NICE National Institute for Health and Care Excellence

Biomarker tests to help diagnose preterm labour in women with intact membranes

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Parsagen Diagnostics Inc.	1	2	Declared competing interests of the authors	The declaration of interest by Prof. Shennan indicates that there are multiple studies ongoing comparing the performance of ParotSure and quantitative fetal fibronectin (qfFN). However, only one of the studies listed involves comparing PartoSure and qfFN, which is the QUIDS study. Additionally, QIAGEN provided 80 test kits to Prof. Shennan in 2013 for protocol entitled “Evaluation of Fetal Fibronectin with a Quantitative Instrument for the Prediction of Preterm birth.” The results of that study were not published. Neither QIAGEN nor Parsagen have provided PartoSure test kits for any other investigation conducted by Prof. Shennan.	Response from Prof. Shennan. The ERG (PenTAG) is not involved in any studies referred to. All the women in these studies (except Quids) have had both fFN and Partosure taken at our institution, and all the samples were donated by Quiagen. The primary aim of these studies, including Quids, was not to compare these, they are add ons to the original studies with appropriate consent when applicable. The study they mention that isn’t published is on going. There are more than 80 women already recruited and these were all given by Quiagen (their statement is incorrect). The donation of Partosure samples was to allow comparison with other biomarkers, and I was an informal agreement so I don’t expect the company to know which studies the test is being compared in. I hope this clarifies my declaration which remains valid.

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					I think it is appropriate to declare all the studies in which the biomarkers in question are being studied, for transparency reasons, even if it is not the primary aim of the study.
Parsagen Diagnostics Inc.	2	20	Review of test accuracy	The current NICE guidelines recommend the fFN test @ 50 ng/ml to be used in the diagnosis of preterm labour when Cervical Length measurement is not available or not suitable.[1] Due to the limited number of publications comparing all 3 biomarker tests (PartoSure, Actim Partus, and quantitative fFN) concomitantly, it would be most clinically- and scientifically-appropriate to compare each test to the reference test recommended by the latest NICE guidelines (fFN @ 50 ng/ml). To date, there have been three large studies published totalling 1425 patients comparing the performance of the PartoSure (PAMG-1) test to the reference of the fFN test @ 50 ng/ml. However, 2 of these studies were not included in the analysis despite abstracts for both having been provided to the assessment team, and which were published shortly after the review (Wing et al. and Melchor et al). The third study by Nikolova et al. was not included as it did not compare PartoSure directly to either Actim Partus of quantitative fFN.	We report the DTA data for studies that report fFN@50ng/ml and an index test in section 2.3. This work was beyond the initial scope, but since it is of clinical interest, as you suggest, we report it. The additional studies suggested could not be included because they were published after the end date of the systematic review. We would ideally have liked to up-date the systematic review, but this would have necessitated re-searching for all the index tests, and there was insufficient time to achieve this. To include asymmetrically studies for just one index test, identified via notification by the test developer rather than a systematic search, runs the risk of introducing bias in the ascertainment of the literature. Publication bias and time to publication bias are particular concerns.

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				• Wing et al.[2] – n= 796 (711 patients evaluated) • Melchor et al.[3] – n= 410 (367 patients evaluated) • Nikolova et al.[4] – n= 219 (203 patients evaluated; 66 patients compared to fFN @ 50 ng/ml) 1. Preterm labour and birth. NICE Guideline. 20 November 2015. nice.org.uk/guidance/ng25 2. Wing DA, Haeri S, Silber AC, Roth CK, Weiner CP, Echebiri NC, et al. Placental Alpha Microglobulin-1 Compared With Fetal Fibronectin to Predict Preterm Delivery in Symptomatic Women. Obstet Gynecol. 2017;130(6):1183-91 3. Melchor JC, Navas H, Marcos M, Iza A, de Diego M, Rando D, et al. Retrospective cohort study of PAMG-1 and fetal fibronectin test performance in assessing spontaneous preterm birth risk in symptomatic women attending an emergency obstetrical unit. Ultrasound Obstet Gynecol. 2017.	

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				4. Nikolova T, Bayev O, Nikolova N, Di Renzo GC. Comparison of a novel test for placental alpha microglobulin-1 with fetal fibronectin and cervical length measurement for the prediction of imminent spontaneous preterm delivery in patients with threatened preterm labor. Journal of Perinatal Medicine. 2015;43(4):395-402.	
Parsagen Diagnostics Inc.	3	21	Review of test accuracy	The accuracy of the PartoSure test used for modelling scenarios was based on a single publication by Hadzi-Lega et al.[1] This publication is based on the inclusion of 57 patients comparing PartoSure and Actim Partus. Since the study selection for the review conducted in July 2017, 2 large studies have been published comparing the performance of PartoSure to the NICE reference standard of fFN @ 50 ng/ml.[2] As stated previously, as there have been three major studies published with 1425 patients comparing the performance of the PartoSure (PAMG-1) test to the reference test of fFN @ 50 ng/ml, the analysis should be rerun based on the latest clinical evidence and accuracy data available. • Wing et al.[3] – n= 796 (711 patients evaluated)	As in our answer to comment 2, the inclusion of these studies in our analysis risks producing biased results due to the non-systematic means used to identify those studies. Nevertheless we provide these results as requested by NICE. These studies[3-8] were not available when the screening and review took place. At the time, Hadzi-Lega et al.[1] was the only suitable study that compared the performance of PartoSure with that of another index test in the same population. There is not a cohort of more than 1000 patients, as the studies by different lead authors consider distinct populations. Since none of the studies consider all of the index tests, indirect comparisons would still need

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				• Melchor et al.[4] – n= 410 (367 patients evaluated) • Nikolova et al.[5] – n= 219 (203 patients evaluated; 66 patients compared to fFN @ 50 ng/ml) Another large study has been completed and submitted for publication (Nikolova et al.) comparing the performance of PartoSure and Actim Partus in a large European cohort of 403 patients, and is therefore critical to this review. The study manuscript was provided as Academic in Confidence, along with these comments. We suggest that the analysis should be rerun based on the latest clinical evidence and accuracy data available. • Nikolova et al.[6] – n= 403 (383 patients evaluated) A meta-analysis has also been recently completed comparing PartoSure, fFN @ 50 ng/ml and Actim Partus across a range of varying prevalence populations for low risk, intermediate risk and high risk. As prevalence of the patient cohort may change based on the underlying patient population and testing protocol, this study aims to compare	to be carried out should any or all of the additional studies be included. This has been done for Wing et al.[3] and Nikolova et al.[6], which have been included in the base-case analysis through indirect comparison with Bruijn et al.[9] and the results updated accordingly in the addendum. The results of a scenario analysis using the test accuracy data from Ravi et al.[8] have also been added to the addendum. The retrospective cohort study by Melchor et al.[4], which involves 'baseline' and 'comparative' time periods, was not included since it does not provide a direct comparison between index tests or indeed two tests in the same patients. The meta-analysis by Melchor et al.[7] does not use the less confounded approach of including only direct comparisons between index tests in the same patients that we have used in our modelling approach (for Actim Partus vs fFN 50ng/ml; 4 studies): pooled predictive values are not the advised approach given the confounding from heterogeneous population characteristics across tests; disease prevalence, the importance of which Parsagen has noted elsewhere is one but not the only confounder. The failure to take account of

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				the publications available to date in similar patient cohorts. The study manuscript was provided on December 13th, 2017 as Academic in Confidence and again along with these comments. The analysis should be rerun based on the latest clinical evidence and accuracy data available. • Melchor et al.[7] – PAMG-1 (n= 2278); fFN @ 50 ng/ml (n=7431); phIGFBP-1 (n=3087) Lastly, yet another study has been submitted for publication (Ravi et al.) that compares PartoSure directly to the quantitative fFN test at the following thresholds: 10, 50, 200, and 500, and is therefore critical to this review. The manuscript was provided as Academic in Confidence on November 20, 2017 and again along with these comments. The analysis should be rerun based on the latest clinical evidence and accuracy data available from this study, as it is the only investigation to date comparing the performance of PartoSure and quantitative fFN head to head. • Ravi et al.[8] – n= 101 (72 patients evaluated) 1. Hadzi-Lega M, Maier JT, Helmer H, Hellmeyer L, Markova AD, Poposka A. Comparison of PAMG-1 and phIGFBP-1 Tests for the Prediction of Preterm Delivery	the considerable clinical and statistical heterogeneity between the results of all groups of studies for each index test makes the use of pooled summary estimates invalid. A search of EMBASE, which would be expected in a publication standard systematic review, was also not undertaken. 1. Bruijn MM, Vis JY, Wilms FF, Oudijk MA, Kwee A, Porath MM, et al. Comparison of the Actim Partus test and the fetal fibronectin test in the prediction of spontaneous preterm birth in symptomatic women undergoing cervical length measurement. Eur J Obstet Gynecol Reprod Biol. 2016;206:220-4. It is worth noting that the new studies produce results that look worse than Hadzi-Lega's, especially in terms of sensitivity, which drives the effectiveness side of the cost-effectiveness analysis. In particular the diagnostic accuracy results from Wing et al. 2017 suggest PartoSure saves less than £20,000 per QALY lost relative to fFN 50ng/ml in women presenting to a level 2 unit at 26 weeks.

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				in Patients with Preterm Labor. Open Journal of Obstetrics and Gynecology. 2017;Vol.07No.03:11. 2. Preterm labour and birth. NICE Guideline. 20 November 2015. nice.org.uk/guidance/ng25 3. Wing DA, Haeri S, Silber AC, Roth CK, Weiner CP, Echebiri NC, et al. Placental Alpha Microglobulin-1 Compared With Fetal Fibronectin to Predict Preterm Delivery in Symptomatic Women. Obstet Gynecol. 2017;130(6):1183-91 4. Melchor JC, Navas H, Marcos M, Iza A, de Diego M, Rando D, et al. Retrospective cohort study of PAMG-1 and fetal fibronectin test performance in assessing spontaneous preterm birth risk in symptomatic women attending an emergency obstetrical unit. Ultrasound Obstet Gynecol. 2017. 5. Nikolova T, Bayev O, Nikolova N, Di Renzo GC. Comparison of a novel test for placental alpha microglobulin-1 with fetal fibronectin and cervical length measurement for the prediction of imminent spontaneous preterm delivery in patients	

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				with threatened preterm labor. Journal of Perinatal Medicine. 2015;43(4):395-402. 6. Nikolova T, Uotila J, Nikolova N, Bolotkhikh V, Borisova V, DiRenzo GC. Comparison of the placental alpha microglobulin-1 test to the phosphorylated insulin-like growth factor-binding protein-1 test alone and in combination with cervical length measurement for the prediction of spontaneous preterm delivery in women with symptoms of preterm labor. Submitted manuscript 2018. Academic in Confidence. 7. Melchor JC, Khalil A, Wing D, Schleussner E, Surbek D. The prediction of preterm delivery in symptomatic women using the placental alpha-microglobulin-1, fetal fibronectin and phosphorylated insulin-like growth factor-binding protein-1 tests: systematic review and meta-analysis stratified by risk. Submitted Manuscript 2017. Academic in Confidence. 8. Ravi et al. Evaluation of the quantitative fetal fibronectin test and PartoSure (PAMG-1) for the prediction of sPTB in patients with signs and symptoms suggestive of preterm labour J Pediatr Neonat Individual Med.	

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				2017 6 1 e060125. Full manuscript submitted Academic in Confidence.	
Parsagen Diagnostics Inc.	4	22	Review of economic evaluations	Gibson (2014)[1] was included in the analysis, however, this study has not been published and only information from the abstract was available. It is imperative that the same standard should be applied to all studies submitted for evaluation as part of this NICE assessment, whether in abstract or fully published form and regardless of their status as Academic in Confidence. Additionally, data from this study should be provided without redaction to all stakeholders. The following studies on the PartoSure test were submitted in abstract form, and since other abstracts were evaluated in such form, these studies should be as well in order to prevent scientific-bias: • Nikolova et al.[2] (2017) n= 328 • Lotfi et al.[3] (2015) n=151 • Ravi et al.[4] (2017) n= 72 • Konoplyannikov et al.[5] (2016) n=71 • Lou et al.[6] (2016) n= 65 • Heverhagen et al.[7] (2015) n= 64 • Van Holsbeke et al.[8] (2016) n= 50 • Fatkullin et al.[9] (2016) n= 45 1. Gibson S, Hezelgrave NL, Shennan AH. The impact of quantitative fetal fibronectin	Firstly, these are two separate systematic reviews conducted by different members of the EAG. The review of test accuracy studies identified from their searches 105 abstracts. It would be unreasonable for the EAG to contact all 105 authors for clarifications to their abstracts, given the number of full text publications were identified for each test. However, given the economic evaluation review only identified 1 abstract, it was not unreasonable for the economics team to contact the author. Please note that the Gibson study was the only study on an index test that reported some form, however limited, of economic results. Admittedly this study was not a full economic evaluation but its abstract reported economically meaningful outcomes, in this case in the form of number of patients needed to be treated to prevent one case of respiratory distress syndrome.

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				on the clinical management of women symptomatic of preterm labour. Archives of Disease in Childhood: Fetal and Neonatal Edition. 2014;99:A151-A5. 2. Nikolova et al. Do PAMG-1 or phIGFBP-1 biomarkers improve the prediction of imminent spontaneous preterm delivery in PTL symptomatic women with non-obvious cervical length (CL)? AJOG Jan 2017; 216 (1): Supplement S11-S12. 3. Lofti G et al. Evaluation of PAMG-1 for the prediction of preterm birth in patients symptomatic of preterm labor. J. Perinat. Med. 2015; 43 (S1):250. 4. Ravi et al. Evaluation of the quantitative fetal fibronectin test and PartoSure (PAMG-1) for the prediction of sPTB in patients with signs and symptoms suggestive of preterm labour J Pediatr Neonat Individual Med. 2017 6 1 e060125. 5. Konoplyannikov et al. PAMG-1 biomarker test (PARTOSURE) in combination with transvaginal ultrasound for improved assessment of spontaneous preterm birth in patients with threatened preterm labor. J Matern Fetal Neonatal Med, 2016; 29(S1): 278.	

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				6. Lou YY et al. Is PartoSure effective in assessing preterm birth? BJOG An International Journal of Obstetrics and Gynaecology. 2016; 123(S2): 89. 7. Heverhagen A. Placental alpha macroglobulin-1 in combination with transvaginal ultrasound for prediction of preterm birth. J. Perinat. Med. 2015; 43(S1): 240. 8. Van Holsbeke et al. Comparison of the fetal fibronectin (Rapid fFN) and placental alpha microgloibulin-1 (PartoSure) tests for predicting imminent spontaneous preterm birth. Ultrasound in Obstetrics & Gynecology 2016; 48 (S1): 84. 9. Fatkullin et al. Utilization of a novel biomarker test (PartoSure PAMG-1) to reduce the length of stay in patients with threatened preterm labor and a short cervix. J Matern Fetal Neonatal Med, 2016; 29(S1): 283.	
Parsagen Diagnostics Inc.	5	25	Independent economic assessment	Given the low number of subjects included in the Hadzi-lega publication (n= 57) and the variation in prevalence between Brujin et al.[1] (19.7%) and Hadzi-Lega et al.[2] (10.5%) publications, we suggest comparing the test being evaluated	This was not undertaken due to the high risk of bias due to the mixing of data from different populations across pooled analyses for each test and study selection

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				against the current NICE reference standard, which is fFN @ 50 ng/ml as outlined in Comment #2. Additionally, a meta-analysis has been completed comparing PartoSure, fFN @ 50 ng/ml and Actim Partus across a range of varying prevalence populations for low risk, intermediate risk and high risk. As prevalence of the patient cohort may change based on the underlying patient population and testing protocol, this study aims to compare the publications available to date in similar patient cohorts. The study manuscript is provided as Academic in Confidence along with these comments. We suggest that the analysis should be rerun and based on the latest clinical data. a. Melchor et al.[3] – PAMG-1 (n= 2278); fFN @ 50 ng/ml (n=7431); phIGFBP-1 (n=3087) 1. Bruijn MM, Vis JY, Wilms FF, Oudijk MA, Kwee A, Porath MM, et al. Comparison of the Actim Partus test and the fetal fibronectin test in the prediction of spontaneous preterm birth in symptomatic women undergoing cervical length measurement. Eur J Obstet Gynecol Reprod Biol. 2016;206:220-4.	bias. Please see our response to Comment 3 above for details.

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				2. Hadzi-Lega M, Maier JT, Helmer H, Hellmeyer L, Markova AD, Poposka A. Comparison of PAMG-1 and phIGFBP-1 Tests for the Prediction of Preterm Delivery in Patients with Preterm Labor. Open Journal of Obstetrics and Gynecology. 2017;Vol.07No.03:11. 3. Melchor JC, Khalil A, Wing D, Schleussner E, Surbek D. The prediction of preterm delivery in symptomatic women using the placental alpha-microglobulin-1, fetal fibronectin and phosphorylated insulin-like growth factor-binding protein-1 tests: systematic review and meta-analysis stratified by risk. Submitted Manuscript 2017. Academic in Confidence.	
Parsagen Diagnostics Inc.	6	31	Table 1 Summary of Index tests PartoSure (Parsagen Diagnostics Inc.)	Please confirm where the following statement was extracted from: "Inaccurate results may be likely … in presence of meconium, anti-fungal creams, suppositories, lubricants, moisturisers, talcum powder or baby oil", as that statement is not the same as that which is included on the PartoSure test's Instructions for Use.[1] Werlen et al[2] (2015) studied the reproducibility of the PartoSure test after digital examination, finding	The text in question was taken from the NICE briefing note from this appraisal. If this is incorrect, this can be corrected.

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				a 100% correlation between test results performed before and after vaginal exam. 1. Parsagen Diagnostics Inc. PartoSure, Assess the risk of preterm birth: Instructions for use 2015. 2. Werlen S, Raia T, Di Bartolomeo A, Chauleur C. Preterm labor: Reproducibility of detection test of PAMG-1 before and after digital examination, and transvaginal ultrasound cervical length. Gynecol Obstet Ferti. 2015;43(10):640-5.	
Parsagen Diagnostics Inc.	7	31	Table 1 fFN	Step 1 outlined in the fFN test's Instructions for Use procedure states the following: "Perform daily analyser quality control". The performance of the daily analyser quality control is an integral step to ensure that the analyser is functioning properly. The procedure takes approximately 15 minutes daily and must be performed by midwifery/physician staff." Please clarify if this step's time has been built into the independent economic assessment.	The advice received from a practising clinician is that no additional costs need to be included for this. The daily quality control is performed by a night matron amongst other routine checks of other equipment. This involves simply inserting the Cassette into the machine and filing the printed results afterwards, which does not correspond to 15 minutes of staff time.
Parsagen Diagnostics Inc.	8	43	2.1.1.2.3	The DAP40 review undertook a literature database search for study inclusion in July 2017. Since that date, three large studies assessing the performance of the PartoSure test have been published. These and several other large studies were submitted for publication and provided as	Our work uses the method of a systematic review in order to maintain an unbiased approach to identifying all published evidence. The company submitted abstracts at the time the project started. Abstracts cannot

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				Academic in Confidence for the assessment team's consideration. We suggest the inclusion of these publications into the analysis for the most up to date clinical and scientific evidence. • Wing DA, Haeri S, Silber AC, Roth CK, Weiner CP, Echebiri NC, et al. Placental Alpha Microglobulin-1 Compared With Fetal Fibronectin to Predict Preterm Delivery in Symptomatic Women. Obstet Gynecol. 2017;130(6):1183-91 • Melchor JC, Navas H, Marcos M, Iza A, de Diego M, Rando D, et al. Retrospective cohort study of PAMG-1 and fetal fibronectin test performance in assessing spontaneous preterm birth risk in symptomatic women attending an emergency obstetrical unit. Ultrasound Obstet Gynecol. 2017. • Lotfi G, Faraz S, Nasir R, Somini S, Abdeldayem RM, Koratkar R, Alsawalhi N, Ammar A. Comparison of the effectiveness of a PAMG-1 test and standard clinical assessment in the prediction of preterm birth and reduction of unnecessary hospital admissions.J Matern Fetal Neonatal Med. 2017 Oct 26:1-5. doi:	generally be included in a systematic review because their methodological quality cannot be assessed to the same standard as full-text papers. The additional full text papers suggested could not be included because they were published after the end date of the systematic review. We would ideally have liked to up-date the systematic review, but this would have necessitated re-searching for all the index tests, and there was insufficient time to achieve this. To include asymmetrically studies for just one index test, identified via notification by the test developer rather than a systematic search, runs the risk of introducing bias in the ascertainment of the literature. Publication bias and time to publication bias are particular concerns. We also note serious limitations with the systematic review of Melchor et al. 2017, as discussed in our response to Comment 3. To aid the DAC, the EAG provide an addendum summarising the most recently published and unpublished (AIC) evidence. We note that this does not constitute a systematic review, and that there may be

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				10.1080/14767058.2017.1391782. [Epub ahead of print] • Nikolova T, Uotila J, Nikolova N, Bolotkhikh V, Borisova V, DiRenzo GC. Comparison of the placental alpha microglobulin-1 test to the phosphorylated insulin-like growth factor-binding protein-1 test alone and in combination with cervical length measurement for the prediction of spontaneous preterm delivery in women with symptoms of preterm labor. Submitted manuscript 2018. Full manuscript submitted Academic in Confidence. • Melchor JC, Khalil A, Wing D, Schleussner E, Surbek D. The prediction of preterm delivery in symptomatic women using the placental alpha-microglobulin-1, fetal fibronectin and phosphorylated insulin-like growth factor-binding protein-1 tests: systematic review and meta-analysis stratified by risk. Submitted Manuscript 2017. Full manuscript submitted Academic in Confidence. • Ravi et al. Evaluation of the quantitative fetal fibronectin test and	other undiscovered papers published in the period after our systematic review search closed.

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				PartoSure (PAMG-1) for the prediction of sPTB in patients with signs and symptoms suggestive of preterm labour J Pediatr Neonat Individual Med. 2017 6 1 e060125. Full manuscript submitted Academic in Confidence.	
Parsagen Diagnostics Inc.	9	48	Table 2	Please clarify that The Basildon and Thurrock study is comparing PartoSure and fFn, not Actim Partus and fFN.	Based on the study details on https://clinicaltrials.gov/ct2/show/study/NCT02853656 the study aims to: *prospectively compare study of fFN (control) and PhIGFBP-1 test (comparator)* Therefore, based on this information we are correct in that the study is looking at Actim Partus and fFN
Parsagen Diagnostics Inc.	10	48	Table 2	Please explain why one of the studies has been redacted. If this study was considered for analysis as Academic in Confidence, the following manuscripts submitted as Academic in Confidence should also be included in the analysis to prevent scientific bias: • Nikolova T, Uotila J, Nikolova N, Bolotkhikh V, Borisova V, DiRenzo GC. Comparison of the placental alpha microglobulin-1 test to the phosphorylated insulin-like growth	The redacted study was marked as AIC as per your request in the document 'PartoSure Request for Information Final 05May17' in answer to question 12 on page 10. This is also an ongoing study, therefore no data would have been available for use.

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				factor-binding protein-1 test alone and in combination with cervical length measurement for the prediction of spontaneous preterm delivery in women with symptoms of preterm labor. Submitted manuscript 2018. Full manuscript submitted Academic in Confidence. • Melchor JC, Khalil A, Wing D, Schleussner E, Surbek D. The prediction of preterm delivery in symptomatic women using the placental alpha-microglobulin-1, fetal fibronectin and phosphorylated insulin-like growth factor-binding protein-1 tests: systematic review and meta-analysis stratified by risk. Submitted Manuscript 2017. Full manuscript submitted Academic in Confidence. • Ravi et al. Evaluation of the quantitative fetal fibronectin test and PartoSure (PAMG-1) for the prediction of sPTB in patients with signs and symptoms suggestive of preterm labour J Pediatr Neonat Individual Med. 2017 6 1 e060125. Full manuscript submitted Academic in Confidence.	

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Parsagen Diagnostics Inc.	11	59	2.2.3.1	The accuracy of the PartoSure test used for modelling scenarios was based on a single publication by Hadzi-Lega et al.[1] This publication is based on the inclusion of 57 patients comparing PartoSure and Actim Partus. Since the study selection for the review conducted in July 2017, 2 large studies have been published comparing the performance of PartoSure to the NICE reference standard of fFN @ 50 ng/ml.[2] As stated previously, as there have been three major studies published with 1425 patients comparing the performance of the PartoSure (PAMG-1) test to the reference test of fFN @ 50 ng/ml, the analysis should be rerun based on the latest clinical evidence and accuracy data available. • Wing et al.[3] – n= 796 (711 patients evaluated) • Melchor et al.[4] – n= 410 (367 patients evaluated) • Nikolova et al.[5] – n= 219 (203 patients evaluated; 66 patients compared to fFN @ 50 ng/ml) Another large study has been completed and submitted for publication (Nikolova et al.) comparing the performance of PartoSure and	We have conducted further analysis based on Wing et al. [3], Nikolova et al. [6], and Ravi et al.[8] . See our response to Comment 3 and Addendum for details.

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Stakeholder	Comment no.	Page no.	Section no.	Comment	EAG Response
				Fibronectin to Predict Preterm Delivery in Symptomatic Women. Obstet Gynecol. 2017;130(6):1183-91 4. Melchor JC, Navas H, Marcos M, Iza A, de Diego M, Rando D, et al. Retrospective cohort study of PAMG-1 and fetal fibronectin test performance in assessing spontaneous preterm birth risk in symptomatic women attending an emergency obstetrical unit. Ultrasound Obstet Gynecol. 2017. 5. Nikolova T, Bayev O, Nikolova N, Di Renzo GC. Comparison of a novel test for placental alpha microglobulin-1 with fetal fibronectin and cervical length measurement for the prediction of imminent spontaneous preterm delivery in patients with threatened preterm labor. Journal of Perinatal Medicine. 2015;43(4):395-402. 6. Nikolova T, Uotila J, Nikolova N, Bolotkhikh V, Borisova V, DiRenzo GC. Comparison of the placental alpha microglobulin-1 test to the phosphorylated insulin-like growth factor-binding protein-1 test alone and in combination with cervical length measurement for the prediction of spontaneous preterm delivery in women	

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Stakeholder	Comment no.	Page no.	Section no.	Comment	EAG Response
				with symptoms of preterm labor. Submitted manuscript 2018. Academic in Confidence. 7. Melchor JC, Khalil A, Wing D, Schleussner E, Surbek D. The prediction of preterm delivery in symptomatic women using the placental alpha-microglobulin-1, fetal fibronectin and phosphorylated insulin-like growth factor-binding protein-1 tests: systematic review and meta-analysis stratified by risk. Submitted Manuscript 2017. Academic in Confidence. 8. Ravi et al. Evaluation of the quantitative fetal fibronectin test and PartoSure (PAMG-1) for the prediction of sPTB in patients with signs and symptoms suggestive of preterm labour J Pediatr Neonat Individual Med. 2017 6 1 e060125. Full manuscript submitted Academic in Confidence.	
Parsagen Diagnostics Inc.	12	60	2.2.3.3	The Werlen et al.[1] (2015) study identified is not a test accuracy study. The purpose of the study was to test reproducibility of detection of PAMG-1 before and after digital examination and transvaginal ultrasound. This study should not be included in the test accuracy review, as it is not relevant. 1. Werlen S, Raia T, Di Bartolomeo A, Chauleur C. Preterm labor: Reproducibility	Although the purpose of the study was not specifically for test accuracy, the paper met our inclusion criteria and provided usable test accuracy data. We calculated all test accuracy from the 1st reading of the PartoSure test. We were only able to include this study in our review because Parsagen provided a certified translation.

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				of detection test of PAMG-1 before and after digital examination, and transvaginal ultrasound cervical length. Gynecol Obstet Ferti. 2015;43(10):640-5.	
Parsagen Diagnostics Inc.	13	75	2.2.6.1.1	Please update acronym from "NVP" to "NPV", this is an error.	Thank you for spotting these, we have amended in our main report
Parsagen Diagnostics Inc.	14	76	2.2.6.1.1	Please update acronym from "NVP" to "NPV", this is an error.	Thank you for spotting these, we have amended in our main report
Parsagen Diagnostics Inc.	15	110	5.3.1	Gibson (2014)[1] was included in the analysis. However, this study has not been published and only information from the abstract was available. Please provide the data for review by all stakeholders. Additionally, since this study was considered for analysis in its abstract form, please provide the reasoning for not including clinical studies provided in abstract form for the PartoSure test. The submitted studies are as follows: • Nikolova et al.[2] (2017) n= 328 • Lotfi et al.[3] (2015) n=151 • Ravi et al.[4] (2017) n= 72 • Konoplyannikov et al.[5] (2016) n=71 • Lou et al.[6] (2016) n= 65 • Heverhagen et al.[7] (2015) n= 64 • Van Holsbeke et al.[8] (2016) n= 50 • Fatkullin et al.[9] (2016) n= 45	See our response to Comment 4

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				1. Gibson S, Hezelgrave NL, Shennan AH. The impact of quantitative fetal fibronectin on the clinical management of women symptomatic of preterm labour. Archives of Disease in Childhood: Fetal and Neonatal Edition. 2014;99:A151-A5. 2. Nikolova et al. Do PAMG-1 or phIGFBP-1 biomarkers improve the prediction of imminent spontaneous preterm delivery in PTL symptomatic women with non-obvious cervical length (CL)? AJOG Jan 2017; 216 (1): Supplement S11-S12. 3. Lofti G et al. Evaluation of PAMG-1 for the prediction of preterm birth in patients symptomatic of preterm labor. J. Perinat. Med. 2015; 43 (S1):250. 4. Ravi et al. Evaluation of the quantitative fetal fibronectin test and PartoSure (PAMG-1) for the prediction of sPTB in patients with signs and symptoms suggestive of preterm labour J Pediatr Neonat Individual Med. 2017 6 1 e060125. 5. Konoplyannikov et al. PAMG-1 biomarker test (PARTOSURE) in combination with transvaginal ultrasound for improved assessment of spontaneous preterm birth in patients with threatened preterm labor. J	

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Stakeholder	Comment no.	Page no.	Section no.	Comment	EAG Response
				Matern Fetal Neonatal Med, 2016; 29(S1): 278. 6. Lou YY et al. Is PartoSure effective in assessing preterm birth? BJOG An International Journal of Obstetrics and Gynaecology. 2016; 123(S2): 89. 7. Heverhagen A. Placental alpha macroglobulin-1 in combination with transvaginal ultrasound for prediction of preterm birth. J. Perinat. Med. 2015; 43(S1): 240. 8. Van Holsbeke et al. Comparison of the fetal fibronectin (Rapid fFN) and placental alpha microgloibulin-1 (PartoSure) tests for predicting imminent spontaneous preterm birth. Ultrasound in Obstetrics & Gynecology 2016; 48 (S1): 84. 9. Fatkullin et al. Utilization of a novel biomarker test (PartoSure PAMG-1) to reduce the length of stay in patients with threatened preterm labor and a short cervix. J Matern Fetal Neonatal Med, 2016; 29(S1): 283.	
Parsagen Diagnostics Inc.	16	137	6.1.3	According to the guidelines followed by Guy's and St Thomas' Hospital (London),[1] patients with a positive result on an fFN test @ 50 ng/ml threshold are to be admitted for observation and treated with	It is not certain that the procedure described is in place at Guy's and St Thomas' Hospital. On the advice of Prof Shennan, the guideline only recommends

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				ACS at the fFN @ 200 ng/ml threshold. The model needs to reflect the clinical reality and cost of this protocol, as the admission and treatment cost are not binary in this scenario. 1. Shennan A, Carter J. Threatened Preterm Labour: guideline for management. In: Guy's and St Thomas', editor. 2017.	that admission at an fFN 50ng/ml threshold be considered by the attending obstetrician. In any case current practice at St. Thomas is being guided by the predicted risk of spontaneous preterm delivery, which depends on clinical history and other patient characteristics in addition to fFN, as opposed to fFN concentration on its own. A scenario analysis corresponding to the procedure at the Royal Devon and Exeter NHS Foundation Trust has been conducted and the results included in the addendum. In this scenario, patients are treated with ANS given a positive test result and admitted given a positive test result at an fFN threshold of 200 ng/ml. For the fFN 500 ng/ml test option, though, treatment with ANS and admission occur at the threshold of 500ng/ml, as in the base-case scenario.
Parsagen Diagnostics Inc.	17	139	6.1.5.1.1	Abbott (2013)[1] unpublished data was included in the analysis that has been redacted. Please provide the data for review by all stakeholders. Since data that has not been published was included in the analysis for the fetal fibronectin test, the inclusion of data from the multiple large clinical studies submitted for publication and	Unfortunately we are directed by NICE processes to redact all academic confidential information made available to people other than members of the Appraisal Committee of this review.

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				provided as Academic in Confidence, should also be included in order to prevent scientific-bias. • Nikolova T, Uotila J, Nikolova N, Bolotkhikh V, Borisova V, DiRenzo GC. Comparison of the placental alpha microglobulin-1 test to the phosphorylated insulin-like growth factor-binding protein-1 test alone and in combination with cervical length measurement for the prediction of spontaneous preterm delivery in women with symptoms of preterm labor. Submitted manuscript 2018. Full manuscript submitted Academic in Confidence. • • Melchor JC, Khalil A, Wing D, Schleussner E, Surbek D. The prediction of preterm delivery in symptomatic women using the placental alpha-microglobulin-1, fetal fibronectin and phosphorylated insulin-like growth factor-binding protein-1 tests: systematic review and meta-analysis stratified by risk. Submitted Manuscript 2017. Full manuscript submitted Academic in Confidence.	Likewise all the academic in confidence information provided by Parsagen, used in the additional analyses (i.e. Nikolova et al. 2018, Ravi et al. 2017) and circulated to non-ACM members has been redacted. For reasons which we have not used Melchor et al 2017, please see our response to Comment 3.

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				• Ravi et al. Evaluation of the quantitative fetal fibronectin test and PartoSure (PAMG-1) for the prediction of sPTB in patients with signs and symptoms suggestive of preterm labour J Pediatr Neonat Individual Med. 2017 6 1 e060125. Full manuscript submitted Academic in Confidence. 1. Abbott DS, Radford SK, Seed PT, Tribe RM, Shennan AH. Evaluation of a quantitative fetal fibronectin test for spontaneous preterm birth in symptomatic women. American journal of obstetrics and gynecology. 2013;208(2).	
Parsagen Diagnostics Inc.	18	140	Table 22	Abbott (2013)[1] unpublished data was included in the analysis that has been redacted. Please provide the data for review by all stakeholders. Since data that has not been published was included in the analysis for the fetal fibronectin test, the inclusion of data from the multiple large clinical studies submitted for publication and provided as Academic in Confidence, should also be included in order to prevent scientific-bias. • Nikolova T, Uotila J, Nikolova N, Bolotkhikh V, Borisova V, DiRenzo	See our response to Comment 17.

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Diagnostics Assessment Report (DAR) - Comments

Stakeholder	Comment no.	Page no.	Section no.	Comment	EAG Response
				GC. Comparison of the placental alpha microglobulin-1 test to the phosphorylated insulin-like growth factor-binding protein-1 test alone and in combination with cervical length measurement for the prediction of spontaneous preterm delivery in women with symptoms of preterm labor. Submitted manuscript 2018. Full manuscript submitted Academic in Confidence. • Melchor JC, Khalil A, Wing D, Schleussner E, Surbek D. The prediction of preterm delivery in symptomatic women using the placental alpha-microglobulin-1, fetal fibronectin and phosphorylated insulin-like growth factor-binding protein-1 tests: systematic review and meta-analysis stratified by risk. Submitted Manuscript 2017. Full manuscript submitted Academic in Confidence. • Ravi et al. Evaluation of the quantitative fetal fibronectin test and PartoSure (PAMG-1) for the prediction of sPTB in patients with signs and symptoms suggestive of preterm labour J Pediatr Neonat Individual	

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				Med. 2017 6 1 e060125. Full manuscript submitted Academic in Confidence. 1. Abbott DS, Radford SK, Seed PT, Tribe RM, Shennan AH. Evaluation of a quantitative fetal fibronectin test for spontaneous preterm birth in symptomatic women. American journal of obstetrics and gynecology. 2013;208(2).	
Parsagen Diagnostics Inc.	19	173	Table 42	Abbott (2013)[1] unpublished data was included in the analysis that has been redacted. Please provide the data for review by all stakeholders. Since data that has not been published was included in the analysis for the fetal fibronectin test, the inclusion of data from the multiple large clinical studies submitted for publication and provided as Academic in Confidence, should also be included in order to prevent scientific-bias. • Nikolova T, Uotila J, Nikolova N, Bolotkhikh V, Borisova V, DiRenzo GC. Comparison of the placental alpha microglobulin-1 test to the phosphorylated insulin-like growth factor-binding protein-1 test alone and in combination with cervical length measurement for the prediction of	See our response to Comment 17.

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				spontaneous preterm delivery in women with symptoms of preterm labor. Submitted manuscript 2018. Academic in Confidence. • Melchor JC, Khalil A, Wing D, Schleussner E, Surbek D. The prediction of preterm delivery in symptomatic women using the placental alpha-microglobulin-1, fetal fibronectin and phosphorylated insulin-like growth factor-binding protein-1 tests: systematic review and meta-analysis stratified by risk. Submitted Manuscript 2017. Academic in Confidence. • Ravi et al. Evaluation of the quantitative fetal fibronectin test and PartoSure (PAMG-1) for the prediction of sPTB in patients with signs and symptoms suggestive of preterm labour J Pediatr Neonat Individual Med. 2017 6 1 e060125. Full manuscript submitted Academic in Confidence. 1. Abbott DS, Radford SK, Seed PT, Tribe RM, Shennan AH. Evaluation of a quantitative fetal fibronectin test for	

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				spontaneous preterm birth in symptomatic women. American journal of obstetrics and gynecology. 2013;208(2).	
Parsagen Diagnostics Inc.	20	178	7	In the absence of a biomarker test, only clinical evaluation is available to assess the risk of spontaneous preterm delivery within 7 days. When standard clinical assessment is used alone, up to 61% of women presenting with threatened preterm labour may be admitted.[1] The PartoSure test has several important characteristics compared to other commercially available biomarker tests that can reduce the frequency that clinical assessment alone is used. These differences should be included in the report and the cost effectiveness model. Specifically: 1. **PartoSure is the only test for which the specimen can be collected without a speculum examination.**[2] The PartoSure sample is collected via a blind vaginal swab that can be performed by either a physician or midwife. This lack of a requirement for a speculum examination can significantly decrease triage time and is more comfortable for the patient. In a UK national survey, up to 32% of midwives responded that they are not able to perform a	Please note that although our model and report did not address the case of these specific subpopulations, we included in our report and addendum comparisons against the 'no test, treat-all' option. Looking at these results should provide answers to most of these questions. In response to your specific questions our experts' opinions are: 1. 1st expert: If a patient presents with signs and symptoms of preterm labour a speculum is necessary primarily to exclude rupture of membranes and secondarily to see if the cervix is dilated. If the cervix is dilated and labour confirmed the test does not need to be taken regardless of what test you use. 2nd exeprt: Correct re not passing speculum for the test. However, the next statement is misleading. The hospital policies are about doing tests on preterm women, ie not passing speculums on women before 37 weeks. All

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				speculum examination, primarily due to hospital policy.[3] 2. **Vaginal examination shortly before specimen collection does not lead to false positive PartoSure test results.[4]** However, qfFN cannot be performed for 24 hours after vaginal exam as manipulation of the cervix may lead to falsely elevated fFN results.[5] This difference regarding vaginal examination interference may allow for testing in more patients who otherwise would not have benefited from the evaluation of a biomarker test. 3. **PartoSure has a wider gestational age limitation compared to fFN.** PartoSure can be used up to 36 weeks and 6 days of gestation,[2] compared to 35 weeks and 6 days for quantitative fFN (qfFN)[5]. This difference in gestational age limitation may allow for testing in up to 9.1% more patients who otherwise would not have benefited from the evaluation of a biomarker test.[6] 4. **PartoSure can be used in patients with a cervical dilation of 3 cm, whereas qfFN cannot.** PartoSure is intended for use in	midwives can pass speculums. The issue is about the gestation, not the speculum, and the policies that do not allow the test with speculums would also not allow the test without speculums. It is a professional responsibility issue. These 32% would also not be allowed to use Partosure and this cannot be viewed as a reason to purchase it. I would say there is no evidence that the lower swab is any more acceptable. There is an assumption that passing a swab is more acceptable than a speculum. This might be the case, but I'm not aware of any comparison studies. There is evidence that women find speculums acceptable 2. 1st expert: I agree this comment is correct but most units advise no VE on preterm women until a bio marker test can be performed. It is unusual for our midwives to do a VE without discussing it with a doctor. The benefit of ffn is that you can take the sample but not process (and store in fridge for 3/7). Taking the sample costs nothing. So we advise if in doubt take the sample and then ask whether to process. (Our understanding is that despite this limitation qfFN would still be used routinely as its ability to detect true negative cases; see answer to point 5 below)

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				patients with a cervical dilation of ≤3 cm,[2] whereas qfFN is intended for use in patients with a cervical dilation of <3 cm.[5] This difference in cervical dilation limitation may allow for testing in up to 18.7% more patients who otherwise would not have benefited from the evaluation of a biomarker test.[6] 5. **Semen does not lead to false positive PartoSure test results.** However, the presence of semen can lead to falsely elevated fFN results. Consequently, fFN specimens should not be collected less than 24 hours after intercourse[3]; it should be noted that published clinical data suggest that falsely elevated values of fFN may still be present up to 48 hours after intercourse.[7] This difference regarding semen interference may allow for testing in up to 12% more patients who otherwise would not have benefited from the evaluation of a biomarker test.[8] 1. Lotfi G, Faraz S, Nasir R, Somini S, Abdeldayem RM, Koratkar R, Alsawalhi N,	2nd expert: This was a recommendation brought in for licencing reasons some time ago, but with no evidence. There is now evidence to the contrary. The American College now state this is not a concern and ffn maybe used close to an examination. 3. 1st expert: This is a poor argument - we only give steroids and tocolytics up to 36/40 and therefore no need to test past this gestation. I wouldn't our waste money on testing any patient past 36/40. 2nd expert Actually ffn can be used from 18 weeks, so strictly speaking the opposite is true (ffn has a wider gestational age limit). It depends on what indication you want to use it for. For the purposes of threatened preterm labour this may be correct. Again these limits are not evidence based, just a licencing issue ie one could easily use ffn later 4. 1st expert I wonder how many women test negative that are 3 cm dilated! This goes against Parsagen's first point - if you dongent negative that are 3 cm dilated!cs up to

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				Ammar A. Comparison of the effectiveness of a PAMG-1 test and standard clinical assessment in the prediction of preterm birth and reduction of unnecessary hospital admissions.J Matern Fetal Neonatal Med. 2017 Oct 26:1-5. doi: 10.1080/14767058.2017.1391782. [Epub ahead of print] 2. Parsagen Diagnostics Inc. PartoSure, Assess the risk of preterm birth: Instructions for use 2015. 3. United Kingdom National Survey of Midwives, 2017. 4. Werlen S, Raia T, Di Bartolomeo A, Chauleur C. Preterm labor: Reproducibility of detection test of PAMG-1 before and after digital examination, and transvaginal ultrasound cervical length. Gynecol Obstet Ferti. 2015;43(10):640-5. 5. Hologic. Rapid fFN 10Q Cassette Kit: Instructions for use 2016. 6. *Calculated from source data of:* Nikolova T, Bayev O, Nikolova N, Di Renzo GC. Comparison of a novel test for placental alpha microglobulin-1 with fetal fibronectin and cervical length measurement for the prediction of imminent spontaneous preterm delivery in patients with threatened	36/40 a? Also 29mm vs 30 mm is very arbitrary. Finally the reason other tests use <3cm is that if you are contracting and 3cm the majority of women will labour and should be managed accordingly. If a patient is contracting and 3cm I would not send home and would doubt the ffn would be negative. 2nd expert Not sure I understand this. <3 and <=3 are virtually identical, and for all practical purposes the same. They must be assuming <= 2 is the same as <3. Otherwise how could they calculate 18.7% difference. 5. 1st expert This point I do agree and it is one frustration of ffn, but the number of women who have had intercourse is small and I wouldn't say in clinical practice it's 12%. Sometimes we decide to go test as dementia will give you a false positive test so if it's negative then it's useful. Often women have had a bath after intercourse/or to help with tightenings and the semen has been washed away. 2nd expert This is true but again the 12 % statistic is misleading as everyone is tested regardless of intercourse and negative tests (which happen in most women) are still valid ie you

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				preterm labor. J Perinat Med. 2015 Jul;43(4):395-402. 7. QUiPP App version 2.0.1 released Oct 2017. 8. Bruijn MM, Hermans FJ, Vis JY, et al. Which Factors Contribute to False-Positive, False-Negative, and Invalid Results in Fetal Fibronectin Testing in Women with Symptoms of Preterm Labor? Am J Perinatol. 2017 Feb;34(3):234-239	can not have a false negative with semen. False positives are in a far smaller percentage.
Parsagen Diagnostics Inc.	21	182	8.1.2	The accuracy of the PartoSure test used for modelling scenarios was based on a single publication by Hadzi-Lega et al.[1] This publication is based on the inclusion of 57 patients comparing PartoSure and Actim Partus. Since the study selection for the review conducted in July 2017, 2 large studies have been published comparing the performance of PartoSure to the NICE reference standard of fFN @ 50 ng/ml.[2] As stated previously, as there have been three major studies published with 1425 patients comparing the performance of the PartoSure (PAMG-1) test to the reference test of fFN @ 50 ng/ml, the analysis should be rerun based on the latest clinical evidence and accuracy data available. • Wing et al.[3] – n= 796 (711 patients evaluated)	See our response to Comment 3.

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				• Melchor et al.[4] – n= 410 (367 patients evaluated) • Nikolova et al.[5] – n= 219 (203 patients evaluated; 66 patients compared to fFN @ 50 ng/ml) Another large study has been completed and submitted for publication (Nikolova et al.) comparing the performance of PartoSure and Actim Partus in a large European cohort of 403 patients, and is therefore critical to this review. The study manuscript was provided as Academic in Confidence, along with these comments. We suggest that the analysis should be rerun based on the latest clinical evidence and accuracy data available. • Nikolova et al.[6] – n= 403 (383 patients evaluated) A meta-analysis has also been recently completed comparing PartoSure, fFN @ 50 ng/ml and Actim Partus across a range of varying prevalence populations for low risk, intermediate risk and high risk. As prevalence of the patient cohort may change based on the underlying patient population and testing protocol, this study aims to compare	

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				the publications available to date in similar patient cohorts. The study manuscript was provided on December 13th, 2017 as Academic in Confidence and again along with these comments. The analysis should be rerun based on the latest clinical evidence and accuracy data available. • Melchor et al.[7] – PAMG-1 (n= 2278); fFN @ 50 ng/ml (n=7431); phIGFBP-1 (n=3087) Lastly, yet another study has been submitted for publication (Ravi et al.) that compares PartoSure directly to the quantitative fFN test at the following thresholds: 10, 50, 200, and 500, and is therefore critical to this review. The manuscript was provided as Academic in Confidence on November 20, 2017 and again along with these comments. The analysis should be rerun based on the latest clinical evidence and accuracy data available from this study, as it is the only investigation to date comparing the performance of PartoSure and quantitative fFN head to head. • Ravi et al.[8] – n= 101 (72 patients evaluated) 1. Hadzi-Lega M, Maier JT, Helmer H, Hellmeyer L, Markova AD, Poposka A. Comparison of PAMG-1 and phIGFBP-1 Tests for the Prediction of Preterm Delivery	

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				in Patients with Preterm Labor. Open Journal of Obstetrics and Gynecology. 2017;Vol.07No.03:11. 2. Preterm labour and birth. NICE Guideline. 20 November 2015. nice.org.uk/guidance/ng25 3. Wing DA, Haeri S, Silber AC, Roth CK, Weiner CP, Echebiri NC, et al. Placental Alpha Microglobulin-1 Compared With Fetal Fibronectin to Predict Preterm Delivery in Symptomatic Women. Obstet Gynecol. 2017;130(6):1183-91 4. Melchor JC, Navas H, Marcos M, Iza A, de Diego M, Rando D, et al. Retrospective cohort study of PAMG-1 and fetal fibronectin test performance in assessing spontaneous preterm birth risk in symptomatic women attending an emergency obstetrical unit. Ultrasound Obstet Gynecol. 2017. 5. Nikolova T, Bayev O, Nikolova N, Di Renzo GC. Comparison of a novel test for placental alpha microglobulin-1 with fetal fibronectin and cervical length measurement for the prediction of imminent spontaneous preterm delivery in patients	

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				with threatened preterm labor. Journal of Perinatal Medicine. 2015;43(4):395-402. 6. Nikolova T, Uotila J, Nikolova N, Bolotkhikh V, Borisova V, DiRenzo GC. Comparison of the placental alpha microglobulin-1 test to the phosphorylated insulin-like growth factor-binding protein-1 test alone and in combination with cervical length measurement for the prediction of spontaneous preterm delivery in women with symptoms of preterm labor. Submitted manuscript 2018. Academic in Confidence. 7. Melchor JC, Khalil A, Wing D, Schleussner E, Surbek D. The prediction of preterm delivery in symptomatic women using the placental alpha-microglobulin-1, fetal fibronectin and phosphorylated insulin-like growth factor-binding protein-1 tests: systematic review and meta-analysis stratified by risk. Submitted Manuscript 2017. Academic in Confidence. 8. Ravi et al. Evaluation of the quantitative fetal fibronectin test and PartoSure (PAMG-1) for the prediction of sPTB in patients with signs and symptoms suggestive of preterm labour J Pediatr Neonat Individual Med.	

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Royal College of Obstetricians and Gynaecologists	22	General		There aren't enough studies with direct comparisons to draw any meaningful conclusions. Furthermore, the methodology and outcomes in the various studies are so heterogeneous that conclusions cannot be drawn. The recommendation in the current NICE preterm labour and delivery guideline that symptomatic women presenting at 30 weeks of gestation be admitted and 'treated' may not be cost effective. Larger studies are currently in progress and may provide useful information in due course. In addition, future studies should assess all 3 tests in the same woman to allow unbiased assessment of efficacy and – that final health outcome parameters in mother and babies should be included in any recommendations in the future. Our position – we agree with the findings of the report. We acknowledge that there is insufficient evidence at present to allow direct comparisons of the biomarkers. We await the results on ongoing trials with interest.	No response required.

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