorithms based on 5-FU plasma measurements

Dose adjustment algorithms for people with colorectal cancer

5.9 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 received an 8-hour infusion of 5-FU plus folinic acid (8-hour 5-FU + folinic acid). The dose of 5-FU administered to the patients increased in increments of 250 mg/m^2 every 3 to 4 weeks, until a maximum dose of 2,000 mg/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 with patients who had a minimal response, stable disease or progressive disease. The algorithm established that patients with a 5-FU plasma concentration of 2,000 to 3,000 micrograms/litre (or area under the curve of 16 to 24 milligram hours per litre) do not require a dose adjustment.

5.10 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 5-FU + folinic acid + oxaliplatin (FOLFOX) 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 the My5-FU assay) recorded during 2 consecutive infusion cycles that included a dose adjustment. This resulted in 307 paired observations. Regression analysis was used to model the change in area under the curve recorded for the 5-FU plasma measurements compared with the recorded dose adjustments. The resulting dose adjustment algorithm is based on area under the curve measurements (reported as milligram hours per litre) and established that patients with an area under the curve value of 20 to 30 milligram hours per litre do not require a dose adjustment.

5.11 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 having treatment with 5-FU + folinic acid using a de Gramont regimen with a 22-hour 5-FU infusion. Consecutive participants were placed into 1 of 2 groups (A or B). Group A received a progressive increase of 5-FU of between 25% and 50% in 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 that was used in group B. Group B then received a dose increase in 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 area under the curve value of greater than 20 milligram hours per litre per m^2 did not require a dose increase.

Dose adjustment algorithm for people with head and neck cancer

5.12 One study, Santini et al. (1989), reported a dose adjustment algorithm developed from a retrospective analysis of 89 patients having 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 area under the curve value that is predictive of toxicity. An area under the curve threshold for day 3 was established as 15,000 nanograms per millilitre hours, and was validated in a prospective study of 81 patients, in which 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 area under the curve of 15,000 to 30,000 nanograms per millilitre hours on day 3, and treatment should be stopped in patients with an area under the curve of greater than 30,000 nanograms per millilitre hours.

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

Colorectal cancer clinical outcome data

5.13 The review identified 5 studies that provided data on the following clinical outcomes: progression-free survival, overall survival, treatment response rates, toxicity and side effects, and incidence of over- and under-dosing. Insufficient data were available for the subgroups included in the scope: people with DPD (dihydropyrimidine dehydrogenase) 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. A sixth study (Patel et al. 2014), published after the systematic review was carried out, was submitted during public consultation and considered by the External Assessment Group.

5.14 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 2 chemotherapy regimens, 5-FU + folinic acid with either a weekly 4-hour 5-FU infusion or modified de Gramont schedule, and pharmacokinetic dose adjustment was performed using high-performance liquid chromatography with the dose adjustment algorithm reported in Gamelin et al. (1996). The median length of follow-up was 3.5 years. The study did not report patient selection methods, which may limit the generalisability of the findings.

5.15 A second study, Gamelin et al. (1998), reported results from a prospective multicentre case series of 152 patients (mean age 62 years) with metastatic colorectal cancer. The study used a weekly 5-FU + folinic acid regimen and pharmacokinetic dose adjustment was performed using liquid chromatography with the dose adjustment algorithm reported in Gamelin et al. (1996). The median length of follow-up was 3 years. The generalisability of this study's findings is limited by the use of an obsolete 8 hour 5-FU + folinic acid regimen and by the absence of an intention to treat analysis.

5.16 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 received 5-FU + folinic acid chemotherapy for colorectal cancer (stage not specified) and were randomised to 2 arms. Patients (n=104, mean age 71.5 years) received pharmacokinetic dose adjustment with high-performance liquid chromatography and an adjustment algorithm with a target area under the curve of 20 to 24 milligram hours per litre (adapted from Gamelin et al. 1996), and 104 patients (mean age 71.2 years) received body surface area dosing. The median length of follow-up was 3 years. The generalisability of this study's findings is limited by the use of an obsolete 8-hour 5-FU + folinic acid regimen, and insufficient details on randomisation methods and allocation concealment.

5.17 A fourth study, Capitain et al. (2012), reported results from a retrospective proof of concept study that included 157 patients having FOLFOX chemotherapy for colorectal cancer (stage not specified). The study included 2 groups: 118 patients (median age 65 years) drawn from 8 centres who 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 years) 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 generalisability of this study's findings is limited by incomplete reporting of patient selection methods, a non-randomised design including historical controls and limited reporting of survival data for the control arm.

5.18 A fifth study, Kline et al. (2013), reported results from a retrospective analysis of patients with stage 2/3 or stage 4 colorectal cancer, who received either a FOLFOX or 5-FU + folinic acid + irinotecan (FOLFIRI) regimen. 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 area dosing patients. The My5-FU assay was used to measure 5-FU plasma levels. Patients included in this study were able to choose whether they received pharmacokinetic dose adjustment which increases the risk of allocation bias and limits the generalisability of the study's results.

5.19 A sixth study, Patel et al. (2014), reported results of a single-arm study of 70 patients with colorectal cancer having modified FOLFOX6 (46-hour continuous infusion) chemotherapy with or without bevacizumab in 1 academic cancer centre and 5 community cancer centres in the USA. The My5-FU assay was used to measure 5-FU plasma levels and dose adjustments were in line with an algorithm based on Gamelin et al. (2008). Patients were followed up until cycle 5 and 44 patients completed 4 cycles. The generalisability of this study's findings is limited by the absence of a control arm; the authors compared their results with those obtained in previous studies, including a study that incorporated an obsolete 8-hour 5-FU + folinic acid regimen.

5.20 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 External Assessment Group compared survival estimates with data extracted from 7 body surface area dosing studies included in the systematic review of the NICE guideline on colorectal cancer, supplemented with data from the COIN study (Adams et al. 2011). The External Assessment Group concluded that the survival estimates for body surface area dosing reported in Gamelin et al. (2008) and Capitain et al. (2012) were sufficiently similar to the published literature to suggest that their pharmacokinetic dose adjustment comparisons were not biased by non-representative control arms.

Progression-free survival

5.21 All 5 studies reported data on progression-free survival and, where possible, the reported data were used to reconstruct Kaplan–Meier survival curves. Of the 2 single-arm pharmacokinetic dose adjustment studies, data from Capitain et al. (2008) reported a median progression-free survival of 3.3 months, whereas data from Gamelin et al. (1998) suggested a median progression-free survival of 11 months. A Kaplan–Meier curve was reconstructed for Gamelin et al. (1998).

5.22 Mean duration of response data reported in Gamelin et al. (2008) were used to construct Weibull and log-normal progression-free survival curves that, under 2 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.

5.23 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. A reconstructed Kaplan–Meier curve for the pharmacokinetic dose adjustment arm resulted in a median survival estimate of 16 months (95% CI 12 to 20 months). A survival curve for body surface area dosing was estimated using the reported median survival (10 months) and a Weibull distribution that assumed a proportional hazard of 0.4817 between pharmacokinetic dose adjustment and body surface area dosing.

5.24 Kline et al. (2013) reported Kaplan–Meier curves for both stage 2/3 patients and stage 4 patients and a log-rank test was used to determine equivalence between 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 suggested delayed progression in the pharmacokinetic dose adjustment group.

5.25 Results for progression-free survival could not be pooled because of heterogeneity in the data reported for this outcome, which comprised response rates in Gamelin et al. (2008), median survival estimates only in Capitain et al. (2008) and survival estimates from a mixed treatment group (FOLFOX and FOLFIRI) in Kline et al. (2013).

Overall survival

5.26 Four studies reported data on overall survival. In the 2 single-arm pharmacokinetic dose adjustment studies, Kaplan–Meier plots were reconstructed 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.

5.27 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). These data were used to reconstruct Kaplan–Meier plots; a hazard ratio of 0.82618 (95% CI 0.6198087 to 1.101265) for pharmacokinetic dose adjustment was estimated using Cox proportional hazards regression, and an alternative

hazard ratio of 0.829255 was estimated using a Weibull model assuming proportional hazards.

5.28 Capitain et al. (2012) reported median overall survival of 28 months for pharmacokinetic dose adjustment and 22 months for body surface area dosing. These data were used to reconstruct a Kaplan–Meier plot for pharmacokinetic dose adjustment, and a hazard ratio of 0.586 for pharmacokinetic dose adjustment was estimated using a Weibull distribution that assumed proportional hazards.

5.29 Reconstructed Kaplan–Meier plots from single arms of the 4 studies that reported overall survival were combined with reconstructed Kaplan–Meier plots from body surface area dosing studies included in the systematic review of the NICE guideline on colorectal cancer, and from the COIN study (Adams et al. 2011), to compare pharmacokinetic adjusted dosing with body surface area dosing. Pooled data from studies reporting 5-FU + folinic acid regimens resulted in an estimated median overall survival of 19.6 months (95% CI 17.0 to 21.0; 3 studies) for pharmacokinetic dose adjustment, and 14.6 months (95% CI 14.1 to 15.3; 5 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; 1 study) for pharmacokinetic dose adjustment, and 20.6 months (95% CI 18.4 to 22.9; 3 studies) for body surface area dosing.

Treatment response rates

5.30 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. 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.

5.31 Gamelin et al. (2008) used response rates as the primary outcome measure and provided sufficient data to allow the calculation of relative risks for response types. The results suggested that, although a greater number of patients who received pharmacokinetic dose adjustment achieved complete response and

partial response compared with those who received body surface area dosing, the differences did not appear to be statistically significant: complete response relative risk was 6.00 (95% CI 0.74 to 48.97) and partial response relative risk was 1.71 (95% CI 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. Relative risks for the 3-month data were calculated, which appeared to favour pharmacokinetic dose adjustment for both partial (relative risk 1.56; 95% CI 1.07 to 2.27) and overall response (relative risk 1.52; 95% CI 1.06 to 2.18).

Toxicity and side effects

5.32 All 5 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%), whereas Gamelin et al. (1998) reported that most of the recorded side effects were diarrhoea (39%) and hand-foot syndrome (30%). In addition, Patel et al. (2014) reported that there were similar rates of neutropenia but a decrease in the incidence of grade 3 and 4 diarrhoea and mucositis (5.6% compared with 12%, and 1.9% compared with 15% respectively), when compared with the body surface area dosing arm of Gamelin et al. (2008).

5.33 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 4 World Health Organization grades. The analysis of these data indicated that the risk of diarrhoea and, to a lesser extent, leukopenia, was reduced with pharmacokinetic dose adjustment, whereas the risk of hand-foot syndrome and conjunctivitis was increased. 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 'National Cancer Institute's Common Terminology Criteria Scale'). The analysis of these data indicated 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 National Cancer Institute's Common Cancer Terminology Scale,

or necessitated dose adjustment. This study reported that grade 3 toxicity occurred equally in 37% of patients with stage 4 disease, whereas in patients with stage 2/3 disease, grade 3 toxicity was more common for body surface area dosing than for pharmacokinetic dose adjustment (69% compared with 32%; p=0.0437). The data also indicated that the number of 5-FU doses given before toxicity had occurred was greater for patients who received pharmacokinetic dose adjustment.

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

5.34 Four of the included studies reported data on 5-FU plasma levels. Of the 2 single-arm pharmacokinetic dose adjustment studies, Gamelin et al. (1998) reported that only 4% of patients had 5-FU plasma levels in the target optimal range after the first cycle, although under-dosing occurred in 82% of patients and over-dosing in 9% of patients. The target optimal range was achieved in 94.1% of patients after dose adjustment. In addition, Patel et al. (2014) reported that in cycle 1 (n=54), 29.6% of patients had 5-FU plasma levels within the target range, 18.5% had 5-FU plasma levels above the target range and 51.9% had 5-FU plasma levels below it. In cycle 4 (n=47), 46.8% of patients had 5-FU plasma levels within the target range, 21.3% had 5-FU plasma levels above the target range and 31.9% had 5-FU plasma levels below it.

5.35 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 had levels in the target range. Capitain et al. (2012) reported that at 3 months, 91% of patients having pharmacokinetic dose adjustment were having an adjusted dose. Additionally, around two-thirds of patients who had 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% to 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

5.36 Fety et al. (1998) reported a randomised prospective study that 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 internal validity of this study could not be assessed because the results reported in the analysis did not correspond with the published methods. Additionally, 4 patients in the body surface area dosing arm and 12 patients in the pharmacokinetic dose adjustment arm were excluded from the analysis of toxicity data. The study reported that grade 2 and 4 neutropenia and thrombocytopenia were reduced in the pharmacokinetic dose adjustment arm (7.6% compared with 17.5%; p=0.013), and that grade 2 and 4 mucositis was only reported in the body surface area dosing arm (5.1%).

Costs and cost effectiveness

5.37 The External Assessment Group 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 External Assessment Group also constructed a de novo economic model to assess the cost effectiveness of the My5-FU assay in people having continuous infusion 5-FU chemotherapy for metastatic colorectal cancer, and carried out an exploratory cost-effectiveness analysis for people with advanced head and neck cancer.

Systematic review of cost-effectiveness evidence

5.38 The systematic review identified an abstract (Becker et al. 2013), which reported the results of a cost–utility analysis of the My5-FU assay compared with body surface area dosing in patients with metastatic colorectal cancer in the UK. The abstract reported incremental cost-effectiveness ratios (ICERs) per quality-adjusted life year (QALY) gained for the following chemotherapy

regimens: 5-FU + folinic acid (£28,862), FOLFOX4 (two 22-hour continuous infusions) (£3467), FOLFOX6 (£3,594), FOLFIRI (£23,428), FOLFOX6 + bevacizumab (£3,508) and FOLFIRI + bevacizumab (£21,874). The External Assessment Group received a copy of the model from the authors, which is considered to be academic in confidence at this time and so cannot be presented here.

Metastatic colorectal cancer economic analysis

5.39 The External Assessment Group 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

5.40 The model was based on a cohort distributed between 4 health states over a 20-year time horizon. The following health states were included in the model:

- progression-free survival with first-line therapy
- progression-free survival with second-line therapy
- survival with progression
- death.

5.41 The cycle length was 2 weeks, which was chosen to reflect the length of a FOLFOX6 chemotherapy cycle, and a half-cycle correction was applied.

5.42 The distribution of the cohort among the 4 health states was determined by the underlying survival curves, which were constructed using evidence from the clinical-effectiveness section. The model took the perspective of the health and personal social services.

Model inputs

5.43 The model was populated using data derived from the clinical-effectiveness review, published literature and routine sources of cost data. Where published data were unavailable, expert opinion was used to derive estimates to populate the model. A discount rate of 3.5% was applied to both costs and effects. Survival data obtained from the clinical-effectiveness review were supplemented with survival data for body surface area dosing obtained from 7 studies included in the systematic review of the NICE guideline on colorectal cancer and the COIN study (Adams et al. 2011).

Costs

5.44 A cost per completed My5-FU assay of £61.03 was calculated, 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 was also applied to the My5-FU assay arm of the model. It was 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.

5.45 A cost of £584.54 per cycle was applied for FOLFOX6 and £595.44 per cycle for FOLFIRI chemotherapy. In addition, an ongoing monthly cost of £128 for secondary or tertiary care consultations, £103 for imaging and laboratory tests, and £17 for primary care costs was applied.

5.46 Estimates of the resource use associated with adverse events were combined with NHS reference costs for non-elective hospitalisations. Medication costs were only applied for adverse events that did not require hospitalisation.

Health-related quality of life and QALY decrements

5.47 Data on quality of life associated with progression-free survival and survival with progression were drawn from the literature; quality-of-life values of 0.820 for progression-free survival and 0.643 for survival with progression were applied in the base case.

5.48 QALY decrements associated with adverse events (diarrhoea, nausea and vomiting, hand-foot syndrome, mucositis, neutropenia, thrombocytopenia and leukopenia) 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.

5.49 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.

Base-case analyses

5.50 Overall and progression-free survival curves were extrapolated from Gamelin et al. (2008), Gamelin et al. (1998) (5-FU + folinic acid) and Capitain et al. (2012) (FOLFOX6). Because the overall survival curves differed substantially between the studies, 2 base-case analyses were developed:

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

5.51 The following assumptions were applied to both base-case analyses:

- First-line treatment is 12 cycles of FOLFOX6, and second-line treatment is 12 cycles of FOLFIRI (while patients remain in progression-free survival).
- By default, patients move from progression-free survival into survival with progression, and then to death. Moving directly from progression-free

survival to death only applies when there is an adding-up constraint determined by the Weibull survival curves, that is, if 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 that used high-performance liquid chromatography to measure plasma 5-FU are applicable to the My5-FU assay.
- The duration, effect and cost of second-line therapy are independent of the duration, effect and cost of first-line therapy.
- Neutropenia, thrombocytopenia and leukopenia have no impact on 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).
- The number of My5-FU assays needed per patient over the course of treatment is 3.23.
- The blood sample needed for the My5-FU assay is taken in the community by a health visitor.
- Ten minutes of consultant time are needed for each dose adjustment in the My5-FU assay arm.
- No end-of-life costs are applied.

FOLFOX6 base-case results

5.52 The FOLFOX6 base case applied the Weibull survival curves from the pharmacokinetic dose adjustment arm in Capitain et al. (2012) to the My5-FU assay 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 assay arm.

5.53 A deterministic analysis of the FOLFOX6 base case produced an ICER of £4,148 per QALY gained for the My5-FU assay, based on an estimated gain of 0.599 QALYs and an incremental cost of £2,483. A probabilistic sensitivity analysis based on 10,000 iterations was run, which also produced an ICER of £4,148 per QALY gained for the My5-FU assay. At a maximum acceptable ICER of £20,000 per QALY gained, the probability that dose adjustment using the My5-FU assay is cost effective compared with body surface area dosing is 100%.

FOLFOX6 scenario analyses

5.54 Five scenario analyses were reported for the FOLFOX6 base case, which applied different progression-free and overall survival estimates to the body surface area dosing arm only. The scenario analyses resulted in ICERs ranging from £3,514 to £3,950 per QALY gained.

FOLFOX6 sensitivity analyses

5.55 A number of univariate sensitivity analyses were reported that varied assumptions relating to: the cost and frequency of use of the My5-FU assay, the impact of treatment breaks and second-line FOLFIRI, the addition of end-of-life costs, taking blood samples in an oncology outpatient setting, the impact of different quality-of-life estimates and adverse event rates, and excluding overall and progression-free survival.

5.56 With the exception of excluding overall and progression-free survival, the sensitivity analyses resulted in ICERs ranging from £4,100 to £6,016 per QALY gained. The sensitivity analyses that assumed that a proportion of patients received a second course of FOLFOX6, applied alternative quality-of-life estimates, or those that assumed that blood samples were taken in an oncology outpatient setting had a noticeable impact on the cost effectiveness of the

My5-FU assay 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 the My5-FU assay is largely dependent on increased progression-free and overall survival being achieved in practice. A threshold analysis of the FOLFOX6 base case showed that, depending on the quality of life values applied, a hazard ratio of either 0.87 or 0.98 for overall survival would be needed for the My5-FU assay to be considered cost effective at a maximum acceptable ICER of around £20,000 per QALY gained.

5-FU + folinic acid base-case results

5.57 The 5-FU + folinic acid 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 assay and body surface area dosing arms respectively. It applied the Weibull progression-free survival curve, estimated by pooling results from 3 body surface area dosing studies included in the systematic review of the NICE guideline on colorectal cancer, to both the My5-FU assay 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 5-FU + folinic acid base case:

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

5.58 A deterministic analysis of the 5-FU + folinic acid base case produced an ICER of £5,853 per QALY gained for the My5-FU assay. A probabilistic sensitivity analysis based on 10,000 iterations was run, which produced an ICER of £5,852 per QALY gained for the My5-FU assay. At a maximum acceptable ICER of £20,000 per QALY gained, the probability that dose adjustment using the My5-FU assay is cost effective compared with body surface area dosing is 90%.

5-FU + folinic acid scenario analyses

5.59 Six scenario analyses were reported for the 5-FU + folinic acid base case, each of which used a different combination of progression-free and overall survival estimates for both the My5-FU assay and body surface area dosing. The scenario analyses resulted in ICERs ranging from £3,989 to £8,615 per QALY gained, and in 2 of the scenario analyses, the ICER was sensitive to changes in progression-free survival that impact on the number of patients having ongoing first-line FOLFOX6 treatment, resulting in ICERs of £6,965 and £8,615 per QALY gained.

5-FU + folinic acid sensitivity analyses

5.60 The univariate sensitivity analyses carried out for the FOLFOX6 base case were repeated for the 5-FU + folinic acid base case, applying adverse event estimates from Capitain et al. (2012). With the exception of excluding overall and progression-free survival, the sensitivity analyses resulted in ICERs ranging from £5,344 to £17,485 per QALY gained. Using alternative quality-of-life estimates or assuming that blood samples are 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 estimates were excluded, the ICER rose to £435,804 per QALY gained. A threshold analysis of the 5-FU + folinic acid base case showed that, depending on the quality of life values applied, a hazard ratio of either 0.85 or 0.97 for overall survival would be needed for the My5-FU assay to be considered cost effective at a maximum acceptable ICER of around £20,000 per QALY gained.

Economic analysis of head and neck cancer

5.61 The External Assessment Group reported an exploratory analysis of the cost effectiveness of the My5-FU assay in people with locally advanced head and neck cancer. 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 having

subsequent chemo-radiotherapy suggested 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 the My5-FU assay.

6 Considerations

6.1 The Diagnostics Advisory Committee reviewed the evidence available on the clinical and cost effectiveness of the My5-FU assay for guiding dose adjustment in patients having 5-fluorouracil (5-FU) chemotherapy by continuous infusion. The Committee noted that the evidence for clinical effectiveness included: studies and manufacturer validation data that compared the My5-FU assay with the analytical reference standard technologies (high-performance liquid chromatography and liquid chromatography-mass spectrometry); studies that reported algorithms developed to facilitate pharmacokinetic dose adjustment of continuous infusion 5-FU; and studies that reported clinical outcomes in patients with colorectal cancer who received either pharmacokinetic dose adjustment or body surface area dosing.

6.2 The Committee discussed whether the My5-FU assay could be considered equivalent to high-performance liquid chromatography and liquid chromatograph-mass spectrometry for the quantitative determination of 5-FU in plasma. The Committee noted that the available comparative data appeared to show that despite high correlation between the My5-FU assay and high-performance liquid chromatography or liquid chromatography-mass spectrometry, there was substantial variability between the methods, particularly with regard to the imprecision of the assay in its lower measuring range. The Committee considered that in clinical practice, patients who had under-dosing would be likely to have 5-FU plasma levels that would fall within the lower end of the My5-FU assay's measuring range. This imprecision could therefore impact on the My5-FU assay's reliability for clinical decision-making, specifically it may be less likely to detect patients who have low 5-FU plasma levels and who would potentially benefit from an increased dose of 5-FU at the next cycle. The Committee therefore concluded that it was not appropriate to consider the My5-FU assay equivalent to high-performance liquid chromatography and liquid chromatography-mass spectrometry for determining plasma levels of 5-FU and guiding dose adjustment in clinical practice. The Committee noted that this conclusion introduced substantial uncertainty into the interpretation of both the clinical outcome data (based mainly on studies using high-performance liquid chromatography) and the cost-effectiveness modelling.

6.3 The Committee discussed the published dose adjustment algorithms that had been included in the clinical-effectiveness review, and noted that 3 dose adjustment algorithms had been developed for use in patients having 5-FU chemotherapy for colorectal cancer and 1 for patients having 5-FU chemotherapy for head and neck cancer. The Committee heard from clinical specialists that only 1 of the published dose adjustment algorithms, which is based on a 5-FU + folinic acid + oxaliplatin (FOLFOX) regimen for colorectal cancer (Kaldate et al. 2012), could be considered applicable to current practice. The Committee considered whether the target range that had been established by Kaldate et al. (2012) could be extrapolated to head and neck, stomach, and pancreatic cancer. The Committee noted that, although it was plausible that the dose-outcome relationship suggested for people with colorectal cancer may be applicable to people with other types of cancer, no data were available to support this assumption. The Committee concluded that it was uncertain whether target ranges, and their associated dose adjustment algorithms, were transferrable between cancer types.

6.4 The Committee considered both the applicability and quality of the studies included in the colorectal cancer clinical outcomes analysis. The Committee noted that Gamelin et al. (2008) is a randomised controlled trial and considered that, despite using an outdated chemotherapy regimen, it may provide more robust survival estimates than Capitain et al. (2012), a retrospective study that reported results from a FOLFOX regimen. However, the Committee also noted that the External Assessment Group had identified concerns with the study design reported by Gamelin et al. (2008), in particular, the methods of randomisation were uncertain and it was not clear whether patients and investigators were blinded to allocation. The Committee considered that the studies included in the analysis could be regarded as 'proof of concept' studies, which demonstrated that the use of pharmacokinetic dose adjustment in the treatment of colorectal cancer was both feasible and had the potential to improve outcomes. However, the Committee concluded that these studies did not provide sufficiently robust effect estimates to determine whether pharmacokinetic dose adjustment was clinically effective compared with body surface area dosing, and noted that it was uncertain whether adjusting doses of 5-FU would translate into an improvement in clinical outcomes.

6.5 The Committee discussed the overall and progression-free survival data that had

been included in the colorectal cancer clinical outcomes analysis and noted that the limited outcome data available for this comparison were largely drawn from Kaplan–Meier curves that had been reconstructed and modelled by the External Assessment Group. The Committee considered that median survival estimates from each of the included studies indicated a trend towards increased progression-free and overall survival in patients who received pharmacokinetic dose adjustment, but noted that the clinical and statistical significance of the reported increases were uncertain and that the effect estimates obtained from the modelled Kaplan–Meier curves were open to substantial bias because of incomplete reporting of survival data in the included studies. Additionally, the Committee noted that 2 studies (Kline et al. 2013 and Patel et al. 2014) used the My5-FU assay to measure 5-FU plasma levels, although Patel et al. did not report survival data. The Committee also heard from clinical specialists that the overall survival estimates reported for pharmacokinetic dose adjustment (19 to 28 months) did not appear to be representative of current clinical practice. The Committee concluded that, because of potential biases from both study designs and the use of reconstructed survival data, there was substantial uncertainty around the magnitude of the effect of pharmacokinetic dose adjustment on progression-free and overall survival.

6.6 The Committee considered the toxicity data included in the colorectal cancer clinical outcomes analysis and discussed the likely impact of pharmacokinetic dose adjustment on toxicities associated with 5-FU chemotherapy. The Committee questioned which toxicities reported in the analysis were likely to be dose-dependent and heard from a clinical specialist that cardiac toxicities were unlikely to be related to 5-FU dosing. The Committee considered that the available data suggested pharmacokinetic dose adjustment may result in a significant reduction in the number of patients who experience diarrhoea, but that the impact of pharmacokinetic dose adjustment on other side effects was uncertain. Additionally, the Committee noted that the lack of blinding in the included studies, combined with the subjective nature of side effect reporting, could have introduced bias into the reported effect estimates. The Committee heard from patient experts that side effects associated with continuous infusion 5-FU may have a significant impact on a patient's quality of life and that an intervention that reduced the severity or duration of these side effects could have a substantial impact. The Committee also heard from clinical specialists that some toxicities have a greater impact than others and that most of the hospital

admissions associated with 5-FU toxicity are as a result of diarrhoea or neutropenic sepsis. The Committee concluded that although pharmacokinetic dose adjustment appeared to reduce the incidence of diarrhoea, there was insufficient evidence to determine whether it would have a substantial impact on other toxicities that may be associated with a negative impact on quality of life.

6.7 The Committee noted that no clinical outcome data were found for pharmacokinetic dose adjustment in people having continuous infusion 5-FU for pancreatic or stomach cancer. The Committee concluded that there was insufficient evidence to make recommendations on the use of the My5-FU assay in these populations.

6.8 The Committee considered that, because of a lack of data, the External Assessment Group had not been able to do any subgroup analyses. The Committee concluded that it was not possible to determine whether differential effects associated with pharmacokinetic dose adjustment would be observed in people with DPD (dihydropyrimidine dehydrogenase) deficiency, people with impaired renal or liver function, people whose body surface area is outside the standard range for dosing 5-FU and people with a less favourable performance status.

6.9 The Committee considered the cost-effectiveness analysis and noted that the economic model included 2 base-case analyses. The first was based on progression-free and overall survival data from a randomised controlled trial (Gamelin et al. 2008), which used a 5-FU + folinic acid regimen. The second was based on progression-free and overall survival data from a retrospective study (Capitain et al. 2012), which used a FOLFOX6 regimen. The Committee discussed the incremental cost-effectiveness ratios (ICERs) for both deterministic base cases and noted that the My5-FU assay appeared to be cost effective (£4,148 per quality-adjusted life year [QALY] gained in the FOLFOX6 base-case analysis and £5,853 per QALY gained in the 5-FU + folinic acid base-case analysis). However, the Committee noted that the results of the deterministic base-case analyses were based on the assumption that the effectiveness of the My5-FU assay is similar to high-performance liquid chromatography, and that the effect estimates obtained from Gamelin et al. (2008) and Capitain et al. (2012) would be observed in routine clinical practice. The Committee considered that, because of the bias observed in the lower measuring range of the assay and the uncertainty

associated with the relative survival estimates for pharmacokinetic dose adjustment, these assumptions would be unlikely to be realised in clinical practice. On this basis, the Committee concluded that the FOLFOX6 and 5-FU + folinic acid deterministic base-case ICERs were subject to substantial uncertainty.

6.10 The Committee considered the results of the base-case sensitivity analyses and noted that the cost effectiveness of the My5-FU assay was dependent on increased overall survival being realised in practice, because the reduction in toxicities alone was not sufficient to offset the increased costs associated with the My5-FU assay in the economic model. When the relative progression-free and overall survival effect estimates were removed from the economic model, the resulting ICERs were £435,819 per QALY gained in the FOLFOX6 analysis and £435,804 per QALY gained in the 5-FU + folinic acid analysis.

6.11 The Committee considered the threshold analyses for both the FOLFOX6 and 5-FU + folinic acid base cases and noted that the analyses showed that the use of the My5-FU assay could be considered cost effective if the small overall survival gains (hazard ratios of between 0.85 and 0.98) could be achieved in clinical practice. The Committee considered the uncertainty in the relative survival estimates obtained from Gamelin et al. (2008) and Capitain et al. (2012) and noted that the My5-FU assay could not be considered similar in effectiveness to high-performance liquid chromatography and liquid chromatography-mass spectrometry because of uncertainty in the precision of the My5-FU assay in its lower measuring range. The Committee also considered that the uncertainty in the clinical-effectiveness data, because of bias in the design of the Gamelin et al. (2008) and Capitain et al. (2012) studies, could not be fully captured in either the probabilistic sensitivity analyses or univariate sensitivity analyses, and therefore the resulting ICERs were likely to be subject to substantial uncertainty. The Committee therefore concluded that the uncertainty associated with the reported ICERs was too great to conclude that the use of the My5-FU assay would be cost effective in routine clinical practice.

6.12 The Committee considered the External Assessment Group's indicative economic analysis for head and neck cancer. The Committee noted that, although the relative survival gains needed for the My5-FU assay to be considered cost effective were relatively small (hazard ratio for overall survival: 0.990), the

uncertainties associated with the clinical effectiveness of the My5-FU assay in people with head and neck cancer meant that the results of the analyses were highly uncertain.

6.13 The Committee considered the likely impact of a reduction in toxicities associated with continuous infusion 5-FU in practice. The Committee heard from patient experts that side effects are often cumulative and increase during a course of chemotherapy, and clinical specialists suggested that it is not always possible to predict which patients will experience toxicities after the first cycle of chemotherapy. The Committee heard from clinical specialists that in current practice, patients who experience severe toxicities may have their dose of 5-FU reduced but that most of the side effects can often be treated with additional medications. The Committee considered that the most severe toxicities are often experienced by patients who have DPD deficiency and heard from clinical specialists that approximately 1 in 300 patients having continuous infusion 5-FU are thought to die within 30 days of their first chemotherapy cycle as a result of severe 5-FU toxicities. The Committee concluded that the incidence of severe side effects that become apparent during the first cycle of continuous infusion 5-FU was unlikely to be reduced by pharmacokinetic dose adjustment, but that an impact on less severe toxicities was more likely to be achieved in practice.

6.14 The Committee considered the likely impact of pharmacokinetic dose adjustment on the doses of 5-FU that would be administered in practice. The Committee noted that the studies included in the clinical-effectiveness review tended to show that most patients needed dose increases as a result of measuring 5-FU plasma levels, and heard from clinical specialists that pharmacokinetic dose adjustment could result in a greater number of patients having an optimal therapeutic dose of 5-FU because current practice does not identify patients who metabolise 5-FU at an increased rate and who consequently receive doses that have a reduced therapeutic effect. However, the Committee concluded that, at present, this may not be achieved if the My5-FU assay were implemented into clinical practice because of concerns regarding the imprecision of the assay within the clinical measuring range and insufficient evidence to demonstrate to clinicians that increasing the dose for patients who do not experience toxicities could result in improved clinical outcomes.

6.15 The Committee heard from patient experts that they would welcome the

opportunity to receive tailored dosing of continuous infusion 5-FU and believed that any inconvenience caused by 5-FU plasma monitoring, such as increased outpatient attendances, would be offset if quantity and quality of life were improved. The Committee considered that the most notable benefit associated with pharmacokinetic dose adjustment of continuous infusion 5-FU was its potential to increase the number of people having optimal therapeutic doses without increasing toxicities, but concluded that further research was needed to confirm whether this would be achieved in practice.

6.16 The Committee acknowledged that many clinicians now prescribe capecitabine as an alternative to 5-FU and noted that the My5-FU assay is not licensed for use with capecitabine. The Committee heard from clinical specialists that around 30% to 40% of colorectal cancer patients currently receive continuous infusion 5-FU and that recently licensed biological agents are marketed for use in conjunction with continuous infusion 5-FU. The Committee concluded that it was likely that there will continue to be a significant proportion of patients who receive continuous infusion 5-FU, and who may benefit from pharmacokinetic dose adjustment in the future.

7 What research is needed

7.1 The Committee recommended further research to validate the accuracy and precision of the My5-FU assay for the quantitative determination of 5-fluorouracil (5-FU) at the lower end of its measuring range with analytical reference standard methods, including high-performance liquid chromatography and liquid chromatography-mass spectrometry. Studies should investigate the comparability of the methods and determine the clinical significance of discordant results with reference to their impact on subsequent dose adjustments.

7.2 The Committee recommended that robust evidence be generated to show the clinical effectiveness of pharmacokinetic dose adjustment of continuous infusion 5-FU in people with colorectal cancer. Where possible, studies should consider the differential impact that pharmacokinetic dose adjustment may have on people with DPD (dihydropyrimidine dehydrogenase) deficiency, people with impaired renal or liver function, people whose body surface area is outside the standard range for dosing 5-FU and people with a less favourable performance status. Future studies might also consider the impact of DPD testing in conjunction with pharmacokinetic dose adjustment.

7.3 The Committee recommended further research to establish optimal target dose ranges for 5-FU plasma levels in people with head and neck cancer, stomach cancer and pancreatic cancer. Future studies should aim to both establish the optimal target dose range for each cancer and quantify its impact on clinical outcomes, taking into account any variation that may occur between different continuous infusion 5-FU regimens.

7.4 The Committee recommended further research to explore the impact of having continuous infusion 5-FU on patients. Future studies should investigate the experiences of patients having continuous infusion 5-FU and take into account the impact on quality of life. The potential consequences of introducing pharmacokinetic dose adjustment should also be explored.

8 Implementation

NICE will support this guidance through a range of activities to promote the recommendations for further research. The research proposed will be passed to the NICE Medical Technologies Evaluation Programme research facilitation team for the development of specific research trial protocols as appropriate. NICE will also incorporate the research recommendations in section 7 into its guidance research recommendations database (available on the NICE website) and highlight these recommendations to public research bodies.

9 Related NICE guidance

Published

- Neutropenic sepsis: prevention and management of neutropenic sepsis in cancer patients (2012) NICE guideline CG151
- Colorectal cancer (2012) NICE quality standard 20
- 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 (2012) NICE technology appraisal guidance 242
- Colorectal cancer: the diagnosis and management of colorectal cancer (2011) NICE guideline CG131
- Bevacizumab in combination with oxaliplatin and either fluorouracil plus folinic acid or capecitabine for the treatment of metastatic colorectal cancer (2010) NICE technology appraisal guidance 212
- Capecitabine for the treatment of advanced gastric cancer (2010) NICE technology appraisal guidance 191
- Cetuximab for the first-line treatment of metastatic colorectal cancer (2009) NICE technology appraisal guidance 176
- Cetuximab for the treatment of head and neck cancer (2008) NICE technology appraisal guidance 145
- Laparoscopic surgery for the treatment of colorectal cancer (2006) NICE technology appraisal guidance 105
- Improving outcomes in head and neck cancers (2004) NICE cancer service guidance
- Improving outcomes in colorectal cancer (2004) NICE cancer service guidance
- Capecitabine and tegafur with uracil for metastatic colorectal cancer (2003) NICE

technology appraisal guidance 61

10 Diagnostics Advisory Committee members and NICE project team

Diagnostics Advisory Committee

The Diagnostics Advisory Committee is an independent committee consisting of 22 standing members and additional specialist members. A list of the Committee members who participated in this assessment appears below.

Standing Committee members

Professor Adrian Newland
Chair, Diagnostics Advisory Committee

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

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

Professor Paul Collinson
Consultant Chemical Pathologist & Professor of Cardiovascular Biomarkers, St George's Hospital

Dr Sue Crawford
General Practitioner (GP) Principal, Chillington Health Centre

Professor Ian A Cree
Senior Clinical Advisor, NIHR Evaluation Trials and Studies Coordinating Centre, University of Southampton

Professor Erika Denton
National Clinical Director for Diagnostics, 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

Mr David Evans
Lay member

Dr Simon Fleming
Consultant in Clinical Biochemistry and Metabolic Medicine, Royal Cornwall Hospital

Mr John Hitchman
Lay Member

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

Mr Matthew Lowry
Director of Finance and Infrastructure, Doncaster and Bassetlaw Hospitals NHS Foundation Trust

Dr Michael Messenger
Deputy Director and Scientific Manager NIHR Diagnostic Evidence Co-operative, Leeds

Dr Peter Naylor
General Practitioner (GP), Chair Wirral Health Commissioning Consortia

Dr Dermot Neely
Consultant in Clinical Biochemistry and Metabolic Medicine, Newcastle upon Tyne NHS Trust

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

Professor Mark Sculpher
Professor of Health Economics, Centre for Health Economics, University of York

Dr Steve Thomas
Consultant Vascular and Cardiac Radiologist, Sheffield Teaching Hospitals Foundation Trust

Mr Paul Weinberger
CEO, DiaSolve Ltd, London

Specialist Committee members

Dr Nick Wadd
Consultant Clinical Oncologist, South Tees Hospitals NHS Foundation Trust

Dr Gireesh Kumaran
Consultant Medical Oncologist, The Mid Yorkshire Hospitals NHS Trust

Joanne Lowe
Clinical Pharmacist (Gastrointestinal/Palliative Care), The Christie NHS Foundation Trust

Ann Cole
Lay member

Anne-Marie Hunter
Lay member

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.

Rebecca Albrow
Topic Lead

Dr Sarah Byron
Technical Adviser

Robert Fernley
Project Manager

11 Sources of evidence considered by the Committee

The diagnostics assessment report was prepared by Warwick Evidence.

- Freeman K, Connock M, Cummins E et al. Fluorouracil plasma monitoring: the My5-FU assay for guiding dose adjustment in patients receiving fluorouracil chemotherapy by continuous infusion. A Diagnostic Assessment Report. June 2014.

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 and the diagnostics consultation document.

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

- Saladax Biomedical 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

Update information

Minor updates since publication

December 2025: Diagnostics guidance 16 has been migrated to HealthTech guidance 360. The recommendations and accompanying content remain unchanged.

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