Australian Government

Medical Services Advisory Committee

Public Summary Document

Application 1335 – Point of Care Tests to exclude preterm labour: Phosphorylated Insulin-like Growth Factor Binding Protein test

Applicant: **Alere Pty Ltd**

Date of MSAC consideration: **MSAC 62nd Meeting, 26-28 November 2014**

Context for decision: MSAC makes its advice in accordance with its Terms of Reference, see at www.msac.gov.au

1. Purpose of application and links to other applications

An application requesting the Medicare Benefits Schedule (MBS) listing of the Phosphorylated Insulin-like Growth Factor Binding Protein (phIGFBP-1) test for excluding false preterm labour was received from Alere Pty Ltd (Inverness Medical Innovations Australia) by the Department of Health in September 2012.

A related application proposing MBS listing of fetal fibronectin (fFN) point of care tests (PoCTs) for predicting false preterm labour was received from Hologic (Australia) Pty (Application Number 1351) and considered by MSAC at the same meeting.

2. MSAC's advice to the Minister

After considering the available evidence in relation to safety, clinical effectiveness and cost-effectiveness phosphorylated insulin-like growth factor binding protein (phIGFBP-1) testing for predicting pre-term labour, MSAC did not support public funding because of inadequate test performance and thus unacceptable overall clinical effectiveness and cost-effectiveness.

MSAC noted that the evidence demonstrated poor and variable accuracy of the test, no verification of additive value over existing methods of assessing the risk of pre-term labour, but also evidence that use of the test would not change current clinical practice.

3. Summary of consideration and rationale for MSAC's advice

MSAC noted the application requested MBS listing of point of care testing of phIGFBP-1 in cervicovaginal secretions of women presenting with symptoms of early labour for the purposes of excluding pre-term labour.

The phIGFBP-1 test can be used to distinguish between false labour and true labour in women threatening pre-term labour. A monoclonal antibody is used to detect for the presence of phIGFBP-1 by isolating it from similar peptides. The presence of phIGFBP-1 is postulated to be predictive of pre-term labour. Identification of false labour can reduce the unnecessary use of therapies to delay premature labour (tocolytics) and to promote fetal lung development (corticosteroids), both of which have potential side effects. It can also reduce unnecessary referral to a tertiary level hospital with appropriate neonatal care facilities. MSAC noted that this was particularly important for women in rural and remote communities, where hospital admission may mean considerable travel away from family.

MSAC noted the overlap between this application and Application 1351 for quantitative fetal fibronectin (fFN) testing for predicting pre-term labour. Therefore, both applications were considered simultaneously.

The proposed item descriptor requested MBS funding for pregnant women between 24 weeks and 33 weeks and 6 days gestation who present with symptoms of threatened pre-term labour and are found to have intact amniotic membranes on sterile speculum examination of the cervix.

MSAC compared the phIGFBP-1 test with routine clinical care with and without the use of transvaginal ultrasound (TVUS) to assess cervical length (CL) across several scenarios presented in the application:

- standard clinical management and phIGFBP-1 test with or without TVUS to measure CL versus cervical assessment with or without TVUS to measure CL
- standard clinical management and fFN test with or without TVUS to measure CL versus cervical assessment with or without TVUS to measure CL
- standard clinical management and phIGFBP-1 test with or without TVUS to measure CL versus standard clinical management and fFN test with or without TVUS to measure CL.

There were no studies identified that investigated the safety of the phIGFBP-1 test in the diagnosis of pre-term labour. The test itself is considered safe so long as it is performed by a qualified health professional using a sterile speculum with a sterile swab after premature rupture of the amniotic membranes has been excluded.

MSAC considered the analytical validity of the phIGFBP-1 test, using pre-term delivery within seven days as the reference standard. The evidence presented suggested that the rate of false negatives is unacceptably high for its intended use as a triage test. A false negative, where a woman is incorrectly excluded from being at risk of pre-term labour, can have serious consequences. Across ten studies, sensitivity values ranged widely between 0.3 and 1.0, clustering around 0.5 to 0.7, with the poorest result coming from the study with the second largest sample size. Although these results suggest the test performs better than chance, there remains unexplained clinically important heterogeneity in this test performance, and clinically important rates of false negatives. The summary operating point (of sensitivity = 0.72; 95%CI: 0.64, 0.79 and specificity = 0.80; 95%CI: 0.74, 0.85) and its prediction contours in the summary receiver operating characteristic (SROC) curve were not considered

to reflect the true extent of underlying heterogeneity, which was likely to be affected by the low event rate of pre-term delivery. Overall, MSAC concluded that these sensitivity results were not sufficient to achieve a reasonable threshold for concluding that test negative results are clinically reliable. In other words, relying on the results from this test is likely to lead to an increased risk of harm compared with not relying on the test and managing threatened pre-term labour conservatively, because of the appreciable number of women with pre-term delivery classified as 'false pre-term labour' by the test.

MSAC considered the evidence from four studies directly comparing the analytical validity of phIGFBP-1 with fFN, again using pre-term delivery within seven days as the reference standard. The results of these studies for phIGFBP-1 were consistent with those of the larger sample of ten studies. The comparative results provided no basis to conclude that one test performs better or worse than the other.

No data were presented that compare the analytical validity of phIGFBP-1 with current clinical assessment without TVUS, which is more relevant to the wider range of clinical settings proposed for its use. Comparisons with TVUS were less relevant because this technology is less likely to be available in these settings. There were also no data presented to examine the extent to which adding phIGFBP-1 to clinical assessment might modify analytical validity, rather than assessing the phIGFBP-1 test result in isolation. It is probable that this test may improve accuracy compared with current clinical assessment, but with insufficient sensitivity to achieve acceptable thresholds to avoid misclassifying women and causing harm compared to a more risk-averse approach to clinical management.

There were no data presented on the consequences of testing for subsequent clinical management, such as use of tocolytics and steroids, or referrals to hospital, nor on the extent to which the test might improve patient outcomes through these changes in clinical management. However, data meta-analysed from six small randomised trials (total N=530) comparing management with and without fFN test results showed no statistically significant difference in the rates of admission to hospital (rate difference = 3% more admissions with fFN results known; 95%CI: 10% more admissions to 3% fewer admissions). MSAC considered the lack of any effect on hospitalisations could be explained by having many inputs to the clinical management decision in this situation, resulting in, at best, a very small net information gain from adding a point of care test result.

The economic evaluation was modelled on the results of the meta-analysis of diagnostic accuracy linked to estimates in the extent of changes in rates of hospital admission based on expert opinion rather than on revealed actions. The analysis suggested that implementing point of care testing would be cost neutral. However, MSAC concluded that there is insufficient evidence available regarding the comparative change in practice following phIGFBP-1 testing compared to standard care or TVUS and that the estimates were inconsistent with the trial data presented for fFN.

MSAC concluded that there was considerable uncertainty around the economic model in four main areas, none of which were adequately examined in the sensitivity analyses:

- the transformation of diagnostic accuracy measures into patient management flows and outcomes across the multiple test settings defined;
- the assumptions regarding the rates of hospitalisation based on advice from experts drawn from the Health Expert Standing Panel;
- in settings where TVUS is available, the extent to which the apparent advantages associated with the use of the point-of-care tests is attributable to the diagnostic performance of TVUS; and

- failure to consider the consequences of false negative results or the consequences for mother or baby health outcomes when determining the measure of outcome in the evaluation (proportion of women correctly categorised).

MSAC noted that, per test conducted, phIGFBP-1 testing is less costly than fFN testing at the proposed MBS fees.

4. Background

An application for listing of an earlier form of the fFN test was assessed by MSAC in November 2006. MSAC determined that the test is safe but that effectiveness had not been demonstrated and did not support public funding.

A separate application for another test for excluding preterm labour, the fFN test, was under consideration by MSAC at the same time as this application.

5. Prerequisites to implementation of any funding advice

The phIGFBP-1 test is registered by the Therapeutic Goods Administration (TGA) for use in Australia.

ESC suggested that the proposed items be restricted to practitioners in aseptic speculum techniques, which include physicians, participating nurse practitioners or participating midwives. No additional specialised training or qualifications are required by these practitioners to perform this test.

6. Proposal for public funding

The proposed medical service applies to patients presenting with symptoms of pre-term labour. The phIGFBP-1 test can be used to assist health care practitioners to distinguish between:

-false labour (where there may be contractions and other signs of labour but the woman does not give birth in the next seven days); and
-true labour (where the woman does give birth in the next seven days).

Identification of false labour can reduce the unnecessary use of therapies such as tocolytics and corticosteroids, both of which have potential side effects, as well as reduce unnecessary hospital admissions.

The majority of these women will go onto deliver at term but a significant number are at risk of delivering pre-term which is associated with serious health-risks to the infant. The MBS item descriptors proposed by the applicant are presented below.

Proposed MBS item descriptor

Category 2 – Diagnostic Procedures and Investigations
MBS [item number] Detection of Phosphorylated Insulin-like Growth Factor Binding Protein (phIGFBP-1) in cervical secretion specimen by an immunochemical method for the assessment of threatened preterm labour where premature rupture of membranes (PROM) has been excluded Fee: $81.97 Benefit 75%= $61.44 85%=$69.83

MBS [item number] Detection of Phosphorylated Insulin-like Growth Factor Binding Protein (phIGFBP-1) in cervical secretion specimen by an immunochemical method for the assessment of threatened preterm labour where premature rupture of membranes (PROM) has been excluded—by a participating nurse practitioner Fee: $81.97 Benefit 75%= $61.44 85%=$69.83
MBS [item number] Detection of Phosphorylated Insulin-like Growth Factor Binding Protein (phIGFBP-1) in cervical secretion specimen by an immunochemical method for the assessment of threatened preterm labour where premature rupture of membranes (PROM) has been excluded—by a participating midwife Fee: $81.97 Benefit 75%= $61.44 85%=$69.83

Access to the intervention is suggested for pregnant women, between 24 and 33 weeks and 6 days gestation who present with the symptoms of threatened preterm labour and are found to have intact amniotic membranes on sterile speculum examination of the cervix.

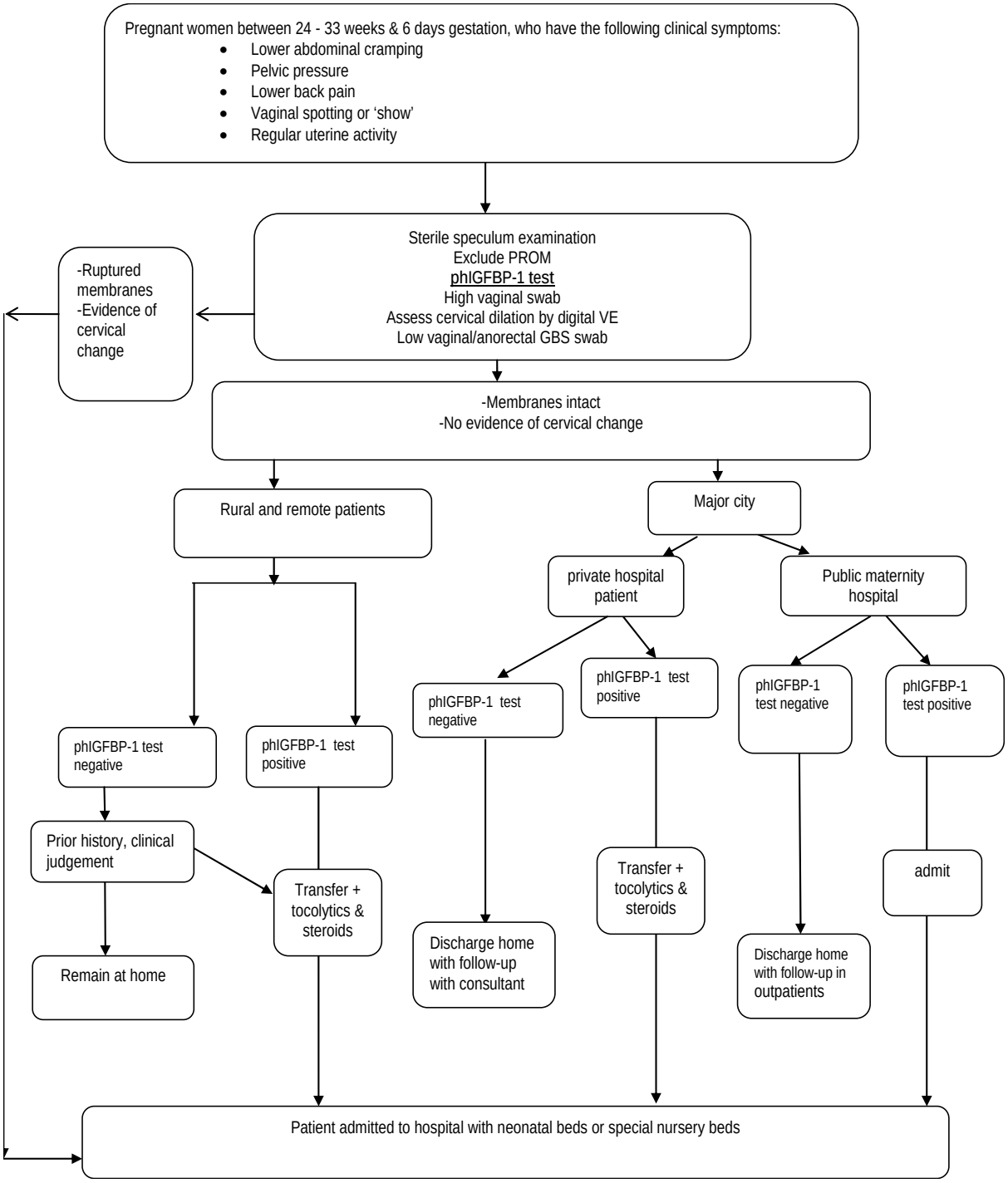
The application proposed that it will be physicians, participating nurse practitioners or participating midwives, who are speculum trained, who will perform the phIGFBP-1. No additional specialised training or qualifications are required by these practitioners to perform this test.

7. Summary of Public Consultation Feedback/Consumer Issues

The consumer perceived advantage for this service is that the use of the test could inform patients' risk management decisions, particularly in remote communities or situations where people need to make significant arrangements or to travel long distances to be admitted to an appropriate care facility. It was noted the cost is already being met by the consumer (state budgets) and that some consumers might choose to pay a fee for this service to reassure them in certain circumstances, even when the service is not publicly funded.

8. Proposed intervention's place in clinical management

Below is the proposed clinical management algorithm with the phIGFBP-1 test reimbursed on MBS.



9. Comparator

The comparison is a scenario where standard clinical management and a phIGFBP-1 test is performed with or without transvaginal ultrasound (TVUS) to measure cervical length (CL) (depending on setting of the test) versus a scenario where only cervical assessment is performed with or without TVUS to measure CL (depending on setting of the test).

An alternative comparison is a scenario where standard clinical management and fFN test (either qualitative or quantitative) is performed with or without TVUS to measure CL (depending on setting of the test) versus a scenario where only cervical assessment is performed with or without TVUS to measure CL (depending on the setting of the test).

In addition, a head to head comparison may be done where standard clinical management and phIGFBP-1 test with or without TVUS to measure CL will be compared to a scenario where standard clinical management and fFN (either the qualitative or quantitative test) with or without TVUS to measure CL.

It is not anticipated that there is likely to be any change to the way that pregnant women in whom pre-term labour (PTL) is suspected will be managed clinically as a consequence of making either phIGFBP-1 or fFN available on the MBS. However, there may be differences in the proportion of pregnant women for whom clinicians are able to exclude PTL and as a consequence avoid hospitalisations, unnecessary tocolytics administered to mothers, steroid treatment for neonates and maternal transfers to tertiary hospitals.

10. Comparative safety

No studies that specifically investigated the safety of phIGFBP-1 and fFN tests in diagnosis of preterm labour were identified. However, these tests are generally considered to be safe as long as they are performed by health professionals qualified in sterile speculum examination, and use of a sterile swab only after a diagnosis of ruptured membranes has been excluded.

The risk analysis of the false negative rate for the phIGFBP-1 test and the fFN tests for Pre Term Delivery (PTD) within 7 days of testing indicated no significant difference between the tests. There was a statistically significant difference in false positive rates in favour of the phIGFBP-1 test in the meta-analysis of three head-to-head comparative studies.
The risk analysis of the results for false negative and false positive rates for the phIGFBP-1 test and fFN tests for PTD within 14 days from testing indicated no statistically significant difference between the two tests in diagnosing PTL.

11. Comparative effectiveness

The application presented thirteen full reports of eleven observational cohort studies of phIGFBP-1 test (level II and level III-1 evidence); four of these studies were head-to-head comparisons of phIGFBP-1 test and fFN tests. Two observational cohort studies of fFN test were regarded as level II evidence. The body of evidence also included two detailed conference abstracts of the same study that directly compared qualitative phIGFBP-1 test with quantitative fFN test for the range of fFN concentration thresholds.

Pooled analysis of results of diagnostic accuracy studies was conducted for the primary outcomes of PTD within 7 days and 14 days of testing and for the secondary outcome of PTD before 33 week and 6 days of gestation. A direct comparison of diagnostic accuracy of

phIGFBP-1 test and fFN tests was conducted using the results of the head-to-head comparison studies.

Head-to-head comparison studies were used for assessment of risk of misdiagnosing women who are in preterm labour but are not identified as such (false negatives) and risk of over-treating women with tocolytics and corticosteroids who are incorrectly diagnosed with PTL (false positives). A true positive diagnosis of PTL indicates that a pregnant woman diagnosed with PTL goes on to deliver within 7 or 14 days, respectively, and a true negative diagnosis of PTL indicates that a pregnant woman does not deliver within 7 or 14 days, respectively.

Diagnostic accuracy for the outcome of PTD within 7 days was assessed with the summary statistics derived from the pooled analysis of results of 10 studies that included phIGFBP-1 test. The likelihood ratios were LR+ 3.6 (95% CI 2.6– 4.9) and LR– 0.35 (95% CI 0.26– 0.46), which were very similar to the results reported in the systematic reviews indicating a small informational value of the test. The value of DOR was 10 (95%CI 6-18). Diagnostic accuracy for the outcome of PTD within 14 days was assessed with the pooled results from four studies that produced LR+ 3.4 (95% CI 2.0– 5.7) and LR– 0.55 (95% CI 0.34– 0.89). The value of DOR was 6 (95%CI 2-16).

Figure 10 below shows individual studies, along with the summary estimate, plotted in receiver operating characteristic (ROC) space. The area under curve was 0.77 (95% CI 0.74 - 0.81) indicating a moderate degree of diagnostic accuracy.

Figure 10: SROC curve of joint distribution of sensitivity and specificity of the phIGBP-1 test 1 in predicting preterm delivery within 7 days

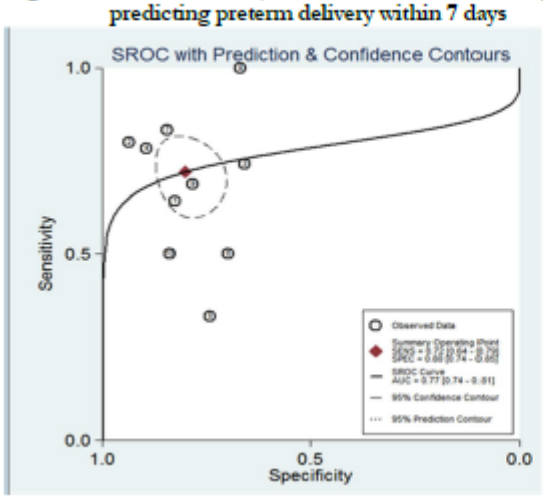
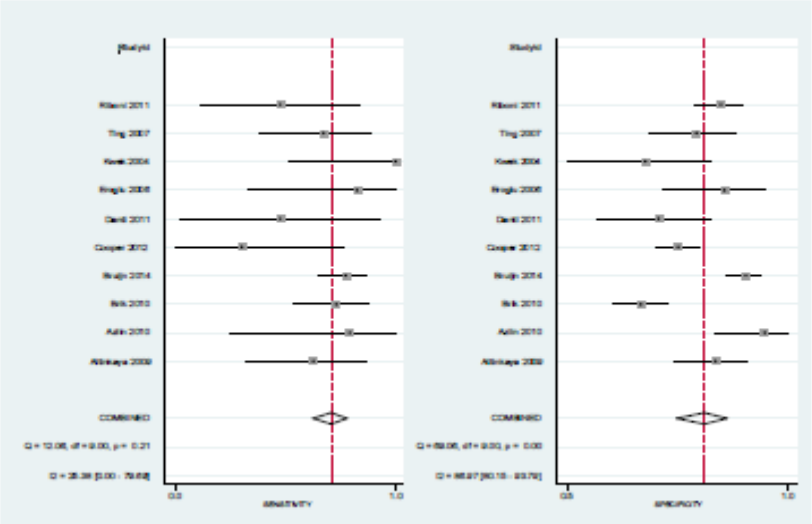


Figure 11 below shows the forest plot of the sensitivity and specificity of the phIGBP-1 in predicting preterm labour within the 7 days after testing.

Figure 11: Forest plot of the sensitivity and specificity of the phIGBP-1 in predicting preterm delivery within 7 days



The pooled estimates of sensitivity and specificity, derived from results of 10 studies that reported the outcomes of preterm delivery within 7 days using a bivariate model, were 0.72 (95%CI 0.64 -0.79) and 0.80 (95% CI 0.74 -0.85) respectively.

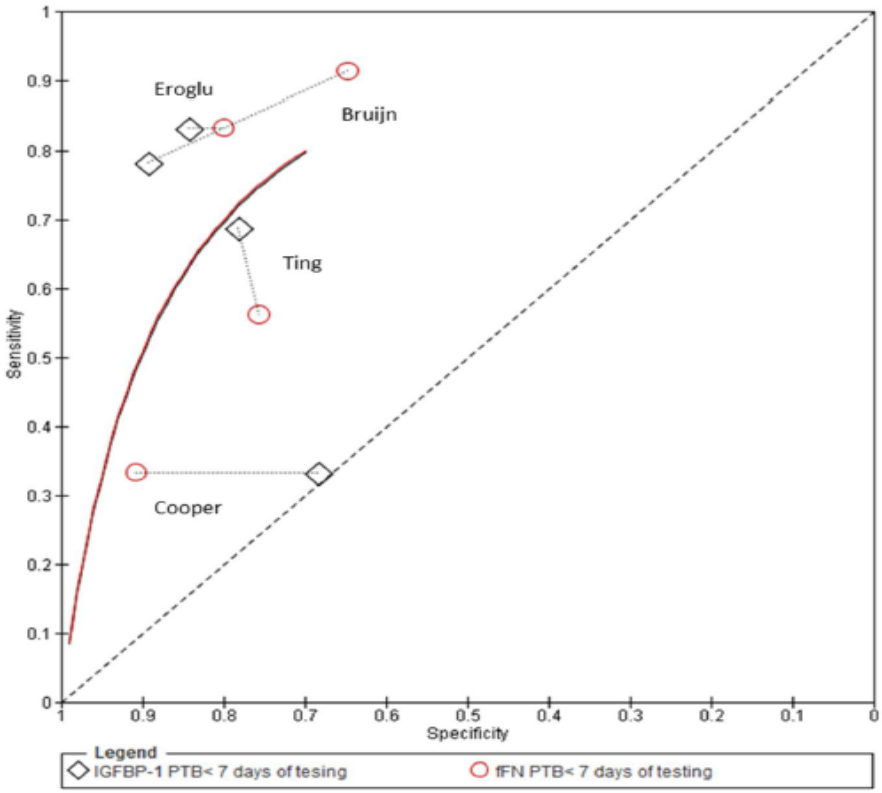
Only a limited evidential basis was available for assessing diagnostic accuracy of the qualitative fFN test for the outcome of PTD with 7 days of testing or 14 days of testing (three studies and two studies respectively). For the outcome of PTD within 7 days LR+ was 3.2 (95% CI 2.4– 4.3) and LR– was 0.42 (95% CI 0.25–0.71). The value of DOR was 7.8 (95%CI 3.4-17.5). These summary statistics were similar to the diagnostic accuracy statistics of the phIGFBP-1 test for the outcome of PTD within 7 days of testing.

There was only one study that reported the outcomes of PTD within 7 days of testing for the quantitative fFN test (LR+ 7.33 (95% CI 5.1– 10.5) and LR– 0.24 (95% CI 0.16–0.38). Another single study reported the outcomes of PTD within 14 days for the quantitative fFN test (LR+ 3.9 (95% CI 2.7– 5.6) and LR– 0.29 (95% CI 0.12–0.69). Based on a single study there is an advantage of using the quantitative fFN test in diagnosing PTD within 7 days of testing. For the outcome of 14 days, the evidence is insufficient to reach a conclusion about diagnostic accuracy.

Head-to head comparisons for the outcome of PTD with 7 days of testing included four studies that assessed a qualitative phIGFBP-1 against different types of fFN test. The results across the fFN tests were combined to obtain pooled estimates using a bivariate model. For the outcome of PTD within 7 days for phIGFBP-1 test LR+ was 4.0 (95% CI 2.1– 7.6) and LR– was 0.4 (95% CI 0.18–0.9). The value of DOR was 10 (95%CI 2.7-40). In comparison fFN test results for the same outcome produced LR+ 2.7 (95% CI 2.3– 3.1) and LR– 0.36 (95% CI 0.13–0.99). The value of DOR was 9 (95%CI 3.5-24).

Figure 12 below presents the overlapping summary receiver-operating characteristic curves (SROC curves) for the outcome of PTD within 7 days of testing for all head to head studies of phIGFBP-1 test versus fFN test (qualitative and quantitative) combined.

Figure 12: Head to head comparison PTD within 7 days (individual studies, along with the summary estimate, plotted in receiver operating characteristic space)



For the outcome of PTD within 14 days based on three head-to-head trial for phIGFBP-1 test LR+ was 2.7 (95% CI 1.6– 4.6) and LR– was 0.65 (95% CI 0.34–1.2). The value of DOR was 4.6 (95%CI 1.6-14). In comparison fFN test results for the same outcome produced LR+4.1 (95% CI 2.5– 6.9) and LR– 0.49 (95% CI 0.32–0.76). The value of DOR was 8 (95%CI 3.7-19).

On the basis of the evidence of diagnostic accuracy of the phIGFBP-1 test for the outcome of PTD within 7 days, the summary results indicate an advantage of using the test over standard management.

On the basis of the evidence of diagnostic accuracy of the fFN test (qualitative) for the outcome of PTD within 7 days, the summary results indicate an advantage of using the test over standard management. On the basis of the evidence of diagnostic accuracy of the fFN test (quantitative) for the outcome of PTD within 7 days, results indicate an advantage of using the test over standard management (results are from a single study).

On the basis of the evidence using direct head-to-head comparisons, it was not possible to establish the difference in diagnostic accuracy between phIGFBP-1 test and fFN tests.

In settings where TVCL is available, the addition of fFN testing or phIGFBP-1 testing to the assessment of TVCL is associated with advantages, in terms of proportion of women accurately classified as delivering or not delivering within 7 days, compared to standard management.

Clinical effectiveness and change in patient management

There were no studies identified, using tests relevant for this assessment that compared standard management and point of care testing to change in patient management. There were however some studies using the superseded TLIiq (fFN) system, that assessed a change in patient management. These individual studies were combined to determine whether knowledge of test results may alter a clinician's decision to admit a patient. A meta-analysis of these studies found no statistical difference in rates of hospitalisation although it was noted that all of these studies were underpowered to detect differences in healthcare resource use.

Table 35 below shows the number of admissions to hospitals from the individual studies and the pooled analysis.

Table 35: Meta-analysis of outcome of RCTs-Admission to hospital

Outcome	Standard management		fFN intervention results known		Risk Difference 95%CI	Odds ratio 95%CI	Risk ratio 95%CI
	n	N	n	N.			
Dutta (2011)*	22	45	21	46	0.03 [-0.17, 0.24]	1.14 [0.50, 2.59]	1.07 [0.69, 1.65]
Grobman (2004)	14	50	13	50	0.02 [-0.15, 0.19]	1.11 [0.46, 2.68]	1.08 [0.56, 2.05]
Lowe (2004)	12	51	16	46	-0.11 [-0.29, 0.07]	0.58 [0.24, 1.40]	0.68 [0.36, 1.27]
Lee et al (2013)	2	32	3	44	-0.01 [-0.12, 0.11]	0.91 [0.14, 5.80]	0.92 [0.16, 5.17]
Ness et al (2007)	2	49	10	51	-0.14 [-0.25, -0.02]	0.20 [0.04, 0.97]	0.23 [0.05, 1.02]
Osorio (2010)	9	33	6	33	-0.14 [-0.25, -0.02]	0.20 [0.04, 0.97]	1.50 (0.60, 3.74)
Pooled	**61**	**260**	**68**	**270**	**-0.03 [-0.10, 0.04]**	**0.87 [0.54, 1.42]**	**0.93 [0.66, 1.31]**
Heterogeneity: $Tau^2 = 0.03$; $Chi^2 = 6.14$, df = 5 (P = 0.29); $I^2 = 19\%$ Test for overall effect: Z = 0.42 (P = 0.68)							

RevMan 5 random effects model

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12. Economic evaluation

A modelled economic evaluation based on the results of meta-analyses of diagnostic accuracy of testing for PTD within 7 days was presented. Consistent with the protocol guiding the assessment, the economic analysis compared several interventions in a population of pregnant women with a gestational age between 24 and 34 weeks and with signs of preterm labour but with intact membranes and cervical dilation less than 3 cm.

The objective of the analysis was to compare the cost-effectiveness of interventions in two settings:

- Setting where TVUS is not available
- Setting where TVUS is available

The evaluation noted that the results for the comparative effectiveness of the various interventions assessed in this report show:

- In settings where TVCL is not available, availability of fFN testing or phIGFBP-1 testing is associated with advantages, in terms of the proportion of women accurately

classified as delivering or not delivering within 7 days, compared to standard management.

- In settings where TVCL is available, availability of fFN testing or phIGFBP-1 testing to assessment of TVCL is associated with advantages, in terms of the proportion of women accurately classified as delivering or not delivering within 7 days, compared to standard management
- Insufficient data are available to differentiate fFN testing from phIGFPB-1 testing in terms of diagnostic accuracy.

The resource variables considered in the economic evaluation include: cost of TVUS, cost of point-of-care testing, and cost of hospitalisation for threatened premature labour.

The application claimed that the rates of hospitalisation for false labour would be reduced and would outweigh the costs of testing, consequentially resulting in cost savings.

The results of the economic analysis for each setting are summarised below. Table 5 provides the results for settings where TVUS is not available. Table 6 presents results for settings where TVUS is available.

Table 5: Results of modelled economic analysis for the scenario where TVUS is not available and assuming phIGFBP-1 and fFN tests are equivalent in terms of diagnostic accuracy

Intervention	Costs of intervention (test ± ultrasound)	Costs of hospitalisation	Total costs	Outcome (proportion of women correctly categorised)
Standard management in the absence of TVCL	$0.00	$2,403.72	$2,403.72	56.8%
phIGFBP-1 test	$55.52	$2,360.63	$2,416.15	78.4%
Increment for phIGFBP-1 vs standard management:			*$12.43*	*21.6%*
Incremental cost per additional woman accurately predicted to have PTD or not within 7 days for phIGFBP-1 vs standard management (in the absence of assessment of TVCL):				*$58*
Rapid 10Q® fFN test	$120.56	$2,360.63	$2,481.19	78.4%
Increment for Rapid 10Q vs standard management:			*$77.47*	*21.6%*
Incremental cost per additional woman accurately predicted to have PTD or not within 7 days for Rapid 10Q vs standard management (in the absence of assessment of TVCL):				*$359*
QuikCheck™ fFN test	$119.00	$2,360.63	$2,479.63	78.4%
Increment for QuikCheck vs standard management:			*$75.92*	*21.6%*
Incremental cost per additional woman accurately predicted to have PTD or not within 7 days for QuikCheck vs standard management (in the absence of assessment of TVCL):				*$351*

Table 6: Results of modelled economic analysis for the scenario where TVUS is available and assuming phIGFBP-1 and fFN tests are equivalent in terms of diagnostic accuracy

Intervention	Costs of intervention (test ± ultrasound)	Costs of hospitalisation	Total costs	Outcome (proportion of women correctly categorised)
Standard management with assessment of TVCL	$147.00	$2,394.17	$2,541.17	62.3%
phIGFBP-1 test + TVCL	$202.52	$2,126.02	$2,328.54	87.1%
Increment for phIGFBP-1 +TVCL vs standard management with assessment of TVCL:			*- $212.63*	*24.8%*
Incremental cost per additional woman accurately predicted to have PTD or not within 7 days for phIGFBP-1 vs standard management (with TVCL):				*dominant*
Rapid 10Q® fFN test + TVCL	$267.56	$2126.02	$2,393.58	87.1%
Increment for Rapid 10Q +TVCL vs standard management with			*- $65.48*	*24.8%*

assessment of TVCL:				
Incremental cost per additional woman accurately predicted to have PTD or not within 7 days for Rapid 10Q vs standard management (with TVCL):				*dominant*
QuikCheck™ fFN test + TVCL	$266.00	$2,126.02	$2,392.02	87.1%
Increment for QuikCheck™ +TVCL vs standard management with assessment of TVCL:			*- $63.48*	*24.8%*
Incremental cost per additional woman accurately predicted to have PTD or not within 7 days for QuikCheck vs standard management (with TVCL):				*dominant*

Results for the scenario where TVUS is not available indicate that making point-of-care testing available in settings where TVUS is not available is approximately cost-neutral and increases the proportion of women accurately predicted to deliver within 7 days or not.

A claim that savings will be generated is not fully supported by the analysis though, the difference in costs across the two scenarios is small and there is substantial uncertainty around the estimate of difference in costs across the two scenarios. It might be more reasonable to conclude that implementation of point-of-care testing is approximately cost-neutral, overall, and is associated with improved prediction of PTD. Sensitivity analyses demonstrate that the conclusion that adding point-of-care testing to standard management where TVUS is not available is relatively cost-neutral is robust.

Results for where TVUS is available, is a dominant strategy. Sensitivity analyses demonstrate that this conclusion is robust.

It is important to note that phIGFBP-1 testing is substantially less costly than fFN testing. Thus, when it is assumed that the tests are approximately equivalent in terms of diagnostic accuracy in accordance with the evidence presented, phIGFBP-1 testing dominates fFN testing.

The conclusions drawn in the assessment are only valid where fees charged in practice for point-of-care testing with phIGFBP-1 are in accordance with the proposed MBS fee. Frequently, fees charged in practice are greater than the MBS fee. If the fee charged in practice is greater than the proposed MBS fee, the conclusions drawn may not apply.

13. Financial/budgetary impacts

The population in which these tests will be used is estimated at 24,316 in Year 1, increasing to 24,414 in Year 5. The proposed population is pregnant women, with fetal gestation between 24 to 33^{+6} weeks and who present with threatened preterm labour and intact membranes. It is assumed that around 10% or less of these women will go on to give birth in ≤7 days.

Table 7 presents the likely population size and the cost of the tests each year. In estimating this population it is not assumed that the population represents individual women. Some women may present a number of times and others not at all or after 34 gestational weeks so are not eligible for these tests. The fee range used in the calculations is $55.52 for phIGFBP-1 to $120.56 for the fFN test. Both fees are included in the calculations, although the lack of any evidence of a difference in the diagnostic accuracy of the tests is likely to influence the MBS fee to be more in accordance to that of phIGFBP-1. The cost of the tests includes an additional labour cost of $15.00 to perform the swab and wait for the result and to interpret and record the result.

Table 7: Estimated costs to the MBS scheme of listing of point of care testing to exclude preterm labour

	Year 1 (2014)*	Year 2 (2015)	Year 3 (2016)	Year 4 (2017)	Year 5 (2018)		Source
Population of symptomatic women presenting with PTL	24,316	24,340	24,365	24,389	24,414	E=C/D	
Cost pphIGFBP-1**	$55.52	$55.52	$55.52	$55.52	$55.52	D	sponsor
Cost to MBS of listing only phIGFBP-1	$1,350,029	$1,351,379	$1,352,731	$1,354,084	$1,355,438	F=E*D	
Cost fFN	$120.56	$120.56	$120.56	$120.56	$120.56	G	sponsor
Cost to MBS of listing only fFN	$2,931,548	$2,934,479	$2,937,414	$2,940,351	$2,943,292	H=G*E	

It is not assumed that there will be any changes to current MBS items, such as TVUS, from the listing of point of care tests to exclude preterm labour. The net financial cost to the MBS will include the cost of the tests additional to any current items, such as MBS items under which women would receive a vaginal examination. Currently, it is unlikely that there will be any out of pocket expenses to women from having this test.

14. Key issues from ESC for MSAC

ESC considered there was insufficient information available regarding the comparative diagnostic accuracy of 'standard care plus TVCL' versus either point of care (PoC) test alone. In other words, the comparison of 'standard care plus TVCL' versus 'PoC test plus TVCL' potentially masks the possibility that the 'PoC tests plus TVCL' are not superior to 'TVCL alone'. ESC further noted that no information was presented regarding the relative availability of TVCL in different settings across the country, and hence the relative proportion of women accessing care with or without TVCL is unknown.

ESC was uncertain how the PoC tests would impact on patient management, as none of the identified studies showed improved outcomes or changed patient management as a result of the test.

ESC suggested that, given the relative performance of the test compared with transvaginal ultrasound, MSAC may wish to consider whether eligibility should be restricted to situations where assessment by transvaginal ultrasound is either equivocal or not possible.

ESC agreed that the test is safe as long as the speculum examination is sterile and the swab is taken only in circumstances where premature rupture of the membranes has not occurred. However, ESC recommended that MSAC appraise the safety of associated flow-on medical interventions if a false-positive test result is obtained. For example, it was not clear to ESC whether it is safe for the patient and/or unborn infant to receive corticosteroid injections if pre-term labour is not actually occurring. However, it was acknowledged by ESC that current

clinical practice is highly conservative and there is a proportion of women in false preterm labour who would currently be admitted and receive tocolytics and/or corticosteroids.

ESC agreed that a greater potential safety issue was that of false negatives: where a woman in true preterm labour is not admitted, and therefore risks giving birth outside a hospital with neonatal beds.

ESC noted that sensitivity and specificity of pathology tests to exclude pre-term labour is considerably less than 100%. This is expected to be a pivotal issue for MSAC consideration; particularly given the pervasive access to ultrasound.

As it is possible that the phIGFB-1 and fFN tests are not incrementally superior to TVUS, ESC recommended that MSAC consider whether the test should only be performed in settings where TVUS is not available, rather than as an additional diagnostic test in settings where TVUS is available.

ESC noted a lack of clarity regarding the clinical setting of the service. In particular, ESC questioned whether it would be appropriate to deliver the service from a general practice, or a patient's home by a trained midwife, compared with transfer to hospital. ESC noted there may be particular benefits to consumers who would otherwise have to travel long distances to be assessed at a hospital.

ESC considered that constructing the modelled economic evaluation based on expert opinion regarding expected changes in management was particularly problematic. The level of risk associated with an incorrect decision would mean that practitioners would continue to err on the side of caution, and it is conceivable and potentially appropriate that treating practitioners would suggest transfer to hospital and precautionary use of steroids irrespective of the test result.

ESC considered there to be three main areas of economic uncertainty: (i) the transformation of diagnostic accuracy measures (based on the reference standard of delivery within 7 days) into patient management flows and outcomes across the multiple test settings defined (without TVUS, TVCL positive, and TVCL negative), (ii) the assumptions regarding the rates of hospitalisation based on advice from the Health Expert Standing Panel, and (iii) in settings where TVUS is available, the extent to which the apparent advantages associated with the use of the point-of-care tests is attributable to the diagnostic performance of TVUS.

ESC considered that the modelled scenarios did not adequately capture the potential value of the phIGFBP-1 or fFN tests, which is that they be available in settings where TVUS is not available. ESC was uncertain of the value of adding a phIGFBP-1 or fFN test to the diagnostic pathway when TVUS is available, and noted that no information is presented regarding the diagnostic performance of TVUS alone. The results of the model were aggregated across all test settings.

The listing of the items on the MBS is not straightforward, as the test is a pathology service, but is neither sent to a laboratory nor performed by a pathologist. Given the types of services listed in Category 2 of the MBS, ESC did not consider the tests to be diagnostic procedures. ESC noted that point-of-care tests in other therapeutic settings are the subject of other current MSAC applications, and decisions regarding the positioning of other PoC tests on the MBS might act as precedents for the current application.

ESC advised that, if the phIGFBP-1 and fFN tests are both supported and found to be as effective as each other, they should be listed with the same MBS fee.

15. Other significant factors

Nil.

16. Applicant's comments on MSAC's Public Summary Document

The assessment of comparative effectiveness concludes that: phIGFBP-1 or fFN testing is associated with advantages compared to standard management, in terms of the proportion of women accurately classified as delivering or not delivering within 7 days. On this basis, Alere considers that the tests do provide clinical benefit. Alere respectfully disagrees that the risk of false-negative results is likely to lead to an increased risk of harm. The woman's complete clinical picture, including any test results, are considered before treatment decisions are made and there is also a risk of a 'false-negative' assessment associated with standard management even when ultrasound is used. The incorporation of the tests into clinical guidelines in Australia and globally indicates that they provide additional useful information to aid in the classification of this clinically difficult condition. The paucity of published data for some aspects of the evaluation is acknowledged. This was particularly evident for estimates of hospitalisation rates for patients presenting with pre-term delivery which in the assessment report were based on Australian expert opinion rather than published studies which are not available. The areas of uncertainty identified by MSAC offer guidance for future research.

17. Further information on MSAC

MSAC Terms of Reference and other information are available on the MSAC Website at: www.msac.gov.au.