NICE National Institute for Health and Care Excellence

Tests to help assess risk of acute kidney injury for people being considered for critical care admission (ARCHITECT and Alinity i Urine NGAL assays, BioPorto NGAL test and NephroCheck test)

Diagnostics Assessment Report (DAR) - Comments

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Faculty of Intensive Care Medicine	1	21		Clinicians should use both creatinine and urine output to recognise AKI. The lag phase in creatinine rise appears a bit silly to the lay person if the patient is anuric…..21	On page 21, plain English summary, we state that "level of creatinine in the blood or urine is used by health professionals to decide whether AKI is present." This has now been modified to: "At present, the level of creatinine (a waste product filtered by the kidneys) in the blood and the urine output are used by health professionals to decide whether AKI is present" (see Erratum).
Faculty of Intensive Care Medicine	2	21		Studies are mainly non-uk : true. But also the ICU criteria may be different when compared to the UK. (As noted on page 43)	No response required.
Faculty of Intensive Care Medicine	3	23		"*The remit of this work was to evaluate the clinical and cost effectiveness of biomarker use in the evaluation of patients not in critical care, but who might be considered for admission to critical care."* This is a slightly odd remit given that most of the studies utilised these tests in patients already on ICU as the authors point out.	The remit of this work is in line with the outcome of the DAP Experts Assessment Subgroup meeting that took place on 15 April 2019 and the subsequent NICE final scope for this assessment, which state: "*Clinical experts highlighted that the tests could be useful for people who are critically ill and being considered for admission to critical care; that is, for whom a decision about admission has not already been made and where information from the test results could guide the use of acute kidney injury care bundles. The decision*

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					question for this assessment therefore focuses on this population." It is worth noting that comments 7, 9, 10, 11, 12 below all relate to the scope/remit of this work.
Faculty of Intensive Care Medicine	4	36		The descriptors of causes of AKI (Pre-renal etc) are somewhat old fashioned now. Most intensivists try to refer to the pathological process Eg: Sepsis rather than the older anatomic criteria.	Even if we agree that information on the underlying pathological process is useful and recognise that ICU doctors describe AKI differently to other physicians, the reported causes of AKI are not incorrect and match those listed in the NICE scope. No revision required.
Faculty of Intensive Care Medicine	5	37		I think there should be no doubt as to the staging criteria : This is the KDIGO classification.	No response required.
Faculty of Intensive Care Medicine	6	40		*In the NHS, the Astute 140 Meter would be used in a laboratory and not at the point of care.* Why is this ? There are plans to combine procalcitonin and NC as a POC test. I have used NC as a POC test in a research study.	This information mirrors that in the NICE final scope and is in line with what was provided by the manufacturer of NephroCheck at the time of the assessment.
Faculty of Intensive Care Medicine	7	47		*In UK clinical practice the NephroCheck test and NGAL assays are likely to be used for the assessment of AKI in people who are considered for admission to critical care rather than in patients already admitted to critical care.*	Again, this is in line with the NICE final scope, which states:

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				Why? What about post major surgery or in Level1/2 areas?	"*Clinical experts highlighted that the tests could be useful for people who are critically ill and being considered for admission to critical care; that is, for whom a decision about admission has not already been made and where information from the test results could guide the use of acute kidney injury care bundles. The decision question for this assessment therefore focuses on this population."*
Faculty of Intensive Care Medicine	8	112		*With regard to the observed low specificy of the NephroCheck test, we do not know with certainty whether this is due to the relative poor performamce of the biomarker or to the fact that serum creatinine is an imperfect reference standard for assessing kidney injury.* This is an important point. The gold standard is far from perfect as is pointed out. There is considerable evidence that a raised biomarker is associated with poor outcomes even when the creatinine rise does not reach the staging criteria. So is this a specificity problem or highlighting how bad creatinine is? Perhaps the gold standard should be the biomarkers….	We agree this is an important point. However, we are not in a position to explore the ground truth of what AKI is, and indeed no such study exists. The current reference standard is serum creatinine.
Faculty of Intensive Care Medicine	9	127		*Based on the External Assessment Group's (EAG) own clinical expert opinion, it is assumed in the base case that patients testing negative would not have any adaptions*	The patient population specified in the NICE final scope are those from all hospital locations who are not in critical care but considered for admission to critical care. Therefore, the biomarker would be used pre-critical care where

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				made to their care pathway. That is because it would be unlikely that care would be de-escalated based solely on a negative NephroCheck or NGAL result, as the conservative practitioner would wait to ensure no rise in serum creatinine before concluding no AKI was present and stepping down care. This is a major bias in my opinion and is a considerable flaw. If the assessors do not believe the results despite the impressive specificity (better than creatinine…) then they do not have equipoise and then their opinion cannot be acted upon. Surely the model should assume that in the base case there is a change in practice such as step down, removing catheters, removing central lines etc etc otherwise no test would prove of economic benefit if they all adopt the "conservative approach".	there is not much scope for de-escalation. The focus is on the early identification of people at risk of AKI pre-critical care and the subsequent reduced need for ICU care. As per responses to comments 3 & 7, we agree that de-escalation from critical care may also be an important application, but this would need to be evaluated fully because the implications of actioning a change in care on the back of a negative test result, and particularly a false negative result, are currently unknown. We do not know whether a potential step-down approach could have negative consequences for a patient. Considering the scope of this assessment and the above uncertainties, our modelling focussed on the value of using the test to guide the implementation of a care bundle primarily outside ICU, to reduce the incidence and severity of AKI and attain associated benefits.
Faculty of Intensive Care Medicine	10	128		*The potential to benefit from use of the biomarkers therefore lies in early adoption of a preventative care bundle.* No. There is the case for deescalation and patient flow. This really is a major bias.	See response to point 9 above. De-escalation may be possible from a critical care setting to a ward setting. However, from a pre-critical care setting (the remit of this work) the case for further de-escalation is unclear. These would not be people receiving continuous monitoring, central lines, etc.

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Faculty of Intensive Care Medicine	11	128		I do not think the KDIGO bundle should be taken as the gold standard. What is the evidence that it works save one paper which shows a difference in urine output in the main. I really do think this part of the methodology is flawed. It assumes that the KDIGO bundle works. Where is the robust evidence. I think one should be examining the use of the biomarker in stopping treatment and interventions.	Please note that the purpose of this work was to model the value of using the test in line with the NICE final scope, and to identify limitations in the evidence base to support the use of testing and intervention strategies. The scope was not defined by the EAG as per previous answers. We acknowledge in our report the considerable limitations of the current evidence base for informing the effect of care bundles on patient relevant health outcomes. We have further highlighted the uncertainties that arise from having to rely on observational evidence of association to model potential effects. As indicated above, the population in the final scope makes the case for de-escalation of care difficult to justify, and this would likewise require sound evidence that stepping down care on the back of a negative test result does not result in patient harms.
Faculty of Intensive Care Medicine	12	138		*Whilst the model describes the impact of biomarker guided early intervention on the distribution of AKI, it is unclear whether these effects translate into final clinical and patient relevant health outcomes like requirement for ICU care, need for RRT,* Surely the KDIGO bundle can only be given in Level 2/3 areas given the potential for advanced haemodynamic monitoring and the use of dobutamine?	We agree with the reviewer that there is a lack of evidence for the effect of early intervention on final health outcomes and have drawn attention to this major limitation in our report. However, we disagree with the statement that the KDIGO care bundle can only be delivered in level 2/3 areas. Most aspects of the KDIGO

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					stage-based management can be delivered on the ward. Those that do not respond to fluid resuscitation, would then be considered for admission to Level 2/3 for extra support.
Faculty of Intensive Care Medicine	13	146		Could the financial model also consider use of the nephrocheck as a POC test given that is what it was developed as? Again I feel this is biased	See response to point 6 above.
Faculty of Intensive Care Medicine	14	151		Saline in potential AKI? No. I think the more expensive buffered solutions would be used.	We acknowledge that a more expensive buffered solution could be used for fluid assistance. Therefore, as an additional scenario analysis, we have instead assumed the use of the Hartmann's solution (conservatively applying the list price). The difference in cost is small and does not materially affect the results.
Faculty of Intensive Care Medicine	15	196		*When it is assumed NGAL cannot avert AKI, but can only reduce its severity, the cost-effectiveness case for NephroCheck improves substantially, but remains highly uncertain with a probability of cost-effectiveness ranging from 0% to 99% across the explored scenarios.* 0-99%. Says it all really.	We acknowledge that there is considerable uncertainty surrounding the cost-effectiveness of using the biomarkers to guide the use of preventive care packages for the population in scope. However, the modelling approach provides a framework for identifying the drivers of cost-effectiveness and identifying the gaps in current the evidence that prevent a definitive conclusion being reached.
Faculty of Intensive Care Medicine	16			With regard to the Nephrocheck studies: the test is licensed to predict development of AKI in critically ill patients with stage 1 AKI who will progress to stage 2/3	Four NephroCheck studies focused on the use of the test to identify stage 2/3 AKI within 12 hours according to the KDIGO classification system. Their primary endpoint was stage 2/3

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				within 12 hours. How many of the reported studies used the test under these conditions?	AKI. None of the NephroCheck studies assessed explicitly the progression from stage 1 to stage 2/3.
bioMérieux	17	77		Inaccuracies in extracted sensitivity and specificity parameters from NephroCheck literature Comment 1.A **Description of the comment** In **Table 5, Page 77** of Diagnostic Assessment Report (DAR), the sensitivity and specificity parameters extracted from the Cummings et al.[1] paper were reported as 0.31 and 0.78, respectively. Based on the definition used for the primary time point for the biomarker measurement in DAR (**Table 2 Page 51**), the correct time point for biomarker testing is immediately after surgery, which in the Cummings et al. paper corresponds to a Sensitivity and Specificity of 0.85 and 0.62, respectively. (Below image, Table E5 of the paper) Although, selecting biomarker measurement upon admission to the ICU is also a criterion for selecting the primary time point in DAR, for surgical patients (i.e., in the case of Cummings paper), the appropriate time to test patients for kidney stress would be immediately after surgery not upon admission to the ICU.	**Comment 1.A** With respect to the Cummings' paper, we used the first suitable measurement after surgery that was ICU admission, which is in line with the other NephroCheck studies. It is worth noting that there is a significant period of further operating between coming off cardiopulmonary bypass (CPB) and the end of the operation. This can be associated with marked cardiovascular instability and need for vasoactive support, which could affect renal function. Moreover, cardiac patients are admitted directly to the ICU from the operating theatre without being awoken; so, the ICU admission time in essence reflects the immediate period after surgery; whereas time off CPB is 2/3 of the way through the surgical procedure. No revision required.

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				TABLE E5. AUROC, sensitivity, specificity, PPV, and NPV of [TIMP-2]·[IGFBP7] with corresponding 95% confidenc 48 hours of surgery with 0.3 and 2.0 thresholds Cutoff of 0.3 [TIMP2]·[IGFBP7] Timepoint | AUROC | Sensitvity | Specificity | PPV | NPV Induction of anesthesia | 0.53 (0.37-0.69) | 0.21 (0.05-0.51) | 0.77 (0.72-0.81) | 0.03 (0.01-0.09) | 0.96 (0.94-0.98) 30 min after start of CPB or OpCAB | 0.52 (0.36-0.68) | 0.21 (0.05-0.51) | 0.67 (0.62-0.72) | 0.02 (0.00-0.07) | 0.96 (0.92-0.98) Immediately after CPB or OpCAB | 0.71 (0.58-0.82) | 0.85 (0.55-0.98) | 0.62 (0.57-0.67) | 0.07 (0.04-0.13) | 0.99 (0.97-1.00) ICU admission | 0.68 (0.54-0.81) | 0.31 (0.09-0.61) | 0.78 (0.74-0.82) | 0.05 (0.01-0.11) | 0.97 (0.94-0.99) **Description of the proposed amendment:** To replace the sensitivity and specificity estimates extracted from Cummings et al. with the numbers corresponding to the correct time point (immediately after surgery) throughout the report (including but not limited to the inputs in the meta-analysis, the cost-effectiveness models, and subgroup analysis. Specifically, the extracted sensitivity should increase from 0.31 to 0.85 and specificity should decrease from 0.78 to 0.62. **Result of amended model or expected impact on the results** Because sensitivity and specificity parameters from Cummings et al. paper were used as an input in the meta-analysis, we suggest rerunning the meta-analysis and subsequently rerunning all the models that include pooled estimate of NephroCheck sensitivity and specificity. We expect to see a pooled estimate that is more aligned with the totality of the literature on NephroCheck's diagnostic test accuracy, including but not limited to the estimates	

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				from Hall et al.[2] report (acknowledged in the last paragraph of Page 201 of DAR). This correction will also reduce the heterogeneity between NephroCheck studies and potentially reduce the propagated uncertainty in the economic model. **Comment 1.B** **Description of the comment** We reviewed the original paper by Di Leo et al.[2] and noticed that there is a discrepancy between the extracted sensitivity and specificity in DAR (Table 5, Page 77) and the corresponding numbers reported in Di Leo et al. Specifically, Table 5 shows the extracted Sensitivity and Specificity of NephroCheck are 0.56 and 0.54, respectively; however, the sensitivity and specificity numbers in the original report of the Di Leo et al. are 0.64 and 0.56, respectively. (Below image, page 273 of the paper) Additionally, the cut-off used in the Di Leo paper was 0.37 (not 0.3), which might slightly underestimate the sensitivity of NephroCheck.	**Comment 1.B** The accuracy data from the Di Leo et al.'s study was extracted and used correctly in the analyses (see forest plot on page 79). The typographical error in Table 5 has now been amended (see Erratum document). In line with the position of the authors of the paper (Di Leo et al.), we considered the cut-off of 0.37 akin to the NephroCheck validation value and decided to include the study in the meta-analysis. No further revision is required.

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				The optimal NC cutoff for our population is 0.37, and it was calculated minimizing the distance between the PROC plot and point (0.1; Fig. 3). AUC was 0.633, Specificity and Sensitivity were 56 and 64%, respectively, demonstrating that the NC test captured the majority of the AKI (positive) cases and a high number who did not manifest AKI. The number of False Positive was 209 (29%) with 86 False Negative. The confusion matrix on Table 2 have **Description of the proposed amendment:** To replace the sensitivity and specificity estimates extracted from Di Leo et al. with the correct numbers estimated in the paper. Specifically, the extracted sensitivity should increase from 0.56 to 0.64 and specificity should increase from 0.54 to 0.56. Similar to Problem 1A, this change needs to be applied throughout the report, including the meta-analysis and the cost-effectiveness model. **Result of amended model or expected impact on the results** Similar to Problem 1A, we suggest rerunning the meta-analysis and subsequently rerunning all the models that include pooled estimate of NephroCheck sensitivity and specificity using the updated input from Di Leo et al. We expect to see a pooled estimate that is more aligned with the totality of the literature on NephroCheck's diagnostic	

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				test accuracy, including but not limited to the estimates from Hall et al. This correction will also reduce the heterogeneity between NephroCheck studies and potentially reduce the propagated uncertainty in the economic model.	
bioMérieux	18	28		Assuming equality of NGAL and NephroCheck in averting AKI in the base case scenario is not supported by peer-reviewed evidence **Description of the comment** On multiple occasions in DAR including **Page 28**, authors referred to two different base case scenarios: Base case #1, assuming a scenario where NephroCheck and NGAL are equally effective in averting AKI and base case #2 assuming a scenario where NephroCheck can avert AKI, but NGAL cannot. Although it is theoretically possible to assume that these biomarkers perform equally well in averting AKI, peer-reviewed literature has demonstrated that this is not the case. Below, we summarized the relevant comparative literature on the differences between NephroCheck and NGAL. 1) In the first validation study for the NephroCheck Test (Kashani et al.)[4], in a cohort of 744 patients, the authors demonstrated that the NephroCheck Test biomarkers outperformed other biomarkers including NGAL in assessing risk for AKI. (Below image, Figure 2 of the paper).	We acknowledge the company's arguments about this assumption and we note that we mulled this issue over during the construction of the model. This is reflected in the fact that we included a set of results for both variations of the assumption. We believe this will be an important issue for the committee to consider and refer them to both sets of modelling results for comparison. If indeed AKI cannot be averted on the back of a positive NGAL test, it does not necessarily stand to reason that it cannot impact on AKI severity in similar manner to the NephroCheck. The test accuracy data, after all, should on average relate to the same selected timepoint.

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				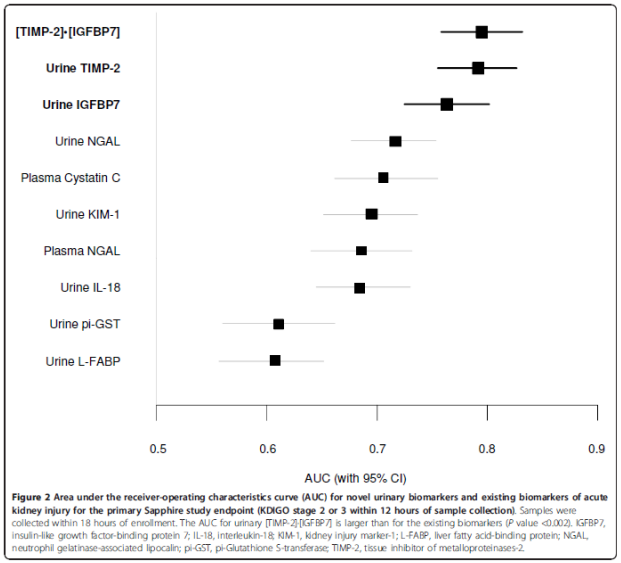 **Figure 2 Area under the receiver-operating characteristics curve (AUC) for novel urinary biomarkers and existing biomarkers of acute kidney injury for the primary Sapphire study endpoint (KDIGO stage 2 or 3 within 12 hours of sample collection)**. Samples were collected within 18 hours of enrollment. The AUC for urinary [TIMP-2]·[IGFBP7] is larger than for the existing biomarkers (*P* value <0.002). IGFBP7, insulin-like growth factor-binding protein 7; IL-18, interleukin-18; KIM-1, kidney injury marker-1; L-FABP, liver fatty acid-binding protein; NGAL, neutrophil gelatinase-associated lipocalin; pi-GST, pi-Glutathione S-transferase; TIMP-2, tissue inhibitor of metalloproteinases-2. 2) In a study by **Meersch et al**.[5], when comparing the NephroCheck Test to NGAL for the prediction of AKI in patients who underwent cardiac surgery, the authors found that the AUC of the NephroCheck Test was higher than the AUC of NGAL, 0.81 (95% CI: 0.68–0.93) and 0.68 (CI: 0.53–0.84), respectively, which demonstrates NephroCheck Test's superior diagnostic performance. (Below image, Figure 3 of the paper)	

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				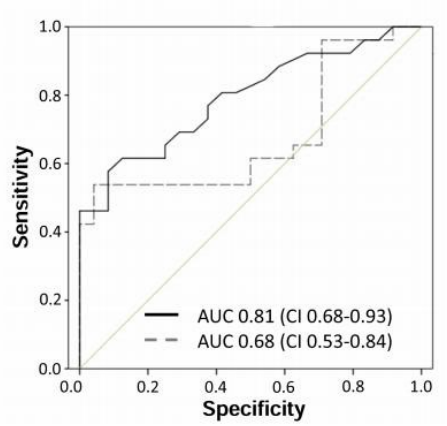 **Figure 3. ROC curves for the maximum early composite and the 4 h value.** (A) This figure displays the receiver operating characteristic (ROC) curve for the maximum early composite (maximum value from the first 24 postoperative hours) for [TIMP-2]*[IGFBP7]. (B) This figure displays the receiver operating characteristic (ROC) curves for the 4 h values of [TIMP-2]*[IGFBP7] (black solid line) and NGAL (gray dashed line). doi:10.1371/journal.pone.0093460.g003 3) **Page 168** DAR offers a justification for equality of NephroCheck and NGAL in averting AKI (base case #1), claiming that it can be assumed that NephroCheck and NGAL rise at the same time points and that no evidence existed to support the contrary. However, in a study by Zarbock et al.[6], the authors demonstrated that the NephroCheck biomarkers increased immediately after	

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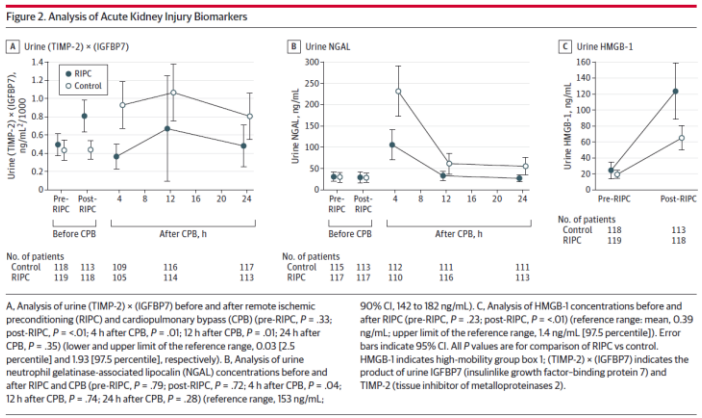
				remote ischemic preconditioning, whereas urinary NGAL remained unchanged. (Below image, Figure 2 of the paper)  Figure 2. Analysis of Acute Kidney Injury Biomarkers A Urine (TIMP-2) × (IGFBP7) B Urine NGAL C Urine HMGB-1 A, Analysis of urine (TIMP-2) × (IGFBP7) before and after remote ischemic preconditioning (RIPC) and cardiopulmonary bypass (CPB) (pre-RIPC, $P = .33$; post-RIPC, $P = <.01$; 4 h after CPB, $P = .01$; 12 h after CPB, $P = .01$; 24 h after CPB, $P = .35$) (lower and upper limit of the reference range, 0.03 [2.5 percentile] and 1.93 [97.5 percentile], respectively). B, Analysis of urine neutrophil gelatinase-associated lipocalin (NGAL) concentrations before and after RIPC and CPB (pre-RIPC, $P = .79$; post-RIPC, $P = .72$; 4 h after CPB, $P = .04$; 12 h after CPB, $P = .74$; 24 h after CPB, $P = .28$) (reference range, 153 ng/mL; 90% CI, 142 to 182 ng/mL). C, Analysis of HMGB-1 concentrations before and after RIPC (pre-RIPC, $P = .23$; post-RIPC, $P = <.01$) (reference range: mean, 0.39 ng/mL; upper limit of the reference range, 1.4 ng/mL [97.5 percentile]). Error bars indicate 95% CI. All P values are for comparison of RIPC vs control. HMGB-1 indicates high-mobility group box 1; (TIMP-2) × (IGFBP7) indicates the product of urine IGFBP7 (insulinlike growth factor-binding protein 7) and TIMP-2 (tissue inhibitor of metalloproteinases 2). 4) An important point about the elevation of the NephroCheck Test occurs when the stress is of sufficient magnitude to lead to AKI. This is evident in the referenced paper by Cummings et al.[1] where the NephroCheck Test is elevated immediately after surgery (sensitivity and specificity of 0.85 and 0.62, respectively; AUROC = 0.86; 95% CI, 0.77-0.94). (Below image, Figure E1 of the paper) Additionally, in a study by Ostermann et al.[7], NephroCheck levels were significantly elevated from the day of surgery to 48 hours later, while there was no significant elevation in urinary NephroCheck levels for patients who did not	

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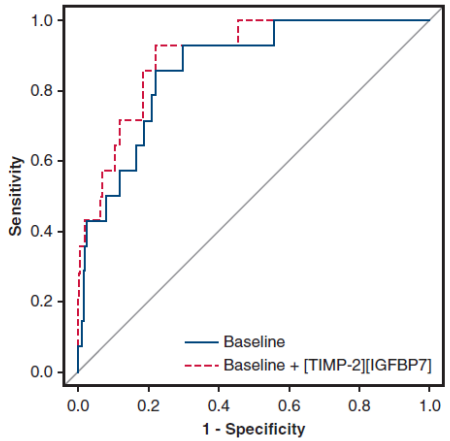
				develop AKI, which means that NephroCheck elevates during kidney stress prior to damage, when preventative measures can have an impact, as shown by Meersch et al.[8] and Gocze et al.[9]  **FIGURE E1.** Area under the receiver operating characteristic (AUROC) curves for the baseline clinical model (AUROC = 0.86; 95% confidence interval [CI], 0.77-0.94) and the model that includes the maximum of the post-cardiopulmonary bypass/OpCAB timepoint and the 6 hours after ICU admission timepoint, in addition to baseline clinical factors (AUROC = 0.90; 95% CI, 0.82-0.96). 5) In a recent publication, McCullough et al.[10] evaluated the serial testing of the NephroCheck biomarkers at baseline, 12 and 24 h, and up to 3 days (which is	

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				prognostic for the occurrence of stage 2/3 AKI over the course of critical illness). Three consecutive negative values <0.3 (ng/ml)2/1,000) are associated with very low (13.0%) incidence of stage 2/3 AKI over the course of 7 days; whereas, strongly positive results [> 2.0 [ng/mLJ2/1,000] predict a high proportion of the incident cases (up to 94.4%) of stage 2/3 AKI. Also, Husain et al.[11] demonstrated in patients with elective cardiac surgery, with normal resting glomerular filtration rates, the NephroCheck Test biomarkers predicted AKI with an AUC of 0.87 (95% CI: 0.79 to 0.84) upon ICU admission. Joannidis et al.[12] also showed that by using the NephroCheck biomarkers, they were able to improve risk stratification for severe outcomes in patients with stage 1 acute kidney injury by urine output, serum creatinine or both, with risk increasing with each acute kidney injury indicator. 6) In addition to the RCTs published by Meersch et al. and Gocze et al., In a recent publication by Engelman et al.[13], the authors studied and compared the incidence of stage 2/3 AKI in 435 patients from pre-urinary biomarker period to 412 patients post-urinary biomarker. The results showed that an early NephroCheck-triggered implementation of a KDIGO “cardiac surgery care bundle” resulted in an 89% relative decrease in the incidence of moderate or severe AKI within 7 days of surgery compared to routine post-operative clinical care. **Description of the proposed amendment**	

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				Based on above summary of evidence, we believe that the literature does not support a base-case, where NGAL and NephroCheck have equal impact on AKI aversion. Generalizing NephroCheck effect size (as shown in Meersch et al. and Gocze et al.) to NGAL is an optimistic assumption that can be more appropriately saved for a sensitivity analysis instead of the preferred base case of the model. Therefore, we suggest using a more conservative scenario as the preferred/only relevant base case, where NephroCheck is the only biomarker that can avert AKI. Obviously, the preferred base case can change upon the future availability of relevant evidence. Additionally, assuming the effect size equality between NephroCheck and NGAL in mitigating AKI severity is also considered optimistic, especially in the absence of any supporting evidence. Although theoretically, it might be more plausible for NGAL to reduce AKI severity than to avert AKI, still no quality evidence exist to support this assumption. Therefore, a more conservative base case analysis would reasonably assume that NephroCheck in the only biomarker that can avert AKI and reduce AKI severity. **Result of amended model or expected impact on the result** We believe that the current base case #2 **(Table 35, DAR Page 179)** is the only feasible base case that is	

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				conservative and compatible with available evidence. Base case #2 is still considered optimistic for NGAL as there is no evidence to support NGAL's equality to NephroCheck in reducing AKI severity.	
bioMérieux	19	135		Including only one trial (PrevAKI) as the sole source of effect size for biomarkers **Description of the comment** To estimate the impact of biomarker-guided interventions on AKI incidence and severity, the authors used Meersch et al.[8] paper as the sole source of the effect size, because Meersch et al. paper was the only source that described the impact of NephroCheck on both incidence and severity of AKI. **(DAR Page 135)** Meersch et al., as a randomized controlled trial, provides a high level of evidence for the rate of AKI aversion as well as reduction in the severity as a result of NephroCheck-guided implementation of KDIGO bundle; however, the scope of this study is limited to post-cardiac surgery patients. Gocze et al.[9], also cited in the NICE report, is a similar study that enrolled major non-cardiac surgery patients and provides high level of evidence in a complementary context across numerous other major surgeries and can improve the generalizability of the evidence. **Description of the proposed amendment:**	We acknowledge the company's point, but we would argue that the greater source of uncertainty in the economic model comes from linking the effect size on AKI incidence and severity to health outcomes through evidence of association rather than direct randomised evidence. This fails to acknowledge that AKI incidence may be a marker of other comorbidities that put an individual at greater risk of adverse outcomes. In this context we chose the single largest trial that provided a consistent source of evidence for the ability of the KDIGO bundle to avert AKI and redistribute its severity versus standard care in people with a positive NephroCheck test. The Gocze study was used to inform the associative effects to apply in the base case analysis (i.e. risk of ICU admission and ICU LoS). We further note the small numbers in Gocze et al and the lack of statistical significance on the primary endpoint (AKI of any severity). We acknowledge the significant effect that the company refer to, on the secondary outcome of

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				We suggest incorporating the results from Gocze et al. in the estimation of the relative risk of AKI associated with biomarker-guided interventions. Below methods are suggested for incorporating estimated effect size reported in Gocze et al. in the cost-effectiveness model: - Estimating a pooled effect size (e.g., relative risk) using estimates from both Meeersch et al. and Gocze et al. studies. The studies can be weighted based on the sample size as well as proportion of the major cardiac surgeries to major non-cardiac surgeries in the UK population. - Alternatively, we suggest running the cost-effectiveness study using effect size estimate from Gocze et al. (relative risk of 0.34 for AKI aversion) as a sensitivity analysis. **Result of amended model or expected impact on the results** We expect that applying the above suggested amendment will provide a more accurate ICER estimates for the biomarkers across a broader patient population than just post-cardiac surgery. The ICER calculated using the current base case assumption about the effect size might on average overestimate the biomarkers ICER for a broader patient population.	AKI stage 2 and 3, but note this secondary outcome is not in keeping with the way our model is structured (i.e. around the primary outcome and secondary outcomes of Meersch et al). Regardless, the uncertainties regarding the impact of AKI redistribution on final health outcomes and potential for harm in false positive cases remain. To address the company's concerns, we have run a further scenario analysis using the relative risk of AKI (0.67) for intervention versus control (from Gocze et al), in combination with relative risks of being in stage 2/3 (conditional on having AKI) versus control (from Gocze et al). This aligns to the RR 0.34 for the incidence of stage 2/3 AKI that the company refer to, without altering the structure of our model.
bioMérieux	20	148 & 374		The estimation of cost per test for NephroCheck and NGAL needs to be modified to reflect real-world usage	4.A) Since we were not advised of this financial model at the outset, we costed the test based on

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				Comment 4.A **Description of the problem** In **Table 24 Page 148 of DAR**, NephroCheck cost calculations included device capital cost, However, this assumption is not reflecting bioMerieux's commercial strategy in Europe and especially UK. **Description of the proposed amendment** As the company will place the device with no capital cost for customers, similar to NGAL, capital cost should not be factored in cost calculations. **Result of amended model or expected impact on the result (if applicable)** Need to re-run the model with new assumption, i.e., – £0.53 on total cost (£91.73 new total); the expectation is to see slightly smaller ICER for NephroCheck. Comment 4.B **Description of the comment (Table 45 Page 374)** A consumption of one Liquid QC for each new Test kit (of 25 tests) is assumed for NephroCheck. **Description of the proposed amendment**	the same approach described in the recently published HTA report by Hall et al. However, from the scenario analyses provided in our report, it can be noted that removal of this capital cost has a negligible impact on the results. 4.B) Liquid QC costs were likewise based on the published report by Hall et al. and assumed QC per test kit for all the tests. We accept that this may be an overestimate depending on how hospitals order batches and carry out liquid QC in practice. 4.C) We accept the companies point that wastage may occur, and that given the shelf life once opened, there may be greater potential for this to occur with BioPorto NGAL. However, without having comparable data on wastage for all the tests, we are not in the position to decide what assumptions are most appropriate. To address the company's concerns, we have run an additional scenario that includes all their proposed changes (4.A-4.C), which could be considered at the committee meeting. In the case a clear set of preferred costing assumptions were determined during the committee discussion, we would be happy to

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				NephroCheck Package Insert (300021 NephroCheck Test Kit Package Insert EU IVD Rev H, page 5 & 6, available at: https://www.nephrocheck.com/documents/300021%20NephroCheck%20Test%20Kit%20Package%20Insert%20EU%20IVD%20Rev%20H.pdf) says Liquid QC to be performed every 30 days, at lot change or at new shipment. Assuming the annual throughput of 1,253 Tests/yr, on average, 104 Tests are done per month, where 1 Liquid QC is sufficient. At each Liquid QC, 2 reagents are needed (at £49.80 each) Calculation: (100£ + 2 x 49.80£) / 104 Tests = £1.92 for Liquid QC cost / Test, instead of £4.00 in the model, i.e., -£2.08 on total cost of maintenance. **Result of amended model or expected impact on the result (if applicable)** Need to re-run the model with new assumption, e.g. –£2.08 on total cost (£90.18 new total); the expectation is to see slightly smaller ICER for NephroCheck that better reflects the real-world usage of the test. Comment 4.C **Description of the comment (Table 45 Page 374)** BioPorto risk of Test wastage not included in the model. Based on 1,253 Tests/yr assumption, on average 104 tests are done per month, however, each package of BioPorto	provide a full set of results reflecting these assumptions.

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				test has 300 kits and manufacturer product summary for Calibrator and control kit (BioPorto control and BioPorto calibrator available at https://bioporto.com/product/the-ngal-test-calibrator-kit/ and https://bioporto.com/product/the-ngal-test-control-kit/) indicates that once opened, storage time should not exceed 4 weeks. **Description of the proposed amendment** NGAL calibrator & control kit should be divided by the number of tests/month, i.e., 104, not 300 Therefore, correct cost: (£385+£185)/104 Tests = £5.48 / Test for maintenance **Result of amended model or expected impact on the result (if applicable)** Re-run the model with new assumption, e.g.+£3.58 on total cost (£63.13 new total). We expect that the above suggested amendment will reduce the NephroCheck ICER compared to BioPorto NGAL tests and is a better reflection of the real-world usage of the biomarkers.	
bioMérieux	21	33		Not including AKI excess cost in the base case model **Description of the comment** In DAR **Table 33 Page 171**, AKI excess cost per day in hospital/ICU was assumed to be zero i.e., no excess cost	We note that in our base case we do apply increased risks of ICU admission and increased LoS in ICU by AKI severity. Therefore, there is a cost reduction associated with averting and reducing the severity of AKI. There is also a cost

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				associated with AKI was applied in the cost-effectiveness model. "Conservative approach to ensure avoidance of double counting" was noted as the reason for this assumption. However, Hobson et al.[14] in a large observational study on 50,314 adult surgical patients showed that "patients with AKI were more likely to have postoperative complications and had longer lengths of stay in the intensive care unit and the hospital. The risk-adjusted average cost of care for patients undergoing surgery was $42,600 for patients with any AKI compared with $26,700 for patients without AKI. The risk-adjusted 90-day mortality was 6.5% for patients with any AKI compared with 4.4% for patients without AKI." The study also shows that after adjusting for the relevant explanatory variables, patients with any AKI still had hospital costs that were 159% of the costs for patients without AKI. (Hobson et al.) **Description of the proposed amendment** We believe that given the literature suggesting independent additional cost of AKI including Hobson et al., the excess cost associated with AKI should be included the base case models. This approach is also compatible with Hall et al. and seems to be the better reflection of available evidence. The "no excess cost assumption" as a less realistic yet still possible scenario needs to be included in the sensitivity analysis.	saving per day applied through reducing the requirement for dialysis. What we have not applied in the base case, is a daily increase in the cost of care for all AKI cases independently of care setting. This is to avoid the potential for double counting. We believe the increased risk of being admitted to ICU or requiring dialysis (included in the base case) may already capture the excess cost per day for having AKI in hospital. In addition, we believe that the excess cost applied for AKI in the Hall model may not be appropriate, as it reflects the cost of an extra day in hospital, rather than the extra cost per day attributable to having AKI versus no AKI. It is worth keeping in mind that the effects of AKI on ICU admission and ICU LoS that are applied in the base case analysis, are based on evidence of association and so may in fact overestimate cost-savings associated with AKI aversion and reduction in severity.

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				Result of amended model or expected impact on the result (if applicable) We expect applying the changes proposed above will provide a more accurate estimate of biomarkers ICER that might be overestimated under current base case assumptions.	
bioMérieux	22	127		Assuming no changes in the care pathway following biomarker negative results in the base case model **Description of the comment** In **DAR page 127**, the authors noted that "... based on the External Assessment Group's (EAG) own clinical expert opinion, it is assumed in the base case that patients testing negative would not have any adaptions made to their care pathway. That is because it would be unlikely that care would be de-escalated based solely on a negative NephroCheck or NGAL results, as the conservative practitioner would wait to ensure no rise in serum creatinine before concluding no AKI was present and stepping down care". Most recently, a consensus of sixteen global AKI experts determined that with the aid of the NephroCheck Test, a KDIGO guideline-based care pathway can be used to manage patients earlier. (**Guzzi et al.**[15]) In this paper, the authors developed a consensus statement regarding the	See response to point 9 above. We thank the company for pointing to the study by Guzzi et al. However, we are not sure about the relevance of the study to the UK setting and population specified in the NICE final scope (pre critical care) with regard to de-escalation of care based on a negative test. This is because the study obtained expert opinion from USA, as well as Europe to generate a potential care pathway for those having a positive/negative test. Furthermore, the study indicates that the users of the test found it most useful within the first 72 hours of ICU admission. Therefore, the expert opinion provided in the study is based on the use of the test in a setting that differs from that specified in the NICE final scope. The applicability of the tests in the UK ICU setting was queried by clinical experts during the scoping phase.

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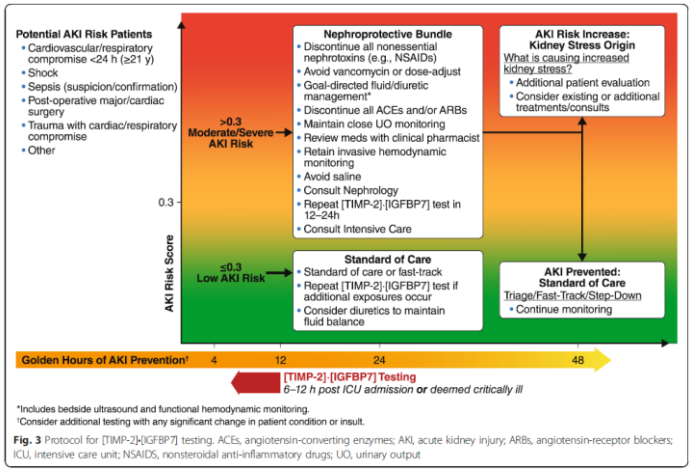
				appropriate use of the NephroCheck Test. This consensus paper offers guidance on how to modify care pathways in the presence of a negative test result, which can include implementing “fast-tracking” protocols. (Below image, Fig. 3 of the paper)  **Fig. 3** Protocol for [TIMP-2]·[IGFBP7] testing. ACEs, angiotensin-converting enzymes; AKI, acute kidney injury; ARBs, angiotensin-receptor blockers; ICU, intensive care unit; NSAIDS, nonsteroidal anti-inflammatory drugs; UO, urinary output **Description of the proposed amendment** Although there is uncertainty about the appropriate clinical approach in the presence of a negative biomarker results, clinical experts with knowledge and experience in using biomarkers suggest considering “fast track” protocols for patients with a negative biomarker results, where clinically	

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				appropriate. Therefore, we suggest considering potential care pathway modifications for test-negative patients in the economic model. **Result of amended model or expected impact on the result (if applicable)** We expect that care pathway modifications as a result of a negative biomarker test lead to some efficiency gains, especially in the context of post major surgery, where fast tracking protocols are more meaningful.	
bioMérieux	23	128		Excluding relevant evidence about biomarkers impact on clinical and economic outcomes **Description of the comment** In **DAR, page 128,** the authors noted that "…there is no direct evidence to describe the impact of the use of the AKI biomarkers on important health outcomes (such as need for ICU care, length of hospital stay, risk of 90-day mortality or development of new / progression of existing chronic kidney disease)". However, on **page 207,** DAR acknowledges that at least partial evidence is available based on Gocze et al.[9]: "the early adoption of a bundle of supportive measures according to the KDIGO guidelines in patients with NephroCheck concentrations higher than 0.3 $(ng/mL)^2/1000$ resulted in a reduced occurrence of AKI, decreased hospital and ICU stay, and reduced costs". Currently, no real-world evidence exists that can directly link biomarkers to important clinical outcomes, however,	See also response to point 19 above. We further note that the EAG base case includes partial associative effects of the biomarkers on the probability of being admitted to ICU, and the LoS in ICU and hospital, modelled through the effects of the care bundle on the incidence and severity of AKI. Further scenario analyses cover the inclusion of full associative effects on ICU admission and LoS, hospital LoS, and wider effects on mortality and long-term follow-up costs. It is difficult to incorporate effects based directly on Gocze, because Gocze reports data for an ICU cohort, and not a cohort being considered for admission to ICU.

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				economic models exist that demonstrate costs savings in ICU LOS, 30-day readmissions, and non-ICU LOS, assuming the effect size reported in Gocze et al. (Berdugo et al.)[16] **Description of proposed amendment** As part of the sensitivity analysis in the economic model, we suggest incorporating the impact of biomarkers on length of stay based on estimates reported in Gocze et al.	
bioMérieux	24			List of citations 1) Cummings JJ, Shaw AD, Shi J, Lopez MG, et al. Intraoperative prediction of cardiac surgery-associated acute kidney injury using urinary biomarkers of cell cycle arrest. J Thorac Cardiovasc Surg. 2018; 10.1016/j.jtcvs.2018.08.090. 2) Hall PS, Mitchell ED, Smith AF, et al. The future for diagnostic tests of acute kidney injury in critical care: Evidence synthesis, care pathway analysis and research prioritisation. Health Technol Assess 2018; 22(32), 1-274. 3) Di Leo L, Nalesso F, Garzotto F, et al. Predicting Acute Kidney Injury in Intensive Care Unit Patients: The Role of Tissue Inhibitor of Metalloproteinases-2 and Insulin-Like Growth Factor-Binding Protein-7 Biomarkers. Blood Purification 2018; 45(1-3), 270-7.	No response required.

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				4) Kashani K, Al-Khafaji A, Ardiles T, et al. Discovery and validation of cell cycle arrest biomarkers in human acute kidney injury. Crit Care. 2013;17(1):R25. 5) Meersch M, Schmidt C, Van Aken H, et al. Urinary TIMP-2 and IGFBP7 as early biomarkers of acute kidney injury and renal recovery following cardiac surgery. PLoS One. 2014;9(3):e93460. 6) Zarbock A, Schmidt C, Van Aken H, et al. Effect of remote ischemic preconditioning on kidney injury among high-risk patients undergoing cardiac surgery: a randomized clinical trial. JAMA. 2015;313(21):2133-2141 7) Ostermann M, McCullough PA, Forni LG, Bagshaw SM, Joannidis M, Shi J, Kashani K, Honore PM, Chawla LS, Kellum JA, all SAPPHIRE Investigators. Kinetics of urinary cell cycle arrest markers for acute kidney injury following exposure to potential renal insults. Critical care medicine. 2018 Mar;46(3):375. 8) Meersch M, Schmidt C, Hoffmeier A, et al. Prevention of cardiac surgery-associated AKI by implementing the KDIGO guidelines in high risk patients identified by biomarkers: the PrevAKI randomized controlled trial. Intensive Care Med. 2017;43(11):1551-1561. 9) Göcze I, Jauch D, Götz M, et al. Biomarker-guided Intervention to Prevent Acute Kidney Injury After Major	

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				Surgery: The Prospective Randomized BigpAK Study. Annals of Surgery. 2017 10) McCullough P, A, Ostermann M, Forni L, G, Bihorac A, Koyner J, L, Chawla L, S, Shi J, Kampf J, P, McPherson P, Kellum J, A: Serial Urinary Tissue Inhibitor of Metalloproteinase-2 and Insulin-Like Growth Factor-Binding Protein 7 and the Prognosis for Acute Kidney Injury over the Course of Critical Illness. Cardiorenal Med 2019. 11) Husain-Syed F, Ferrari F, Sharma A, Hinna Danesi T, Bezerra P, Lopez-Giacoman S, Samoni S, de Cal M, Corradi V, Virzì GM, De Rosa S. Persistent decrease of renal functional reserve in patients after cardiac surgery-associated acute kidney injury despite clinical recovery. Nephrology Dialysis Transplantation. 2018 Jul 19;34(2):308-17. 12) Joannidis M, Forni L, Haase M, Koyner J, Shi J, Kashani K, Chawla L, Kellum, J. Use of Cell Cycle Arrest Biomarkers in Conjunction With Classical Markers of Acute Kidney Injury. Crit Care Medicine. 2019 13) Engelman DT, Crisafi C, Germain M, Greco B, Nathanson BH, Engelman RM, Schwann TA. Utilizing Urinary Biomarkers to Reduce Acute Kidney Injury Following Cardiac Surgery. The Journal of Thoracic and Cardiovascular Surgery. 2019 Oct 17.	

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				14) Hobson C, Ozrazgat-Baslanti T, Kuxhausen A, Thottakkara P, Efron PA, Moore FA, Moldawer LL, Segal MS, Bihorac A. Cost and mortality associated with postoperative acute kidney injury. Annals of surgery. 2015 Jun;261(6):1207. 15) Guzzi LM1, Bergler T, Binnall B, et al. Clinical use of [TIMP-2]•[IGFBP7] biomarker testing to assess risk of acute kidney injury in critical care: guidance from an expert panel. Crit Care. 2019 Jun 20;23(1):225. 16) Berdugo MA, et al. Economic and clinical benefits of early indication of acute kidney injury using a urinary biomarker. Journal of Medical Economics. 2019	
Ortho Clinical Diagnostics	25	210	6	The report concludes further research is required. The Diagnostics Advisory Committee should ensure any such recommendation is accompanied with practical and considered guidance as to how this may be achieved. Considering that such data may be generated demonstrating achievement of cost effectiveness thresholds (according to the standards of this model) there is an imperative to establish such data in the shortest possible timeframe (in this case patients are currently deprived the intervention, with associated health economic cost, solely because of an absence of information, not an absence of cost-effectiveness). (The Expected Value of Perfect Information is high).	No response required.

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				Such guidance must contemplate what might reasonably be expected to be practically implemented and funded and from what funding sources. As such, according to powering, large, multi-centre, double blind randomised controlled trials might be deemed unlikely to be practical nor achieve funding. The Diagnostics Advisory Committee should build on the earlier NIHR report (The future for diagnostic tests of acute kidney injury in critical care: evidence synthesis, care pathway analysis and research prioritisation; Hall et al.) and upon which so much of The External Assessment Group report has relied. Hall et al. report: *'It is apparent that observational studies that aim to better define the current clinical care pathway for patients at risk of AKI in critical care should be a priority, as should further work to understand how the care pathway might change in response to a positive test and the effectiveness of these changes in mitigating against the development of AKI.' (p xxix)* And further, concerning adoption *'… we would recommend that this is undertaken only within the framework of careful observational study, audit and an exit strategy at the point of evidence re-evaluation. Such an approach would allow many of the assumptions on which the economic model relies to be tested or better informed by data'.* The report continues:	

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				'There is interest by national reimbursement decision-makers such as NICE in new models of reimbursement that introduce conditionality on a positive reimbursement decision. We consider AKI diagnostic tests to be a suitable test case for such a model. This could be achieved by clearly defining the indication and putting in place a prospective audit framework that captures key data items that are currently uncertain or absent from the economic model. (p 161) The Diagnostics Advisory Committee should develop the recommendation of The External Assessment Group to ensure practical progress can be made in establishing the true value of NephroCheck guided care bundle through specific recommendations including the careful study of local implementation.	
Ortho Clinical Diagnostics	26	40	2	The test can also be run on the VITROS 7600 Integrated System clinical chemistry analyser. As such: *The test can also be run on the VITROS 3600 immunodiagnostic System and on the VITROS 5600 Integrated System clinical chemistry analysers.* Should be changed to: *The test can also be run on the VITROS 3600 immunodiagnostic System and on the VITROS 5600 and VITOS 7600 Integrated System clinical chemistry analysers*	This statement reflects the information reported in the NICE final scope and that provided by the company at the time of the assessment (point 9 page 12/20 of the Request of Information document). No revision required.

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		28 & 169		Considering only NephroCheck has the potential to avert AKI, the base case (1) should be the case that considers only NephroCheck can avert AKI.	
Ortho Clinical Diagnostics	27	24 &128		States "as there is no evidence to describe the impact of the use of the AKI biomarkers on important health outcomes (such as need for ICU care, length of hospital stay…). The Gocze study published in 2017 did measure LOS as an outcome for a NephroCheck guided bundle. Recommend to include the Gocze data in the assessment of cost effectiveness and also change the wording in the document from there is "no evidence" to there is "limited evidence".	See response to point 19 above. Text has been revised (see Erratum, page 128).
Ortho Clinical Diagnostics	28	207		Statement that "there when biomarker guided care bundles are used alongside KDIGO criteria, there is still considerable uncertainty and confusion about how and when to use them in clinical practice." Recommend to change this wording to: *Guidance from an expert panel on how to use Nephrocheck in clinical practice has been published in an article by Guzzi et al. The panel identified which patients would be appropriate for testing, how the results should be interpreted, and what actions would be taken based on the results of the test.* Reference: Guzzi et al. Clinical Use of [TIMP-2] [IGFBP7] biomarker testing to assess the risk of acute kidney injury	See response to point 22 above. We acknowledge this study but remain uncertain regarding its applicability to the patient population specified in the scope (pre-critical care in those being considered for admission to critical care). We have modified the wording in our Discussion section as follows: *"Overall, despite some evidence suggesting possible improvement of care processes and health care utilisation when biomarker guided care bundles are used alongside KDIGO criteria,*

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				in critical care: guidance from an expert panel". Critical Care (2019) 23:225; https://doi.org/10.1186/s13054-019-2504-8.	*there is still considerable uncertainty regarding effects on health outcomes, particularly when used in the pre-critical care setting."*
Ortho Clinical Diagnostics	29	276		What is DTA? Recommend that this is defined in the report as it is currently not included in the list of abbreviations. We are unable to comment as to why the 2017 Gocze study was excluded without this definition.	
Ortho Clinical Diagnostics	30	145		The NephroCheck test may be run on other VITROS instruments other than just the VITROS 3600. Change: "The test could also be conducted on a VITROS 3600 Immunodiagnostic System; however, UK hospitals rarely have this system in laboratories". To: "The test could also be conducted on a VITROS Immunodiagnostic Systems, although currently, there is a limited installed base in UK hospitals."	This sentence has been amended (see Erratum)
Ortho Clinical Diagnostics	31			We have had the opportunity to review bioMerieux's responses to the Diagnostic Assessment Report and we are aligned with bioMerieux in terms of identified issues and proposed amendments. Below, we presented some of the highlights of bioMerieux's response that we think will have the biggest impact on the model.	
Ortho Clinical Diagnostics	32	77		There are inaccuracies in extracted sensitivity and specificity parameters from NephroCheck literature. We agree with the recommended proposals in the bioMerieux DAR comments document to rerun the meta-analysis and subsequently rerun all the models that	See response above.

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				include a pooled estimate of NephroCheck sensitivity and specificity using the numbers corresponding to the correct time point as defined in the bioMerieux comments section as Problem 1.A and Problem 1.B.	
Ortho Clinical Diagnostics	33	28		Assuming equality of NGAL and NephroCheck in averting AKI in the base case scenario is not supported by peer-reviewed evidence. We believe that the current base case #2 **(Table 35, DAR Page 179)** is the only feasible base case that is conservative and compatible with available literature. Base case 2 can still be considered optimistic for NGAL as there is no evidence to support NGAL's equality to NephroCheck in reducing AKI severity.	See response to point 18 above.
Ortho Clinical Diagnostics	34	135		Including only one trial (PrevAKI) as the sole source of effect size for biomarkers. We suggest incorporating the results from Gocze et al. in the estimation of the relative risk of AKI associated with biomarker-guided interventions.	See response to point 19 above.
Ortho Clinical Diagnostics	35	127		Assuming no changes in the care pathway following biomarker negative results in the base case model Although there is uncertainty about the appropriate approach in the presence of a negative biomarker results, clinical experts with knowledge and experience in using biomarkers suggest considering "fast track" protocols for patients with a negative biomarker results, where clinically appropriate. Therefore, we suggest considering potential	See response to point 9 above.

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				care pathway modifications for test-negative patients in the economic model. Guidance on how to modify care pathways can be found in figure 3 of the article: Guzzi et al. Clinical Use of [TIMP-2] [IGFBP7] biomarker testing to assess the risk of acute kidney injury in critical care: guidance from an expert panel". Critical Care (2019) 23:225; https://doi.org/10.1186/s13054-019-2504-8.	