NICE National Institute for Health and Care Excellence

DIAGNOSTICS ASSESSMENT PROGRAMME

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

Diagnostics Consultation Document – Comments

Diagnostics Advisory Committee date: 17 September 2014

THEME: LEVEL OF EVIDENCE

Comment number	Name and organisation	Section number	Comment	Response
1.	Consultee 1: Saladax Biomedical Inc.	1. Provisional Recommendations (page 2)	• Saladax Biomedical, Inc., the manufacturer of the My5-FU™ assay, is disappointed in the draft decision by NICE to recommend the My5-FU™ assay for use only in a research setting. We feel that the Diagnostics Advisory Committee was overly negative in their assessment of the assay and the available clinical data, particularly given the sheer amount and consistency of clinical evidence showing the failure of body surface area based 5-FU dosing and supporting pharmacokinetically (PK) guided dosing of 5-FU. • The My5-FU™ assay is a new diagnostic test for therapeutic drug monitoring (TDM), not a new drug. Please consider that this is a test that costs less than £20 per test, which is far lower than that provided for a new drug. The level of evidence being required of the My5-FU™ assay appears to be similar to that required for the approval of new drug, which is	Thank you for your comment which the Committee considered. The Committee considered that the relative effect estimates of pharmacokinetic dose adjustment of 5-FU compared to dosing based on body surface area available from the published literature are subject to a range of uncertainties, which limit their applicability to current practice and result in substantial uncertainty around the incremental effectiveness of pharmacokinetic dose adjustment. The Committee's considerations of the uncertainties in the clinical evidence are reported in sections 6.4, 6.5, 6.6, 6.7 and 6.8 of the guidance.

DIAGNOSTICS ASSESSMENT PROGRAMME

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

Diagnostics Consultation Document – Comments

Diagnostics Advisory Committee date: 17 September 2014

THEME: LEVEL OF EVIDENCE

Comment number	Name and organisation	Section number	Comment	Response
			neither economically feasible nor justifiable. • Holding My5-FU™ to the same standard of evidence as a new drug is inconsistent with the historical implementation of TDM. The use of a TDM assay has never required the same level of evidence as is used for new drugs. Large phase 3 trials have not been done nor deemed necessary to implement a TDM assay in the past. We question why a TDM assay for 5-FU in particular is being treated differently by the NICE Diagnostics Advisory Committee.	The evidence relating to the use of the My5-FU assay was reviewed by the independent external assessment group in accordance with the Diagnostics Assessment Programme Manual. This review included non-randomised studies and survival data which were reconstructed by the external assessment group. A linked evidence approach was then used to estimate the relative effect estimates of the My5-FU assay.
2.	Consultee 1: Saladax Biomedical Inc.	6.4 - 6.6 (page 31)	• More consideration and significance should be given to the substantial body of clinical evidence correlating 5-FU pharmacokinetics and patient outcomes. The NICE Diagnostics Advisory Committee assessment focuses on studies where pharmacokinetic dose adjustment of 5-FU has been performed. But historically, clear demonstration of the association of	Thank you for your comment which the Committee considered. The independent external assessment group informed the Committee that evidence on the association between 5-FU pharmacokinetics and clinical outcomes

DIAGNOSTICS ASSESSMENT PROGRAMME

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

Diagnostics Consultation Document – Comments

Diagnostics Advisory Committee date: 17 September 2014

THEME: LEVEL OF EVIDENCE

Comment number	Name and organisation	Section number	Comment	Response
			pharmacokinetics and clinical outcomes has been sufficient to support implementation of TDM in clinical practice. • There have been more than 32 studies over the past 30 years that demonstrate high pharmacokinetic variability of 5-FU exposure based on body surface area based dosing and show a strong association of 5-FU pharmacokinetics with clinical outcomes. These studies are highly applicable to the NICE Diagnostics Advisory Committee assessment and were included in the original diagnostics assessment report prepared independently by Warwick Evidence. Results from these studies are highly consistent over 30 years of research, including the most recent studies that demonstrate improved patient outcomes with pharmacokinetic-based dose adjustments. • The evidence supporting TDM for 5-FU is strong. Although there is no phase 3 trial using the most	was judged to be of low methodological quality and there was substantial heterogeneity in the studies which prevented the pooling of data and subsequent meta-analyses. The Committee concluded that the studies available for a comparison of the clinical effectiveness of pharmacokinetic dose adjustment and dosing based on body surface area did not provide sufficiently robust effect estimates to determine whether pharmacokinetic dose adjustment was clinically effective compared to body surface area dosing. The Committee decided to change section 6.4 of the guidance to clarify that there is uncertainty in whether adjusting doses of 5-FU would translate into an improvement in clinical outcomes.

DIAGNOSTICS ASSESSMENT PROGRAMME

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

Diagnostics Consultation Document – Comments

Diagnostics Advisory Committee date: 17 September 2014

THEME: LEVEL OF EVIDENCE

Comment number	Name and organisation	Section number	Comment	Response
			modern regimens, a large volume of evidence that is consistent over time supports TDM for 5-FU. Evidence includes many phase 1 and phase 2 trials, a phase 3 study with an older regimen, and up-to-date studies with current treatment regimens. The most reasonable interpretation of the complete body of clinical evidence is that patients will benefit from TDM for 5-FU.	The Committee considered that there was substantial uncertainty around the incremental effectiveness of pharmacokinetic dose adjustment compared to dosing based on body surface area. The Committee's considerations of the uncertainties in the clinical evidence are reported in sections 6.4, 6.5, 6.6, 6.7 and 6.8 of the guidance.
3.	Consultee 1: Saladax Biomedical Inc.	7 and 8 (pages 36 – 38)	• Ultimately, we hope that the NICE Diagnostics Advisory Committee will reconsider the need for additional clinical effectiveness data. The level of evidence being asked for to support TDM of 5-FU with the My5-FU™ assay is much more burdensome than has been traditionally needed to implement TDM for most other drugs. There is currently more data and information to support 5-FU TDM than for most	Thank you for your comment, which the Committee considered. The Committee considered that there was substantial uncertainty around the incremental effectiveness of pharmacokinetic dose adjustment compared to dosing based on body

DIAGNOSTICS ASSESSMENT PROGRAMME

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

Diagnostics Consultation Document – Comments

Diagnostics Advisory Committee date: 17 September 2014

THEME: LEVEL OF EVIDENCE

Comment number	Name and organisation	Section number	Comment	Response
			other drugs that currently utilize TDM. We believe the sum total of evidence demonstrates that the My5-FU™ assay can be a cost-effective refinement of BSA-based dosing (the current clinical standard) to aid physicians in optimizing 5-FU dosing and thereby greatly benefit patients.	surface area. The Committee's considerations of the uncertainties in the clinical evidence are reported in sections 6.4, 6.5, 6.6, 6.7 and 6.8 of the guidance.

DIAGNOSTICS ASSESSMENT PROGRAMME

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

Diagnostics Consultation Document – Comments

Diagnostics Advisory Committee date: 17 September 2014

THEME: VALIDATION OF THE MY5-FU ASSAY

Comment number	Name and organisation	Section number	Comment	Response
4.	Consultee 1: Saladax Biomedical Inc.	5.3 (page 8)	• The My5-FU assay was analytically verified following the Clinical Laboratory Standards Institute EP5-A2, EP6-A, EP9-A2, EP12-A2, EP17-A, and EP21-A approved guidelines and rigorously validated. The My5-FU™ assay has been independently assessed by different laboratories in the US, Europe, China, and Japan, and all groups have determined the assay to be reliable and reproducible for the routine monitoring of 5-FU levels in cancer patients. • Accuracy standards established for validation of physical methods allow for +/- 15 - 20% variability, while immunoassays, such as My5-FU™, are designed to have a variability of no more than +/- 5 - 10%. Additionally, immunoassays are manufactured in large quantities in a controlled, regulated environment, and are more reliable and reproducible than physical methods. • In all method comparisons performed with the My5-	Thank you for your comment, which the Committee considered. The Committee considered the evidence that showed there was strong correlation but also substantial bias, between the results of the My5-FU assay and those of the reference standard methods. In particular, the Committee noted the imprecision of the My5-FU assay in its lower measuring range and concluded that the patients who were underdosed would be likely to have 5-FU plasma levels that would fall within the lower end of the My5 FU assay's measuring range. The Committee concluded that analytical validation of an assay did not provide evidence of its utility in clinical practice. The Committee decided not to change section 5.3 of the guidance.

DIAGNOSTICS ASSESSMENT PROGRAMME

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

Diagnostics Consultation Document – Comments

Diagnostics Advisory Committee date: 17 September 2014

THEME: VALIDATION OF THE MY5-FU ASSAY

Comment number	Name and organisation	Section number	Comment	Response
			FU™ assay to date, correlation, slope and intercept values clearly met the criteria used by regulatory agencies around the world to demonstrate equivalence.	
5.	Consultee 1: Saladax Biomedical Inc.	6.2 (page 30)	• We again highlight the fact that in all method comparisons performed with the My5-FU™ assay to date, correlation, slope and intercept values clearly met the criteria used to demonstrate equivalence. The My5-FU assay was analytically verified following the Clinical Laboratory Standards Institute EP5-A2, EP6-A, EP9-A2, EP12-A2, EP17-A, EP21-A approved guidelines and rigorously validated. The My5-FU™ assay has been independently assessed by different laboratories in the US, Europe, China and Japan, and all groups have determined the assay to be reliable and reproducible for the routine monitoring of 5-FU in cancer patients. Buchel et al. (completely independently of Saladax Biomedical, Inc.) concluded that "the My5-FU assay demonstrated robust and	Thank you for your comment, which the Committee considered. The Committee considered the evidence that showed there was strong correlation but also substantial bias, between the results of the My5-FU assay and those of the reference standard methods. In particular, the Committee noted the imprecision of the My5-FU assay in its lower measuring range and concluded that the patients who were underdosed would be likely to have 5-FU plasma levels that would fall within the lower end of the My5 FU assay's measuring range. The

DIAGNOSTICS ASSESSMENT PROGRAMME

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

Diagnostics Consultation Document – Comments

Diagnostics Advisory Committee date: 17 September 2014

THEME: VALIDATION OF THE MY5-FU ASSAY

Comment number	Name and organisation	Section number	Comment	Response
			highly comparable performance on different analyzers" and is therefore "suitable for monitoring 5-FU plasma levels in routine clinical practice".	Committee concluded that analytical validation of an assay did not provide evidence of its utility in clinical practice. The Committee decided not to change section 6.2 of the guidance.

DIAGNOSTICS ASSESSMENT PROGRAMME

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

Diagnostics Consultation Document – Comments

Diagnostics Advisory Committee date: 17 September 2014

THEME: THE MY5-FU ASSAY COMPARED TO REFERENCE STANDARDS

Comment number	Name and organisation	Section number	Comment	Response
6.	Consultee 1: Saladax Biomedical Inc.	5.3 (page 8)	• Both high performance liquid chromatography and liquid chromatography-mass spectrometry are considered to be the reference standard in the independent Diagnostics Advisory Committee assessment. However, when high performance liquid chromatography and liquid chromatography-mass spectrometry are compared to each other, the amount and range of outliers are similar to what is observed when the My5-FU™ assay is compared to liquid chromatography-mass spectrometry. Discrepancies observed when the My5-FU™ assay was tested are similar to what is normally observed / expected when two different physical methods are compared.	Thank you for your comment, which the Committee considered. The Committee considered that high-performance liquid chromatography and liquid chromatography-mass spectrometry were considered to be the reference standard for the purposes of assessing the accuracy of the My5-FU and for facilitating a link between the data on the My5-FU assay and the clinical outcome data obtained using the reference standard technologies to guide dose adjustment. The Committee considered the evidence that showed there was strong correlation but also substantial bias, between the results of the My5-FU assay and those of the reference standard methods. In particular, the Committee noted the

DIAGNOSTICS ASSESSMENT PROGRAMME

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

Diagnostics Consultation Document – Comments

Diagnostics Advisory Committee date: 17 September 2014

THEME: THE MY5-FU ASSAY COMPARED TO REFERENCE STANDARDS

Comment number	Name and organisation	Section number	Comment	Response
				imprecision of the My5-FU assay in its lower measuring range and concluded that the patients who were underdosed would be likely to have 5-FU plasma levels that would fall within the lower end of the My5 FU assay's measuring range. The Committee concluded that analytical validation of an assay did not provide evidence of its utility in clinical practice. The Committee decided not to change section 5.3 of the guidance.
7.	Consultee 1: Saladax Biomedical Inc.	5.4 (pages 8 -9)	• The authors of the NICE diagnostic assessment agree that the study performed by Buchel et al. "reported a strong correlation between the My5-FU™ assay and liquid chromatography mass-spectrometry (R^2 = 0.99)". In their publication of the study, Buchel et al. (completely independently of Saladax Biomedical, Inc.) conclude that "the My5-FU assay demonstrated robust and highly comparable performance on different analyzers" and is therefore	Thank you for your comment, which the Committee considered. The Committee considered the evidence that showed there was strong correlation but also substantial bias, between the results of the My5-FU assay and those of the reference standard methods. Section 5.4 of the guidance states that "In addition,

DIAGNOSTICS ASSESSMENT PROGRAMME

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

Diagnostics Consultation Document – Comments

Diagnostics Advisory Committee date: 17 September 2014

THEME: THE MY5-FU ASSAY COMPARED TO REFERENCE STANDARDS

Comment number	Name and organisation	Section number	Comment	Response
			"suitable for monitoring 5-FU plasma levels in routine clinical practice".	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 Committee concluded that there was uncertainty in the level of imprecision in the My5-FU assay and therefore, uncertainty in its utility in clinical practice. The Committee decided not to change section 5.4 of the guidance.
8.	Consultee 1: Saladax Biomedical Inc.	5.5 (page 9)	• The authors of the NICE diagnostic assessment agree that the study performed by Beumer et al. "reported a strong correlation between the results of the My5-FU™ assay and liquid chromatography-	Thank you for your comment, which the Committee considered. Although the Beumer et al study reported a

DIAGNOSTICS ASSESSMENT PROGRAMME

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

Diagnostics Consultation Document – Comments

Diagnostics Advisory Committee date: 17 September 2014

THEME: THE MY5-FU ASSAY COMPARED TO REFERENCE STANDARDS

Comment number	Name and organisation	Section number	Comment	Response
			mass spectrometry (R^2 = 0.97)". Beumer et al. concluded that the two methods were equivalent, and note that "the immunoassay correlated well to a chromatographic method, validated according to the most recent Food and Drug Administration guidelines". • The NICE diagnostic assessment notes that the Beumer et al. study "did not report details of excluded data". This statement is not correct, as there were no data excluded from the study. All data were included in the published Beumer et al. analysis and no outliers were excluded from any of the evaluations.	strong correlation between the results of the My5-FU assay and liquid chromatography-mass spectrometry (R^2 = 0.97), there was a trend towards higher measurements when using the My5-FU assay. In addition, the confidence intervals, mean bias and limits of agreements were not reported so the significance of the findings of the study is not known. Please see section 5.5 of the guidance. The Committee were informed by the independent external assessment group that the Beumer et al. (2009) study did not state whether there were any exclusions from their analyses. The Committee decided to change section 5.5 of the guidance to state "this study did not state whether any data were excluded from the

DIAGNOSTICS ASSESSMENT PROGRAMME

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

Diagnostics Consultation Document – Comments

Diagnostics Advisory Committee date: 17 September 2014

THEME: THE MY5-FU ASSAY COMPARED TO REFERENCE STANDARDS

Comment number	Name and organisation	Section number	Comment	Response
				analysis".
9.	Consultee 1: Saladax Biomedical Inc.	5.7	• We again note that in all method comparisons performed with the My5-FU™ assay to date, correlation, slope and intercept values clearly met the criteria used to demonstrate equivalence. The manufacturer's validation data and analysis supports equivalence between LC-MS/MS and the My5-FU™ assay. The NICE diagnostic assessment also concludes that the results of manufacturer's data analysis comparing LC-MS/MS and the My5-FU™ assay suggest "no significant difference between the methods".	Thank you for your comment, which the Committee considered. Although the validation data suggested there is no significant difference between the My5-FU assay and LC-MS/MS, the 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. The Committee concluded that this uncertainty in the level of imprecision in the My5-FU assay could impact on its reliability for clinical decision making. The Committee decided not to change section 5.7 of the guidance.

DIAGNOSTICS ASSESSMENT PROGRAMME

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

Diagnostics Consultation Document – Comments

Diagnostics Advisory Committee date: 17 September 2014

THEME: THE MY5-FU ASSAY COMPARED TO REFERENCE STANDARDS

Comment number	Name and organisation	Section number	Comment	Response
10.	Consultee 1: Saladax Biomedical Inc.	6.2 (page 30)	• When evaluating variability between the My5-FU™ assay and other methods (high performance liquid chromatography or liquid chromatography-mass spectrometry), consider carefully the two reference methods. As previously commented, both high performance liquid chromatography (HPLC) and liquid chromatography-mass spectrometry (LC-MS/MS) are considered to be the reference methods in the independent Diagnostics Advisory Committee assessment. However, when HPLC and LC-MS/MS are compared to each other, the amount and range of outliers are similar to those observed when the My5-FU™ assay is compared to LC-MS/MS. Discrepancies observed when the My5-FU™ assay was tested are similar to what is normally observed / expected when two different physical methods are compared. • Thus, the My5-FU™ assay can be considered equivalent to HPLC and LC-MS/MS for determining	Thank you for your comment, which the Committee considered. The Committee discussed whether My5-FU could be considered equivalent to high performance liquid chromatography or liquid chromatography-mass spectrometry for the determining levels of 5-FU in plasma and guiding dose adjustment in clinical practice. The Committee considered that despite high correlation between the methods, there was variability and the Committee noted that there appeared to be substantial imprecision in the lower end of the My5-FU assay's measuring range. The Committee considered that in clinical practice, patients who were underdosed would be likely to have 5-FU plasma levels that would fall within the lower end of the My5 FU assay's

DIAGNOSTICS ASSESSMENT PROGRAMME

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

Diagnostics Consultation Document – Comments

Diagnostics Advisory Committee date: 17 September 2014

THEME: THE MY5-FU ASSAY COMPARED TO REFERENCE STANDARDS

Comment number	Name and organisation	Section number	Comment	Response
			plasma levels of 5-FU and guiding dose adjustment in clinical practice.	measuring range. 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 decided to change section 6.2 of the guidance.

DIAGNOSTICS ASSESSMENT PROGRAMME

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

Diagnostics Consultation Document – Comments

Diagnostics Advisory Committee date: 17 September 2014

THEME: NEW EVIDENCE ON CLINICAL SIGNIFICANCE OF OUTLIERS

Comment number	Name and organisation	Section number	Comment	Response
11.	Consultee 1: Saladax Biomedical Inc.	5.3 (page 8)	• Saladax Biomedical, Inc. in appendix A has submitted additional information and data analysis to NICE that supports the accuracy of the My5-FU™ assay. The analysis was requested by the Diagnostics Advisory Committee and has been resubmitted along with these comments.	Thank you for your comment which the Committee considered.
12.	Consultee 1: Saladax Biomedical Inc.	5.5 (page 9)	• The additional information and data analysis submitted by Saladax Biomedical, Inc. addresses the clinical significance of data from the Beumer et al. study. For this data set, some of the discrepant samples resulted in different dose adjustment recommendations between the two methods (LC-MS/MS and the My5-FU™ assay). However, because of the wide target range for optimal 5-FU exposure and the relatively small differences in dose adjustments, upon subsequent dosing it is equally likely that either dose adjustment recommendation would result in the patient achieving the target range. So there is no clinical significance to the	Thank you for your comment which the Committee considered. The Committee considered the additional information submitted from the Beumer et al. (2009) study and the manufacturer's datasets. The Committee considered that despite high correlation between the methods, there was variability and the Committee noted that there appeared to be substantial imprecision in the lower end of the My5-FU assay's measuring range. The Committee considered that in clinical

DIAGNOSTICS ASSESSMENT PROGRAMME

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

Diagnostics Consultation Document – Comments

Diagnostics Advisory Committee date: 17 September 2014

THEME: NEW EVIDENCE ON CLINICAL SIGNIFICANCE OF OUTLIERS

Comment number	Name and organisation	Section number	Comment	Response
			discrepancies. • These conclusions are consistent with the manufacturer's data set, where 3 of 57 samples could be considered discrepant samples, and all 3 resulted in identical dose adjustment recommendations between the two methods (LC-MS/MS and the My5-FU™ assay). There is no clinical significance to the discrepant samples in either data set.	practice, patients who were underdosed would be likely to have 5-FU plasma levels that would fall within the lower end of the My5 FU assay's measuring range. The Committee therefore considered that the imprecision in the lower measuring range of the My5-FU assay could impact upon its reliability for clinical decision making. The Committee decided to change section 6.2 of the guidance. The Committee also considered that if differences between dose adjustments do not have a significant clinical impact then there is greater uncertainty in whether adjusting the dose results in improved clinical outcomes. The Committee decided to change sections 6.4, 6.9 and 6.11 of the guidance.

DIAGNOSTICS ASSESSMENT PROGRAMME

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

Diagnostics Consultation Document – Comments

Diagnostics Advisory Committee date: 17 September 2014

THEME: NEW EVIDENCE ON CLINICAL SIGNIFICANCE OF OUTLIERS

Comment number	Name and organisation	Section number	Comment	Response
13.	Consultee 1: Saladax Biomedical Inc.	5.7	• The additional information and data analysis submitted by Saladax Biomedical, Inc. addresses the clinical significance of outliers in the manufacturer's data set. Only 3 of 57 samples in the manufacturer's data set could be considered discrepant samples. All 3 resulted in identical dose adjustment recommendations between the two methods (LC-MS/MS and the My5-FU™ assay). Thus, there is absolutely no clinical significance to the differences in measured blood levels for the outliers in this data set. • These conclusions are consistent with the Beumer et al. data set, where 10 of 156 samples could be considered discrepant. 5 of the 10 discrepant samples resulted in different dose adjustment recommendations between the two methods (LC-MS/MS and the My5-FU™ assay), The difference in dose adjustment of these five samples was less than 20% and given the wide target range for optimal 5-FU exposure and the relatively small differences in dose	Thank you for your comment which the Committee considered. The Committee considered the additional information submitted from the Beumer et al. (2009) study and the manufacturer's datasets. The Committee considered that despite high correlation between the methods, there was variability and the Committee noted that there appeared to be substantial imprecision in the lower end of the My5-FU assay's measuring range. The Committee considered that in clinical practice, patients who were underdosed would be likely to have 5-FU plasma levels that would fall within the lower end of the My5 FU assay's measuring range. The Committee therefore considered that the imprecision in the lower measuring range of the My5-FU assay could impact upon its

DIAGNOSTICS ASSESSMENT PROGRAMME

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

Diagnostics Consultation Document – Comments

Diagnostics Advisory Committee date: 17 September 2014

THEME: NEW EVIDENCE ON CLINICAL SIGNIFICANCE OF OUTLIERS

Comment number	Name and organisation	Section number	Comment	Response
			adjustments, upon subsequent dosing it is equally likely that either dose adjustment recommendation would result in the patient achieving the target range. Thus, there is no clinical significance to the discrepant samples in either data set.	reliability for clinical decision making. The Committee decided to change section 6.2 of the guidance. The Committee also considered that if differences between dose adjustments do not have a significant clinical impact then there is greater uncertainty in whether adjusting the dose results in improved clinical outcomes. The Committee decided to change sections 6.4, 6.9 and 6.11 of the guidance.
14.	Consultee 1: Saladax Biomedical Inc	6.2 (page 30)	• As mentioned earlier, the additional information and data analysis previously submitted by Saladax Biomedical, Inc. demonstrates a lack of clinical significance for the discrepancies identified between the methods. In the manufacturer's data set, only 3 of 57 samples could be considered discrepant, and all 3 resulted in identical dose adjustment recommendations between the two methods (LC-	Thank you for your comment which the Committee considered. The Committee considered the additional information submitted from the Beumer et al. (2009) study and the manufacturer's datasets. The Committee considered that despite high correlation between the

DIAGNOSTICS ASSESSMENT PROGRAMME

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

Diagnostics Consultation Document – Comments

Diagnostics Advisory Committee date: 17 September 2014

THEME: NEW EVIDENCE ON CLINICAL SIGNIFICANCE OF OUTLIERS

Comment number	Name and organisation	Section number	Comment	Response
			MS/MS and the My5-FU™ assay). For the Beumer et al. data set, 10 of 156 samples could be considered discrepant, and only 5 of the 10 discrepant samples resulted in different dose adjustment recommendations between the two methods (LC-MS/MS and the My5-FU™ assay). The difference in dose adjustment of these five samples was less than 20% and because of the wide target range for optimal 5-FU exposure and the relatively small differences in dose adjustments, upon subsequent dosing it is equally likely that either dose adjustment recommendation would result in the patient achieving the target range. Thus, there is no clinical significance to the differences in measured blood levels for discrepant samples in these data referenced.	methods, there was variability and the Committee noted that there appeared to be substantial imprecision in the lower end of the My5-FU assay's measuring range. The Committee considered that in clinical practice, patients who were underdosed would be likely to have 5-FU plasma levels that would fall within the lower end of the My5 FU assay's measuring range. The Committee therefore considered that the imprecision in the lower measuring range of the My5-FU assay could impact upon its reliability for clinical decision making. The Committee decided to change section 6.2 of the guidance. The Committee also considered that if differences between dose adjustments do not have a significant clinical impact then there is greater uncertainty in whether

DIAGNOSTICS ASSESSMENT PROGRAMME

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

Diagnostics Consultation Document – Comments

Diagnostics Advisory Committee date: 17 September 2014

THEME: NEW EVIDENCE ON CLINICAL SIGNIFICANCE OF OUTLIERS

Comment number	Name and organisation	Section number	Comment	Response
				adjusting the dose results in improved clinical outcomes. The Committee decided to change sections 6.4, 6.9 and 6.11 of the guidance.
15.	Consultee 1: Saladax Biomedical Inc	7	• As discussed earlier and resubmitted along with these comments, Saladax Biomedical, Inc. has provided additional validation data and analysis to further support equivalence between the My5-FU™ assay and HPLC and LC-MS/MS. The analysis indicates that discordant results between methods have minimal or no clinical significance.	Thank you for your comment, which the Committee considered. The Committee concluded that, because of imprecision in the lower measuring range of the My5-FU assay, 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. This is noted in section 6.2 of the guidance. The Committee therefore decided to change section 7.1 of the guidance to recommend further research

DIAGNOSTICS ASSESSMENT PROGRAMME

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

Diagnostics Consultation Document – Comments

Diagnostics Advisory Committee date: 17 September 2014

THEME: NEW EVIDENCE ON CLINICAL SIGNIFICANCE OF OUTLIERS

Comment number	Name and organisation	Section number	Comment	Response
				to validate the accuracy and precision of the My5-FU assay for the quantitative determination of 5-FU at the lower end of its measuring range.

DIAGNOSTICS ASSESSMENT PROGRAMME

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

Diagnostics Consultation Document – Comments

Diagnostics Advisory Committee date: 17 September 2014

THEME: NEW EVIDENCE ON COLORECTAL CANCER OUTCOME DATA

Comment number	Name and organisation	Section number	Comment	Response
16.	Consultee 1: Saladax Biomedical Inc.	5.13 (pages 12 – 13)	• To ensure that all relevant evidence has been taken into account by the Diagnostics Advisory Committee, we point out two recent publications in the literature that were not included in the assessment. Both publications are submitted to the NICE Diagnostics Advisory Committee along with these comments. • In June 2014, Braiteh et al. presented (attachment 1l) an analysis of clinical data collected by Saladax Biomedical Laboratories at the American Society for Clinical Oncology (ASCO) annual meeting. The data contained patient information (de-identified) and My5-FU™ assay testing results for 380 different colorectal cancer patients treated with the latest regimens from 2013-2014. The majority of patients (62%) were outside the target range when they were first tested, irrespective of 5-FU dosing or regimen. • Braiteh et al. reported on 158 evaluable cycle pairs (defined as two consecutive cycles with My5-FU™	Thank you for your comment which the Committee considered. The External Assessment Group reviewed studies by Braiteh et al. (2014) and Patel et al. (2014), and informed the Committee that only the Patel et al. (2014) study met the inclusion criteria for the clinical outcomes analysis. The Committee decided to change sections 5.13, 5.19, 5.32, 5.34 and 6.5 of the guidance to reflect the inclusion of Patel et al. (2014) study.

DIAGNOSTICS ASSESSMENT PROGRAMME

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

Diagnostics Consultation Document – Comments

Diagnostics Advisory Committee date: 17 September 2014

THEME: NEW EVIDENCE ON COLORECTAL CANCER OUTCOME DATA

Comment number	Name and organisation	Section number	Comment	Response
			results) where a patient was not receiving the optimal dose and had their dose adjusted consistent with the recommendation of the My5-FU™ test. As a result of the dose adjustment, 52% of patients were moved into the target range in the following cycle, clearly demonstrating that therapeutic dose monitoring of 5-FU is effective and results in more patients receiving optimal doses of 5-FU. Consistent with earlier studies, some patients required 3-4 cycles of dose adjustment to achieve optimal dosing. • This study of US clinical experience with My5-FU™ shows that therapeutic dose monitoring of 5-FU using the My5-FU™ assay is feasible in modern clinical practice with modern 5-FU-containing regimens. The dose adjustment algorithm provided with the My5-FU™ assay results (from Kaldate, et al.) is effective and practical in a real-world setting. • In August 2014 Patel et al. published (attachment 2)	

DIAGNOSTICS ASSESSMENT PROGRAMME

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

Diagnostics Consultation Document – Comments

Diagnostics Advisory Committee date: 17 September 2014

THEME: NEW EVIDENCE ON COLORECTAL CANCER OUTCOME DATA

Comment number	Name and organisation	Section number	Comment	Response
			a study of 70 colorectal cancer patients receiving the FOLFOX6 regimen who had dose adjustments done based on My5-FU™ assay results. Compared to historical data, significantly more patients at the end of this study were receiving optimal doses of 5-FU and patients experienced less gastrointestinal toxicity. The authors of this study conclude that the My5-FU™ assay allows for the application of personalized colorectal cancer therapy in the community setting. This study was previously presented as a poster at the 2013 ASCO annual conference. Publication of the manuscript may address questions about methodology, etc. that may have risen from the abstract or poster presentation. • Importantly, both of these studies demonstrate that therapeutic dose monitoring of 5-FU results in more patients receiving optimal doses of 5-FU. They are consistent with earlier studies of 5-FU therapeutic dose monitoring, and provide additional support for	

DIAGNOSTICS ASSESSMENT PROGRAMME

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

Diagnostics Consultation Document – Comments

Diagnostics Advisory Committee date: 17 September 2014

THEME: NEW EVIDENCE ON COLORECTAL CANCER OUTCOME DATA

Comment number	Name and organisation	Section number	Comment	Response
			the benefits of therapeutic dose monitoring of 5-FU in patients receiving modern 5-FU containing regimens.	

DIAGNOSTICS ASSESSMENT PROGRAMME

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

Diagnostics Consultation Document – Comments

Diagnostics Advisory Committee date: 17 September 2014

THEME: COST EFFECTIVENESS OF THE MY5-FU ASSAY

Comment number	Name and organisation	Section number	Comment	Response
17.	Consultee 1: Saladax Biomedical Inc.	6.9 (page 34)	• We believe that despite the uncertainties associated with survival estimates highlighted by the Diagnostics Advisory Committee, the most reasonable interpretation of the evidence and modelling is that TDM of 5-FU with the My5-FU™ assay is cost effective. • Section 5 of the Diagnostics consultation document notes that "at a maximum acceptable ICER threshold of £20,000 per QALY gained, the probability that dose adjustment using the My5-FU assay is cost effective compared to body surface area dosing is 100%." • The only scenario where TDM of 5-FU with the My5-FU™ assay is not cost effective is if the overall survival benefit is completely excluded. Given the volume of evidence supporting the benefit of 5-FU TDM, it is highly likely that at least a minimal survival	Thank you for your comment, which the Committee considered. An additional threshold analysis was undertaken by the External Assessment Group to estimate the likely gain in overall survival required for the My5-FU assay to be considered cost effective in both the FOLFOX6 and 5-FU + folinic acid base case analyses. The Committee further considered that the ICERs reported in the cost effectiveness modelling are based upon the assumption that My5-FU can be considered equivalent to high performance liquid chromatography and liquid chromatography, which could not be accepted because of uncertainty regarding the precision of the My5-FU assay in its lower measuring range. The Committee also considered that bias

DIAGNOSTICS ASSESSMENT PROGRAMME

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

Diagnostics Consultation Document – Comments

Diagnostics Advisory Committee date: 17 September 2014

THEME: COST EFFECTIVENESS OF THE MY5-FU ASSAY

Comment number	Name and organisation	Section number	Comment	Response
			benefit will occur if 5-FU TDM were utilized. • While the magnitude of the survival benefit may be uncertain, pharmacoeconomic modelling shows that even a very small margin of efficacy would result in the test being cost effective.	associated with the design of the Gamelin et al. (2008) study and the Capitain et al. (2012) study introduced additional uncertainty which may not have been captured in sensitivity analyses. The Committee decided to change sections 5.56, 5.60 and 6.11 of the guidance.

DIAGNOSTICS ASSESSMENT PROGRAMME

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

Diagnostics Consultation Document – Comments

Diagnostics Advisory Committee date: 17 September 2014

THEME: FURTHER RESEARCH

Comment number	Name and organisation	Section number	Comment	Response
18.	Consultee 1: Saladax Biomedical Inc.	7 and 8 (pages 36 – 38)	• Generating the level of evidence suggested by the committee may not be feasible. Despite physician enthusiasm, previous attempts to run a large phase 3 trial in the US to measure the survival benefit of the My5-FU™ assay were unsuccessful, primarily due to challenges in getting oncologists to recruit patients (i.e. the per-patient reimbursement that could be provided could not compete with that being provided by pharmaceutical companies for their new drug studies). The assay is an inexpensive test with a relatively low reimbursement, so it will also prove challenging to fund a large long-term study of the assay (i.e. there would be no real financial returns on the investment required). Larger studies in the UK have been proposed in the past but have not obtained funding.	Thank you for your comment, which the Committee considered. The Committee concluded that the research recommendations in section reflect the areas of uncertainty in the evidence base and that further research is needed to show the clinical effectiveness of pharmacokinetic dose adjustment. The Committee therefore decided not to change the guidance.

DIAGNOSTICS ASSESSMENT PROGRAMME

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

Diagnostics Consultation Document – Comments

Diagnostics Advisory Committee date: 17 September 2014

THEME: OTHER COMMENTS

Comment number	Name and organisation	Section number	Comment	Response
19.	Consultee 1: Saladax Biomedical Inc.	1 (page 2)	• My5-FU™ is a tool that can aid physicians in making clinical decisions about dosing and is to be used in conjunction with information available from clinical evaluations and/or other diagnostic procedures. As stated in the package insert of the My5-FU™ assay*: 5-FU drug concentrations should not be the only means of TDM. The assay should be used in conjunction with information available from clinical evaluations and other diagnostic procedures. The patient's current and past medical condition, the complexity of the clinical state, individual differences in sensitivity to 5-FU and toxic effects of 5-FU, co-administration of other drugs, and a number of other factors may result in different optimal blood concentrations of 5-FU for any individual. Each patient should undergo comprehensive clinical assessment prior to modification of the treatment plan and clinicians should carefully monitor patients during therapy initiation and dose adjustments.*	Thank you for your comment, which the Committee considered. The Committee decided to change section 4.3 of the guidance to state that the My5-FU assay is intended to be used in conjunction with clinical assessment.

DIAGNOSTICS ASSESSMENT PROGRAMME

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

Diagnostics Consultation Document – Comments

Diagnostics Advisory Committee date: 17 September 2014

THEME: OTHER COMMENTS

Comment number	Name and organisation	Section number	Comment	Response
			• Dosing adjustments suggested by the dose adjustment algorithm provided along with the results of the My5-FU™ assay are consistent with both current clinical practices and recommended dosing for 5-FU. Ultimately, dose adjustments should reflect the patient's complete clinical condition, with the My5-FU™ assay results being one of the pieces of information used by the physician to help guide 5-FU dosing.	Thank you for your comment, which the Committee considered. The Committee decided to change section 4.3 of the guidance to state that the My5-FU assay is intended to be used in conjunction with clinical assessment.
20.	Consultee 1: Saladax Biomedical Inc.	1 (page 2)	• Saladax Biomedical, Inc. hopes that the NICE Diagnostics Advisory Committee will reconsider the My5-FU™ assay as a tool that oncologists can use to better manage their patients. The My5-FU™ assay is a low cost diagnostic laboratory test demonstrated to be cost effective even at very small survival benefit levels, with additional benefits being a reduction in toxicity and improvement in patient quality of life. The My5-FU™ assay allows for the refinement of BSA-based dosing (the current clinical standard), which	Thank you for your comment which the Committee considered.

DIAGNOSTICS ASSESSMENT PROGRAMME

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

Diagnostics Consultation Document – Comments

Diagnostics Advisory Committee date: 17 September 2014

THEME: OTHER COMMENTS

Comment number	Name and organisation	Section number	Comment	Response
			has been shown again and again to be inaccurate and more harmful than dosing using TDM.	
21.	Consultee 1: Saladax Biomedical Inc.	6.13 (pages 35 – 36)	• Comments from patient experts highlight the significance of adverse events and quality of life benefits associated with 5-FU TDM. Clearly there is an unmet need within the oncology community for TDM of 5-FU. This need can be addressed with use of the My5-FU™ assay.	Thank you for your comment which the Committee considered.
22.	Consultee 2 Royal College of Nursing		• The Royal College of Nursing have no comments to submit to infom on the above ACD at this present time. thank you for the opportunity to review this document.	Thank you for your comment which the Committee considered.