# PECheck™ PAPP-A2 ELISA

**RUO**

## AL-1015-r

## INTENDED USE

The PECheck™ PAPP-A2 Enzyme-Linked Immunosorbent Assay (ELISA) kit provides materials for the quantitative measurement of PAPP-A2 in human maternal serum and other biological fluids. The kit is intended for **research use only**.

## SUMMARY AND EXPLANATION

Pregnancy associated plasma protein-A2 (PAPP-A2) is a metalloproteinase protein identified as a homolog of PAPP-A in the metzincin superfamily of pappalysins[1-8]. PAPP-A2 is a noncovalently linked dimer of two 220-kDa subunits4. PAPP-A2 cleaves insulin-like growth factor-binding protein 5 (IGFBP5) and Insulin like growth factor binding protein 3[4]. PAPP-A2 is function as a local regulator of insulin-like growth factor (IGF) bioavailability[1-8]. PAPP-A2 is expressed in a wide range of tissues and abundantly present in the placental syncytiotrophoblast and the pregnant uterus[3]. The insulin-like growth factors are important in human embryo implantation and placentation[1-8]. Numerous studies have identified the associations between the placental levels of PAPP-A2 and preeclampsia[1-8]. It is being suggested that either altered levels PAPP-A2 cause abnormal placental development, or the production of these proteins is altered to compensate for abnormal placentation[1-8]. Preeclampsia affects 5% - 7% of all pregnant women and poses threat to maternal and fetal well-being. PAPP-A2 is abundantly expressed in the placenta and have been reported to be significantly elevated in the maternal circulation as well as placentas of pregnancies complicated by preeclampsia. PAPP-A2 showed the highest value to predict preeclampsia-related pregnancy complications when added on top of traditional criteria and shows comparable value to that of the angiogenic markers sFlt-1 (soluble Fms-like tyrosinekinase-1), placental growth factor (PlGF), and sFlt-1/PlGF ratio[9].

## PRINCIPLE OF THE TEST

The PECheck™ PAPP-A2 ELISA is a quantitative three-step sandwich type immunoassay. In the first step Calibrators, Controls and unknown samples are added to anti-PAPP-A2 antibody coated micro titer wells and incubated. After first incubation and washing step, the wells are incubated with biotin labelled antibody conjugate. After a second incubation and washing step, the wells are incubated with streptavidin horseradish peroxidase conjugate (SHRP) solution. After the third incubation and washing step, the wells are incubated with substrate solution (TMB). After TMB incubation, an acidic stopping solution is added. In principle, the antibody-biotin conjugate binds to the solid phase antibody-antigen complex which in turn binds to the streptavidin-enzyme conjugate. The antibody-antigen-biotin conjugate-SHRP complex bound to the well is detected by enzyme-substrate reaction. The degree of enzymatic turnover of the substrate is determined by dual wavelength absorbance measurement at 450 nm as primary test filter and 630 nm as reference filter. The absorbance measured is directly proportional to the concentration of PAPP-A2 in the samples and calibrators.

## MATERIALS SUPPLIED

**CAL-1015A** **PECheck™ Calibrator A/Sample Diluent**

One bottle, 8 mL, labeled PAPP-A2 CAL A/Sample Diluent, containing 0 ng/mL PAPP-A2 in a protein-based buffer with a non-mercury preservative. Store unopened at 2 to 8°C until the expiration date.

**CAL-1015B - CAL-1015F** **PECheck™ Calibrators B thru F (Lyophilized)**

Five vials, labeled B-F, containing concentrations of approximately 4.0-480.0* ng/mL PAPP-A2 in a protein-based buffer with non-mercury preservative. Refer to **calibration card** for exact concentrations. Store unopened at 2 to 8°C until the expiration date. Reconstitute calibrators B-F with **1.0 mL** deionized water. Solubilize for **10 minutes**, mix well, and use after reconstitution. For longer storage after reconstitution, aliquot, and freeze at -20°C or colder for up to one year.

*Calibrator Traceability: The calibrators concentration is corrected (5x) for the dilution performed in the assay procedure (steps 3 and 4).

**CTR-1015-I & CTR-1015-II** **PECheck™ Controls I & II (Lyophilized)**

Two vials, labeled Levels I and II containing low and high PAPP-A2 in a protein-based buffer with non-mercury preservative. Refer to **calibration card** for exact control ranges. Store unopened at 2 to 8°C until the expiration date. Reconstitute control Levels I and II with **1.0 mL** deionized water. Solubilize for **10 minutes**, mix well, and use after reconstitution. For longer storage after reconstitution, aliquot, and freeze at -20°C or colder for up to one year.

**PLT-109** **PAPP-A2 Antibody Coated Microtitration Strips**

One strip holder, containing 12 strips and 96 microtitration wells with PAPP-A2 antibody immobilized to the inside wall of each well. Store at 2-8°C until expiration date in the resealable pouch with a desiccant to protect from moisture.

**ASB-109** **PAPP-A2 Assay Buffer**

One bottle, 8 mL, containing a protein based (BSA)-buffer with a non-mercury preservative. Store at 2-8°C until expiration date.

**BCR-1015** **PECheck™ Biotin Conjugate Ready-to-Use (RTU)**

One bottle, 12 mL, containing biotinylated PAPP-A2 antibody in a protein-based buffer with a non-mercury preservative. Store at 2-8°C until expiration date.

**SAR-1015** **PECheck™ Streptavidin-Enzyme Conjugate Ready-to-Use (RTU)**

One bottle, 12 mL, containing streptavidin-HRP (horseradish peroxidase) in a protein-based buffer with a non-mercury preservative. Store undiluted at 2-8°C until expiration date.

**TMB-100** **TMB Chromogen Solution**

One bottle, 12 mL, containing a solution of tetramethylbenzidine (TMB) in buffer with hydrogen peroxide. Store at 2 to 8°C until expiration date.

**STP-100** **Stopping Solution**

One bottle, 12 mL, containing 0.2 M sulfuric acid. Store at 2 to 30°C until expiration date.

**WSH-100 Wash Concentrate A**

One bottle, 60 mL, containing phosphate buffer saline solution with a nonionic detergent. Store at 2 to 30°C until expiration date. Dilute 25-fold with deionized water prior to use.

## MATERIALS REQUIRED BUT NOT PROVIDED

1. Microplate reader capable of absorbance measurement at 450 nm, 405 nm, and 630 nm.
2. Microtitration plate orbital shaker.
3. Microtitration plate washer.
4. Semi-automated/manual precision pipette to deliver 10–250 µL.
5. Vortex mixer.
6. Deionized water.
7. Disposable 12 x 75 mm culture tubes.
8. Tight fitting 12 x 75 mm tube racks.

## WARNINGS AND PRECAUTIONS

**For in vitro research use.**

The following precautions should be observed:

a) Follow good laboratory practice.

b) Use personal protective equipment. Wear lab coats and disposable gloves when handling immunoassay materials.

c) Handle and dispose of all reagents and material in compliance with applicable regulations.

d) If external package is damaged, inspect the components inside for any other damage. Do not use if the components are damaged.

**WARNING: Potential Biohazardous Material**

This reagent may contain some human source material (e.g., serum) or materials used in conjunction with human source materials. Handle all reagents and patient samples at a Biosafety Level 2, as recommended for any potentially infectious human material in the Centers for Disease Control/National Institutes of Health manual "Biosafety in Microbiological and Biomedical Laboratories," 5th Edition, 2007[10].

**WARNING: Potential Chemical Hazard**

Some reagents in this kit contain Pro-Clean 400 and Sodium azide[11] as a preservative. Pro-Clean 400 in concentrated amounts are irritants to skin and mucous membranes.

For further information regarding hazardous substances in the kit, please refer to the MSDS, either at AnshLabs.com or by request.

## SAMPLE COLLECTION AND PREPARATION

a) Serum is the recommended sample type.

b) Use the following recommendations for handling, processing, and storing blood samples[12].

- Allow samples to clot for two hours at room temperature or overnight at 4°C and follow blood collection tube manufacturer's recommendations for centrifugation. Keep tubes stoppered always. Within two hours after centrifugation, transfer at least 500 µL of cell free sample to a storage tube. Tightly stopper the tube immediately.
- Samples if used within 24 hours may be stored at 4°C; otherwise, samples must be stored at -20°C or -80°C to avoid loss of bioactivity and contamination.
- Remove residual fibrin and cellular matter prior to analysis.

c) Avoid assaying lipemic, hemolyzed or icteric samples.

d) Each laboratory should determine the acceptability of its own blood collection tubes and serum separation products.

e) Avoid repeated freezing and thawing of samples. Thaw samples no more than 3 times.

## PROCEDURAL NOTES

1. A thorough understanding of this package insert is necessary for successful use of the PECheck™ PAPP-A2 ELISA. It is the responsibility of the customer to validate the assay for their purposes. Accurate results will only be obtained by using precise laboratory techniques and following the package insert.
2. A calibration curve must be included with each assay.
3. Bring all kit reagents to room temperature before use. Thoroughly mix the reagents before use by gentle inversion. Do not mix various lots of any kit component and do not use any component beyond the expiration date.
4. Use a clean disposable pipette tip for each reagent, calibrator, control, or sample. Avoid microbial contamination of reagents, contamination of the substrate solutions with the enzyme conjugates. The enzyme used as the label is inactivated by oxygen, and is highly sensitive to microbial contamination, sodium azide, hypochlorous acid and aromatic chlorohydrocarbons often found in laboratory water supplies. Use deionized water.
5. Incomplete washing will adversely affect the outcome and assay precision. To minimize potential assay drift due to variation in the substrate incubation time, care should be taken to add the substrate solution into the wells. Avoid exposure of the reagents to excessive heat or direct sunlight during storage and incubation.

## PREPARATION OF REAGENTS

1. **PECheck™ PAPP-A2 Calibrators B-F and Controls I & II**: Tap and reconstitute PECheck™ PAPP-A2 Calibrators B-F and Controls I & II with **1.0** mL deionized water. Solubilize for **10 minutes**, mix well, and use after reconstitution.
2. **Wash Solution:** Dilute wash concentrate 25-fold with deionized water. The wash solution is stable for one month at room temperature when stored in a tightly sealed bottle.
3. **Microtitration Wells:** Select the number of coated wells required for the assay. The remaining unused wells should be placed in the resealable pouch with a desiccant. The pouch must be resealed to protect from moisture.

## ASSAY PROCEDURE

Allow all specimens and reagents to reach room temperature and mix thoroughly by gentle inversion before use. Calibrators, controls, and unknowns should be assayed in duplicate.

**NOTE**: All pregnancy samples reading higher than the highest calibrator should be further diluted two folds in sample diluent prior to assay.

***Do not dilute Calibrators or Controls.***

1. Mark the microtitration strips to be used.
2. Pipette **100 µL** of the **Calibrator and Controls** to the appropriate wells.
3. Pipette **20 µL** of **samples** using precision pipette to the sample designated wells.
4. Pipette **80 µL** of **CAL-1015A** to the sample added wells.
5. Add **50 µL** of the **PAPP-A2 Assay Buffer** to each well using a repeater pipette.
6. Incubate the wells, shaking at a fast speed **(600-800 rpm)** on an orbital microplate shaker, for **45 minutes** at room temperature (23 ± 2°C).
7. Aspirate and wash each well **5 times** with Wash Solution **(350 µL /per well)** using an automatic microplate washer.

8. Add **100 µL** of the **Antibody-Biotin Conjugate solution** to each well using a repeater pipette.
9. Incubate the wells, shaking at a fast speed **(600-800 rpm)** on an orbital microplate shaker, for **20 minutes** at room temperature (23 ± 2°C).
10. Aspirate and wash each well 5 times with the Wash Solution **(350 µL/per well)** using an automatic microplate washer.
11. Add **100 µL** of the **Streptavidin-Enzyme Conjugate-RTU** to each well using a repeater pipette.
12. Incubate the wells, shaking at a fast speed **(600-800 rpm)** on an orbital microplate shaker, for **20 minutes** at room temperature (23 ± 2°C).
13. Aspirate and wash each well **5 times** with the Wash Solution **(350 µL /per well)** using an automatic microplate washer.
14. Add **100 µL** of the **TMB chromogen solution** to each well using a repeater pipette. Avoid exposure to direct sunlight.
15. Incubate the wells, shaking at **600–800 rpm** on an orbital microplate shaker, for **8-12 minutes** at room temperature (23 ± 2°C).
    ***NOTE:*** *Visually monitor the color development to optimize the incubation time.*
16. Add **100 µL** of the **Stopping solution** to each well using a repeater pipette. Read the absorbance of the solution in the wells within 20 minutes, using a microplate reader set to **450 nm**.
    ***NOTE****: Zero calibrator should be programmed as "**Blank**" while reading the optical density. If instrument has a wavelength correction, set the instrument to dual wavelength measurement at **450 nm** with background wavelength correction at **630 nm (OD 450-630 nm)**.*

## RESULTS

***NOTE:*** *The results in this package insert were calculated by plotting the **log optical density (OD) data on the y-axis and log PAPP-A2 concentration on X-axis** using a cubic regression curve-fit. Alternatively, log vs. log quadratic regression curve-fit can be used. Other data reduction methods may give slightly different results.*

1. Optimum results can be obtained at incubation temperature of **23 ± 2°C**.
2. Calculate the mean absorbance for each calibrator, Control, or Unknown. Plot the log of the mean absorbance readings for each of the Calibrators along the y-axis versus log of the PAPP-A2 concentrations in ng/mL along the x-axis, using a cubic regression curve-fit.
3. Determine the PAPP-A2 concentrations of the Controls and Unknowns from the calibration curve by matching their mean absorbance readings with the corresponding PAPP-A2 concentrations.
4. The calibrator concentrations are already corrected for the sample dilution in steps 3 & 4 of the assay procedure, therefore there is no need to multiply the sample values by this dilution factor.
5. Any sample reading higher than the highest Calibrator should be appropriately diluted with the sample diluent and re-assayed. Multiply the value by the dilution factor.
6. Any sample reading lower than the analytical sensitivity should be reported as such.

## LIMITATIONS

The reagents supplied in this kit are optimized to measure PAPP-A2 levels in human serum. If there is evidence of microbial contamination or excessive turbidity in a reagent, discard the vial. For assays employing antibodies, the possibility exists for interference by heterophile antibodies in the samples[13].

## QUALITY CONTROL

- Each laboratory should establish mean values and acceptable ranges to assure proper performance.
- PECheck™ PAPP-A2 ELISA controls or other commercial controls should fall within established confidence limits.
- The confidence limits for PAPP-A2 controls are printed on the **Calibration card**.
- A full calibration curve-, low- and high-level controls, should be included in each assay.
- The TMB chromogen solution should be colorless. Development of a blue color may indicate reagent contamination or instability.

## REPRESENTATIVE CALIBRATION CURVE DATA

| Well Number | Well Contents (Calibrators) | Mean OD | Conc. (ng/mL) |
|---|---|---|---|
| **A1, A2** | A | 0.006 (**Blank**) | 0 |
| **B1, B2** | B | 0.048 | 4.00 |
| **C1, C2** | C | 0.165 | 15.6 |
| **D1, D2** | D | 0.576 | 56.5 |
| **E1, E2** | E | 1.718 | 184.0 |
| **F1, F2** | F | 3.396 | 480.0 |

***CAUTION:*** *The above data must not be employed in lieu of data obtained by the user in the laboratory.*



## ANALYTICAL CHARACTERISTICS

All concentrations listed are in ng/mL.

**Analytical Sensitivity:**
The analytical sensitivity in the assay as calculated by the interpolation of mean plus two standard deviations of 16 replicates of calibrator A (0 ng/mL) and calibrator B (4.0 ng/mL) is 0.37 ng/mL.

**Limit of Blank (LoB):**
The Limit of Blank is 0.102 ng/mL, calculated from a minimum of n=18 measurements of analyte free sample.

**Limit of Detection (LoD):**
The lowest amount of PAPP-A2 in a sample that can be detected with a 95% probability (n=24) is 0.62 ng/mL. The value was determined by processing nine functional samples in the range of 0.56 to 6.05 ng/mL following CLSI EP17 guidelines. 8 assay runs were performed over two days with samples run in triplicates per run.

**Limit of Quantitation (LoQ):**
The estimated minimum dose achieved at 20% total imprecision is 1.68 ng/mL. The value was determined by processing eight samples in the range of 0.56-6.05 ng/mL over eight runs and two days in triplicates (n=24) following CLSI EP17 guidelines.

**Imprecision:**
Reproducibility of the PECheck™ PAPP-A2 ELISA assay was determined in a study using three serum pools. The study included a total of 12 assays, 3 replicates of each per assay (n=36). Representative data were calculated and are presented in the following table.

| Sample | Mean Conc. | Within run | | Between run | | Total | |
|---|---|---|---|---|---|---|---|
| | ng/mL | SD | %CV | SD | %CV | SD | %CV |
| 1 | 12.0 | 0.3 | 2.8% | 0.3 | 2.7% | 0.5 | 3.9% |
| 2 | 137.2 | 3.6 | 2.6% | 6.6 | 4.8% | 7.5 | 5.5% |
| 3 | 394.7 | 15.5 | 3.9% | 17.9 | 4.5% | 23.7 | 6.0% |

**Recovery:**

Known amounts of PAPP-A2 was added to five serum samples containing different levels of endogenous PAPP-A2. The concentration of PAPP-A2 was determined before and after the addition of exogenous PAPP-A2 and the percent recovery was calculated.

| Sample | Endogenous Conc. (ng/mL) | Expected Conc. (ng/mL) | Observed Conc. (ng/mL) | %Recovery |
|---|---|---|---|---|
| S1 | 57.4 | 59.4 | 60.3 | 100% |
| | | 61.3 | 62.0 | |
| | | 63.2 | 61.6 | |
| S2 | 65.2 | 66.7 | 67.3 | 99% |
| | | 68.3 | 67.9 | |
| | | 69.8 | 67.9 | |
| S3 | 90.1 | 90.4 | 103.3 | 112% |
| | | 90.7 | 100.4 | |
| | | 91.0 | 100.0 | |
| S4 | 69.2 | 70.5 | 70.4 | 99% |
| | | 71.9 | 71.5 | |
| | | 73.2 | 72.2 | |
| S5 | 80.4 | 81.2 | 79.7 | 97% |
| | | 82.0 | 80.1 | |
| | | 82.7 | 79.6 | |

**Hook Effect:**

There is no high-dose hook effect at PAPP-A2 Concentrations up to 2250 ng/mL.

**Linearity:**

Two serum samples and Calibrator F containing various PAPP-A2 levels were diluted with Calibrator A/sample diluent. The % recovery on individual samples is represented in the following table.

| Sample ID | Dilution factor (1 in X) | Expected Value in ng/mL | Observed Value in ng/mL | % Recovery | Average %Recovery |
|---|---|---|---|---|---|
| CAL F | NEAT | 480.0 | | | 93% |
| | 2 | 240.0 | 249.8 | 104% | |
| | 4 | 120.0 | 117.1 | 98% | |
| | 8 | 60.0 | 55.1 | 92% | |
| | 16 | 30.0 | 26.1 | 87% | |
| | 32 | 15.0 | 12.3 | 82% | |
| 3T Serum | NEAT | 57.0 | | | 102% |
| | 2 | 28.5 | 29.8 | 104% | |
| | 4 | 14.3 | 15.1 | 106% | |
| | 8 | 7.1 | 7.2 | 101% | |
| | 16 | 3.6 | 3.5 | 98% | |
| RBPIII-013 | NEAT | 77.0 | | | 111% |
| | **2** | 38.5 | 41.3 | 107% | |
| | **4** | 19.3 | 21.6 | 112% | |
| | **8** | 9.6 | 10.8 | 112% | |
| | **16** | 4.8 | 5.4 | 112% | |

**Analytical Specificity:**

The antibody pair used in the PECheck™ PAPP-A2 ELISA measures PAPP-A2 and does not detect other similar molecules. The assay does not detect dimeric PAPP-A, heteromeric PAPP-A, STC-1, STC-2, PAPP-A proMBP, PAPP-A-STC-2, and $\alpha_2$ macroglobulin.

| Cross-Reactant | Concentration | % Cross-reactivity |
|---|---|---|
| Dimeric PAPP-A | 50 ng/mL | ND |
| Heteromeric PAPP-A | 50 ng/mL | ND |
| STC-1 | 50 ng/mL | ND |
| STC-2 | 50 ng/mL | ND |
| PAPP-A proMBP | 50 ng/mL | ND |
| α 2 Macroglobulin | 50 ng/mL | ND |
| PAPP-A STC-2 | 50 ng/mL | ND |

The antibody pair used in PECheck™ PAPP-A2 assay detects Monkey samples. The assay does not detect Bovine, Canine, Equine, Ovine, Rabbit, Porcine, Goat, and Mouse species.

**Interference:**

When potential interferents (hemoglobin, triglycerides, and bilirubin) were added at least at two times their physiological concentration to control sample, PAPP-A2 concentration were within ± 10% of the control as represented in the following table.

| Interferent | Interferent Dose | Analyte Conc. (ng/mL) | Spiked Sample Value (ng/mL) | % Difference |
|---|---|---|---|---|
| Hemoglobin | 1 mg/mL | 50.2 | 54.4 | 8.4 |
| | 0.5 mg/mL | 53.5 | 53.8 | 0.6 |
| | 0.1 mg/mL | 54.7 | 55.0 | 0.5 |
| Hemoglobin | 1 mg/mL | 56.0 | 59.4 | 6.1 |
| | 0.5 mg/mL | 60.0 | 62.8 | 4.6 |
| | 0.1 mg/mL | 62.5 | 61.7 | -1.3 |
| Biotin | 1200 pg/mL | 49.7 | 50.3 | 1.3 |
| | 600 pg/mL | 52.1 | 51.2 | -1.8 |
| Biotin | 1200 pg/mL | 57.5 | 58.3 | 1.4 |
| | 600 pg/mL | 60.2 | 59.4 | -1.3 |
| Intralipids | 20 mg/mL | 49.6 | 50.7 | 2.1 |
| | 10 mg/mL | 52.1 | 51.5 | -1.1 |
| | 5 mg/mL | 53.9 | 55.2 | 2.5 |
| Intralipids | 20 mg/mL | 55.8 | 56.0 | 0.4 |
| | 10 mg/mL | 58.0 | 58.4 | 0.8 |
| | 5 mg/mL | 58.8 | 58.4 | -0.8 |
| Bilirubin | 0.66 mg/mL | 38.5 | 38.2 | -0.6 |
| | 0.2 mg/mL | 49.5 | 47.7 | -3.7 |
| Bilirubin | 0.66 mg/mL | 40.5 | 41.5 | 2.4 |
| | 0.2 mg/mL | 54.2 | 54.5 | 0.5 |

**Expected Value:**

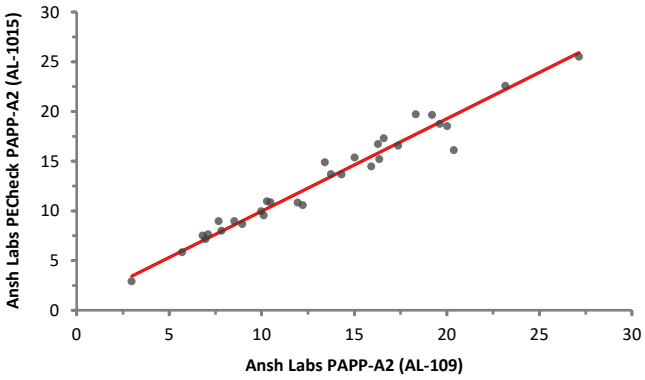
Pregnancy samples were analyzed using Ansh Labs PECheck™ PAPP-A2 ELISA. The expected ranges were calculated using 95% non-parametric estimation in the PECheck™ PAPP-A2 ELISA kit using Analyse-It® for Microsoft Excel and should be used as guidance only.

| Population | n | Median PAPP-A2 Conc. (ng/mL) | PAPP-A2 Range (ng/mL) |
|---|---|---|---|
| 11 – 12 Weeks | 46 | 7.9 | 2.6 – 18.1 |
| 12 – 13 Weeks | 41 | 9.0 | 4.3 – 18.0 |
| 13 – 14 Weeks | 41 | 10.6 | 3.8 – 22.9 |
| 2nd Trimester | 15 | 15.4 | 5.8 – 25.5 |
| 3rd Trimester | 11 | 17.1 | 4.3 – 74.4 |

**Method Comparison:**

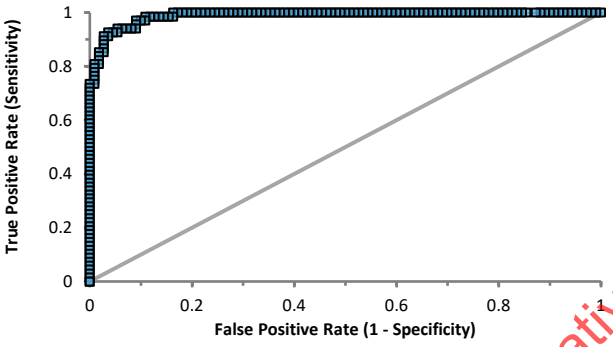
The PECheck™ PAPP-A2 ELISA (AL-1015) has been compared to Ansh Labs PAPP-A2 ELISA (AL-109) with 32 samples.

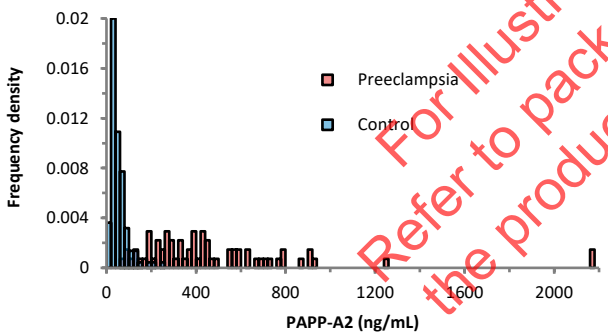
Passing Bablok analysis of the results yielded the following Regression: PECheck™ PAPP-A2 (AL-1015) = 0.6619 ng/mL + 0.9302 PAPP-A2 (AL-109), (R=0.981)




**Clinical Validation:**

A total of 177 (gestation age, 18-34 wks.) serum samples from 109 controls and 68 preeclampsia subjects were analyzed. The ROC analysis showed an area under the curve of 0.99 and the frequency distributions of the two groups with respect to PAPP-A2 concentrations are shown in the figures below.

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