Gain insights on preeclampsia management in pregnant women

PlGF and sFlt-1 biomarkers provide risk stratification of preeclampsia progressing into severe features

What is preeclampsia?

Preeclampsia is a severe complication related to hypertension affecting pregnant women. This life-threatening disease can only be cured by the delivery of the baby and contributes largely to maternal and neonatal mortality and morbidity.

Preeclampsia can start from week 20 and happens up to 6 weeks after delivery[9].

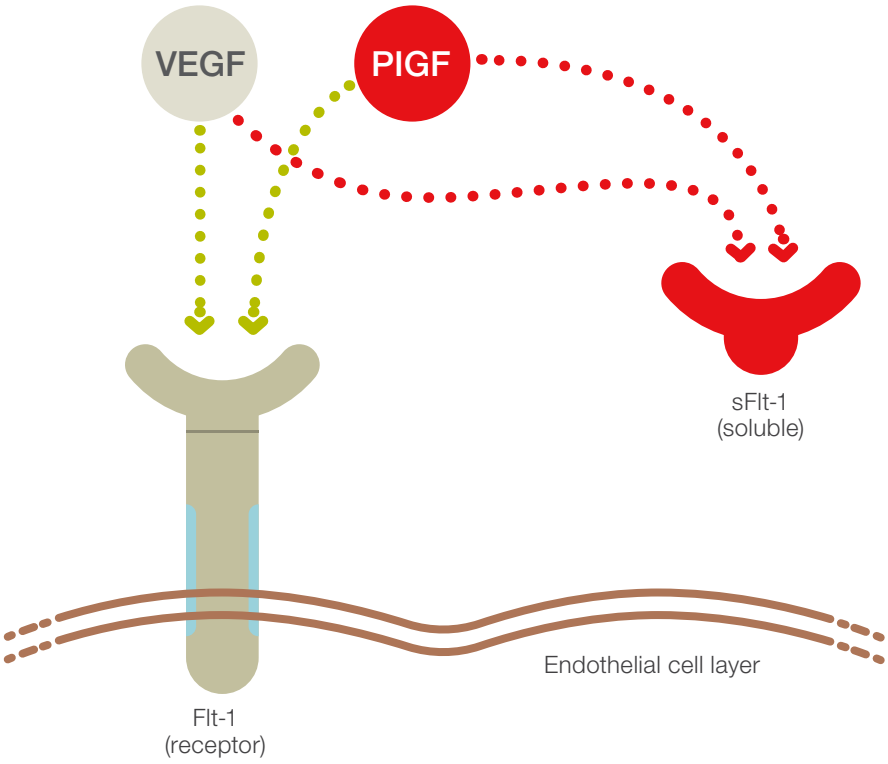
Key facts on preeclampsia in the U.S.

- Incidence of preeclampsia has nearly doubled from 2007 to 2019 with an acceleration since 2014[1]
- Close to 16% of the pregnant women in the U.S. are suffering from hypertensive disorders of pregnancy[2] with half of them developing preeclampsia[3]
- Preeclampsia is the cause of 17% of maternal deaths[4] and 15% of premature birth in the U.S.
- 37.2% of preeclampsia cases present severe features[5]
- Preeclampsia management accounts for 1/3 of all obstetrics costs reaching $2,18 billion, representing a major burden for the U.S. healthcare system[6].

The role of angiogenic factors in preeclampsia

Preeclampsia is a placental related disorder. The default of placentation is mainly responsible of the early onset form of preeclampsia. The syndrome eventually resolves once the placenta is removed. Although the cause of preeclampsia remains unclear, the syndrome may be initiated by an imbalance of placental factors that induce endothelial dysfunction. The antiangiogenic factor sFlt-1 (soluble fms-like tyrosine kinase) acts as potent antagonist of proangiogenic factors, such as Placental Growth Factor (PlGF), by adhering to the receptor-binding domains, preventing the interaction with endothelial receptors and thereby inducing endothelial dysfunction[7].

Angiogenic and anti-angiogenic factors



sFlt-1 is a truncated form of the Vascular Endothelial Growth Factors (VEGF) receptor Flt-1, circulating freely in the blood. sFlt-1 is produced in the placenta and secreted into the bloodstream, where it binds VEGF and PIGF with high affinity and therefore neutralizes their effects[7].

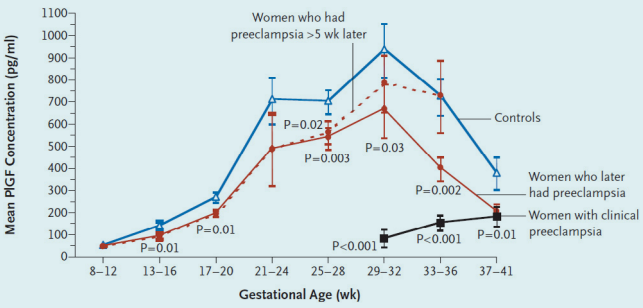
PIGF belongs to the VEGF family, promoting proliferation and survival of endothelial cells and inducing vascular permeability[7].

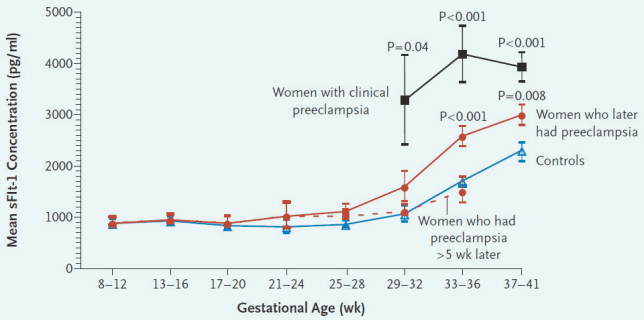
Signal transdution (healthy)
Signal transduction inhibited

sFlt-1 acts as potent antagonist of **PIGF** and **VEGF** by adhering to the receptor-binding domains, thus preventing interacting with endothelial receptors and inducing endothelial dysfunction.

VEGF = Vascular Endothelial Growth factor
PIGF = Placental Growth Factor
(s)Flt-1 = (soluble) fms like tyrosine kinase

Measuring PlGF and sFlt-1 in pregnancy





During the first and second trimesters of pregnancy, PlGF levels increase progressively and decrease towards term. In contrast, sFlt-1 levels are stable until weeks 20-24, before they rise steadily until delivery[13]. While PlGF curves for healthy and preeclamptic pregnancies start to separate already at first trimester, sFlt-1 curves only start separating after 20 weeks of gestation. In women with clinical preeclampsia, sFlt-1 levels are significantly increased while concentrations of circulating free PlGF are significantly decreased[7].

PRAECIS study: A large U.S. multicenter study to stratify pregnant women with PE with severe features

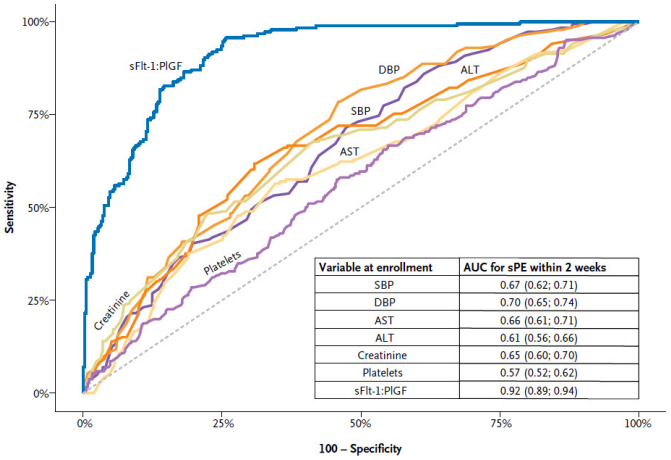
Goal of the PRAECIS study[8]

PRAECIS (Preeclampsia Risk Assessment: Evaluation of Cut-offs to Improve Stratification) study was intended to identify and validate a sFlt-1/PlGF ratio to stratify the short-term risk of developing preeclampsia with severe features (sPE) in women with hypertension hospitalized in late pregnancy.

Study Design

A multicenter, blinded, prospective study was conducted in 18 U.S. hospitals where the ratio of serum sFlt-1/PlGF was measured in pregnant women hospitalized between weeks 23+0 & 34+6/7 of gestation.

556 pregnant women were enrolled in the study.

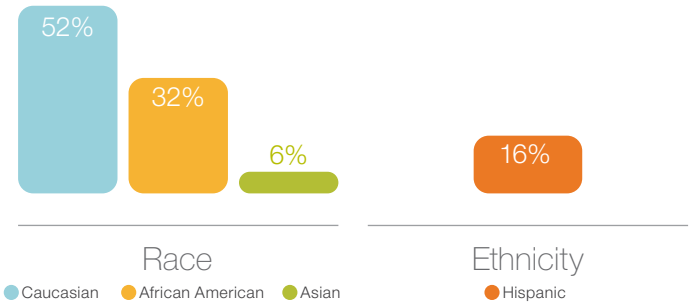


Variable at enrollment	AUC for sPE within 2 weeks
SBP	0.67 (0.62; 0.71)
DBP	0.70 (0.65; 0.74)
AST	0.66 (0.61; 0.71)
ALT	0.61 (0.56; 0.66)
Creatinine	0.65 (0.60; 0.70)
Platelets	0.57 (0.52; 0.62)
sFlt-1:PlGF	0.92 (0.89; 0.94)

https://doi.org/10.1056/EVIDoa2200161

Study population

Women were recruited from 18 U.S. tertiary care and community hospitals in urban and suburban settings to reflect the racial and ethnic heterogeneity of pregnant women in the United States.



Key results

- At a cut-off of 40, the clinical performance of the sFlt-1/PlGF ratio is:
  - 65% PPV (95% CI, 59 to 71)
  - 96% NPV (95% CI, 93 to 98)
  - 93.5% Sensitivity (95% CI, 89 to 96)
  - 75% Specificity (95% CI, 70 to 79).
- The ratio performed better than standard clinical measures (area under the ROC, 0.92 versus <0.75)
- Women with a ratio >=40 were at higher risk for adverse maternal outcomes (16.1% versus 2.8%; relative risk, 5.8; 95% CI, 2.8 to 12.2)

Conclusion

PRAECIS is the largest prospective U.S. study to date and included 30% Black and 16% Hispanic women. The PRAECIS study clearly demonstrated that in women with a hypertensive disorder of pregnancy presenting between 23 and 35 weeks of gestation, measurement of serum sFlt-1/PlGF provided stratification of the risk of progressing to sPE within the coming fortnight as well as a strong association with adverse outcomes.

Implications for the clinical practice

The measurement of serum sFlt-1/PlGF can be used to determine if patients require stepped up care or to follow expectant management per ACOG guidelines [9].

PlGF and sFlt-1 assays on KRYPTOR

B·R·A·H·M·S PlGF plus KRYPTOR
B·R·A·H·M·S sFlt-1 KRYPTOR

Intended use:

The Thermo Scientific™ B·R·A·H·M·S™ PlGF plus KRYPTOR™ is to be used inconjunction with the Thermo Scientific™ B·R·A·H·M·S™ sFlt-1 KRYPTOR™ along with other laboratory tests and clinical assessments to aid in the risk assessment of pregnant women (singleton pregnancies between gestational age 23+0 to 34+6/7 weeks) hospitalized for hypertensive disorders of pregnancy (preeclampsia, chronic hypertension with or without superimposed preeclampsia, or gestational hypertension) for progression to preeclampsia with severe features (as defined by The American College of Obstetricians and Gynecologists guidelines[9]) within 2 weeks of presentation.

Ease of handling [10,11]

	PlGF plus	sFlt-1
Sample volume	70 µL	8 µL
Sample type	Serum, plasma (K2 EDTA)	Serum, plasma (K2 EDTA)
Incubation time	29 min	9 min
Linear direct measuring range	7.6 –4,000 pg/mL	315 –90,000 pg/mL
Limit of Detection	4.9 pg/mL	28.5 pg/mL
Limit of Quantitation	7.6 pg/mL	29.4 pg/mL
Kit stability on board	29 days	29 days
Calibrator	1 point	2 points
Calibration stability	15 days	15 days

Test interpretation[12]

sFlt-1/PlGF < 40 (low risk) **40** sFlt-1/PlGF ≥ 40 (high risk)

If the result of the ratio is lower than 40, pregnant woman is at low risk for progression to preeclampsia with severe features within 2 weeks.

Follow standard of care including expectant management according to The American College of Obstetricians and Gynecologists guidelines[9].

If the result of the ratio is higher or equal to 40, pregnant woman is at high risk for progression to preeclampsia with severe features within 2 weeks.

Consider stepped up care and intensify surveillance before preeclampsia with severe features develop according to The American College of Obstetricians and Gynecologists guidelines.

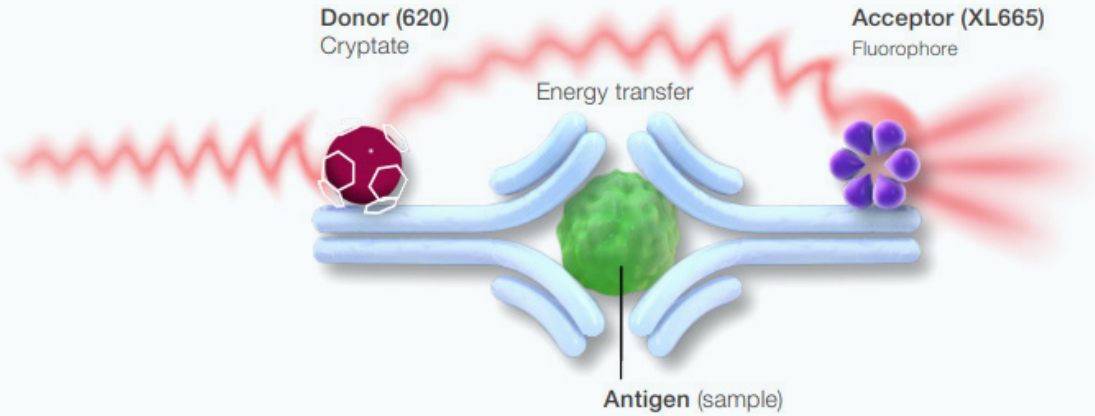
The heart of precision

Nobel Prize®-winning principle behind TRACE technology guarantees highly sensitive and specific test results

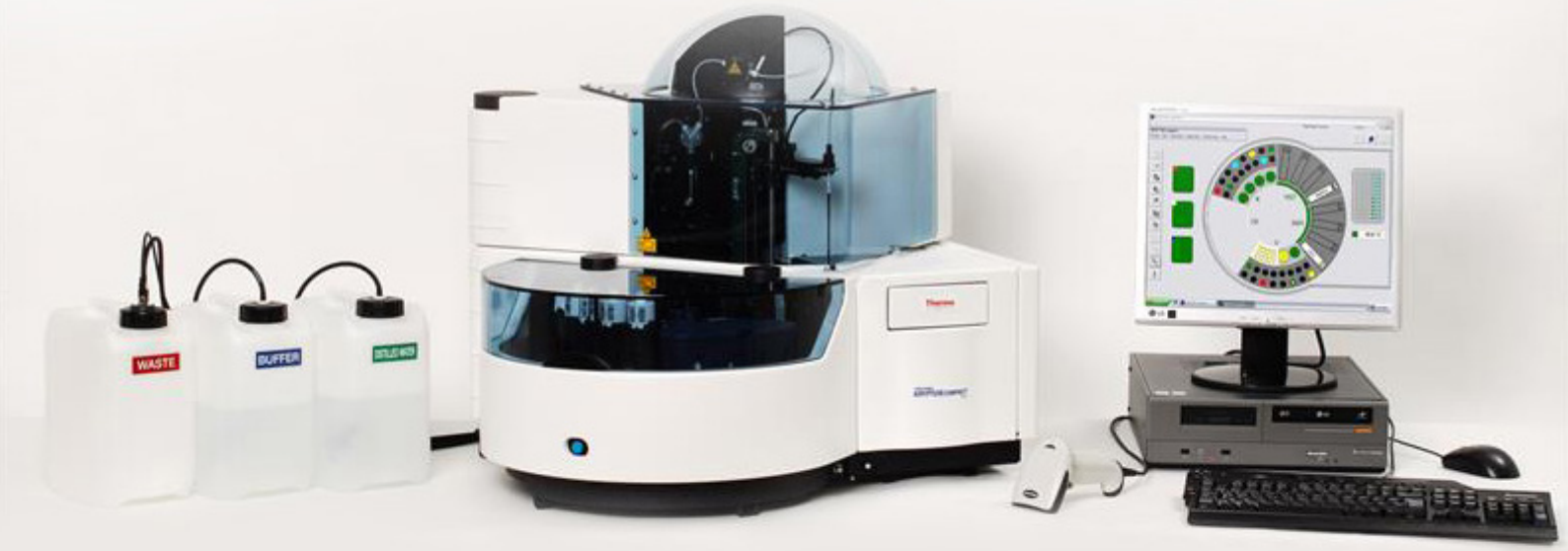
Homogeneous assay design ensures excellent analytical precision and high reproducibility by eliminating the need of washing and separation steps.
TRACE™ technology provides simultaneous measurement of signals of bound and unbound antibodies, which reduces effects of possible interferences. The unspecific signals are excluded by time resolved measurement.

TRACE: Time Resolved Amplified Cryptate Emission

The unique measurement principle underlying the precision and usability of the B·R·A·H·M·S KRYPTOR Analyzers



B·R·A·H·M·S KRYPTOR Analyzers



Exceptionally precise, fast and easy

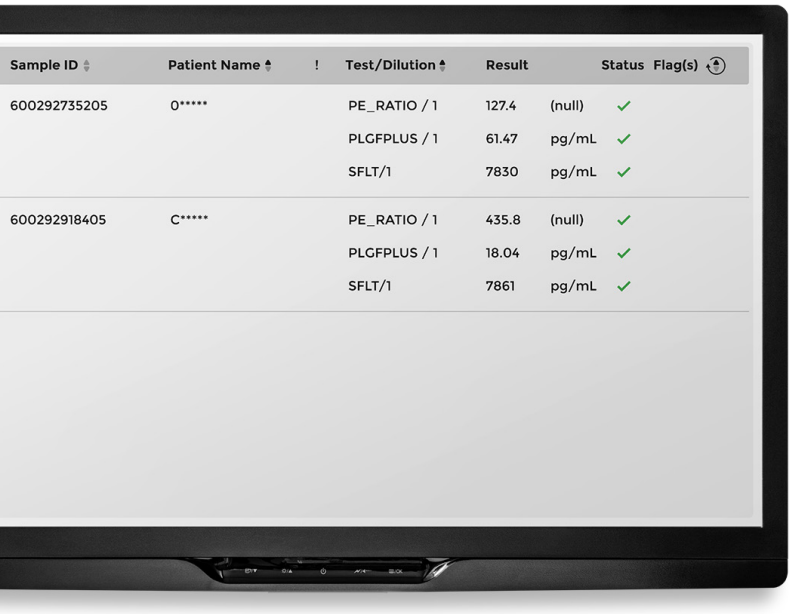
The Thermo Scientific™ B·R·A·H·M·S™ KRYPTOR™ compact PLUS automated random access immunoanalyzer is an user-friendly bench-top instrument that can easily be integrated into any laboratory.

- Easy and straightforward laboratory routine with less operator intervention
- Intelligent dilution and separate calibration significantly reduce the need of sample re-run
- Cost reduction due to efficient sample processing

Extraordinary performance

B·R·A·H·M·S KRYPTOR Analyzers for optimal laboratory routine

Save laboratory time with B·R·A·H·M·S KRYPTOR compact PLUS



Prepare the instrument

Daily maintenance: 5 min

Daily QC: 29 min

Separate calibration: every 2nd week

Run the samples

Flexibility: Random access and STAT sample capacity

Fast time to result

Up to 100 tests without intervention

sFlt-1/PlGF ratio can be provided within 30 minutes

Get your results

sFlt-1/PlGF ratio is calculated and displayed by the instrument

Send data to LIS

Stay confident in your results due to highest analytical precision and minimized interference

For a guided interpretation of the test result the laboratory report should include a link to the following training program for healthcare practitioners: **www.thermofisher.com/brahms-pe-training**.

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13. B·R·A·H·M·S KRYPTOR compact PLUS manual

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