COMPREHENSIVE PRE-ECLAMPSIA MANAGEMENT

PRE-ECLAMPSIA CARE
FOR ALL TRIMESTERS & DIFFERENT NEEDS

PerkinElmer®
For the Better

UNDERSTANDING PRE-ECLAMPSIA
CAUSE AND EFFECT

Pre-eclampsia is a complication of pregnancy marked by high blood pressure and protein in the urine. Left untreated, pre-eclampsia can lead to eclampsia, a serious condition that can, in some cases, lead to death. Pre-eclampsia also affects blood flow to the placenta, often leading to growth-restricted or prematurely born babies. Avoiding this condition would bring substantial improvements to maternal and fetal health. [23]

Early and preterm pre-eclampsia – poor placentation

While the direct cause of pre-eclampsia is unknown, researchers agree that if symptoms such as high blood pressure and proteinuria occur between 20 and 37 weeks, there is a high risk that the placenta will be adversely affected. [23] Early onset pre-eclampsia is also associated with preterm birth and fetal growth restriction, with prematurity accounting for most pre-eclampsia-related healthcare costs. If HELLP syndrome or eclampsia occur alongside pre-eclampsia, ICU care is inevitable. [23]

The good news is that aspirin treatment is highly effective in the prevention of early and preterm pre-eclampsia.[4, 5]

Term pre-eclampsia – maternal origin and cardiac dysfunction

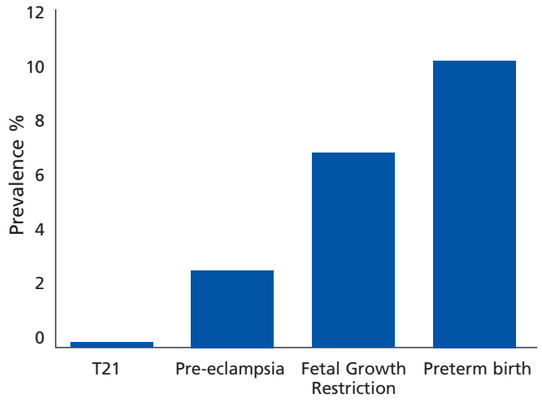
New evidence suggests that if pre-eclampsia develops after 37 weeks (term pre-eclampsia), the resulting condition is more closely related to cardiac and metabolic dysfunction in the mother than poor placentation per se.[6,7]

In fact, according to some researchers, term pre-eclampsia is a completely different pregnancy complication than early and pre-term pre-eclampsia. The alternative view is that pre-eclampsia is a spectrum disorder in which all women eventually develop the condition if the pregnancy is continued indefinitely.[8, 9]

Placental insufficiencies are much more common than Down syndrome. [28, 29, 30,31]

> **Pre-eclampsia is much more common than all aneuploidies combined** [28, 29, 30,31]

> **Both mother and baby are affected**



The global burden of pre-eclampsia [1]

Mothers at risk

>10 million

around the world develop pre-eclampsia annually.

At the same time

76,000

pregnant women die each year from pre-eclampsia and related hypertensive disorders globally.

This means about

19 women

develop pre-eclampsia every minute and more than one woman **every seven minutes** loses her life due to these relatively common and often preventable conditions.

Babies at risk

The impact of hypertension disorders on global infant mortality is enormous, with an estimated

500,000 babies dying from these pregnancy complications each year.

In fact, pre-eclampsia alone is responsible for up to 20% of the total

13 million

preterm births each year globally.

VERY EARLY PRE-ECLAMPSIA
- Delivery needed <32 weeks
- Prevalence 0.2%

EARLY ONSET PRE-ECLAMPSIA
- Delivery needed <34 weeks
- Prevalence 0.4%

PRETERM PRE-ECLAMPSIA
- Delivery needed <37 weeks
- Prevalence 0.7%

TERM PRE-ECLAMPSIA
- Delivery needed ≥37 weeks
- Prevalence 2%

COMPLETE
PRE-ECLAMPSIA CARE

THE NEXT STEP IN SCREENING AND TREATMENT FOR PRE-ECLAMPSIA

Today women expect doctors to offer effective prenatal care based on the latest research evidence and screening solutions. They want the best care possible throughout pregnancy.

When it comes to pre-eclampsia prevention, the growing consensus among caregivers and researchers is that timing matters more than ever. The earlier you identify women as having a high risk for pre-eclampsia, the better the outcome for mother and child.

What is the role of angiogenic factors?

PlGF and sFlt-1 are found to be key factors in the pathophysiology of pre-eclampsia. [33]

In pregnancies that develop pre-eclampsia, maternal serum placental growth factor (PlGF) levels decrease significantly, while soluble fms-like tyrosine kinase 1 (sFlt-1) levels increase several weeks prior to clinical symptom onset. Serum levels of PlGF and sFlt-1 are altered in women with pre-eclampsia compared to those with uncomplicated pregnancies. In pre-eclampsia, there is an imbalance between PlGF and sFlt-1. [33]

Thus, PlGF and sFlt-1 are important biomarkers used to identify high risk women that are likely to develop preterm pre-eclampsia later in their pregnancy and to predict the onset of pre-eclampsia. Biomarker levels are also found to be correlating with severity of disease. [33]

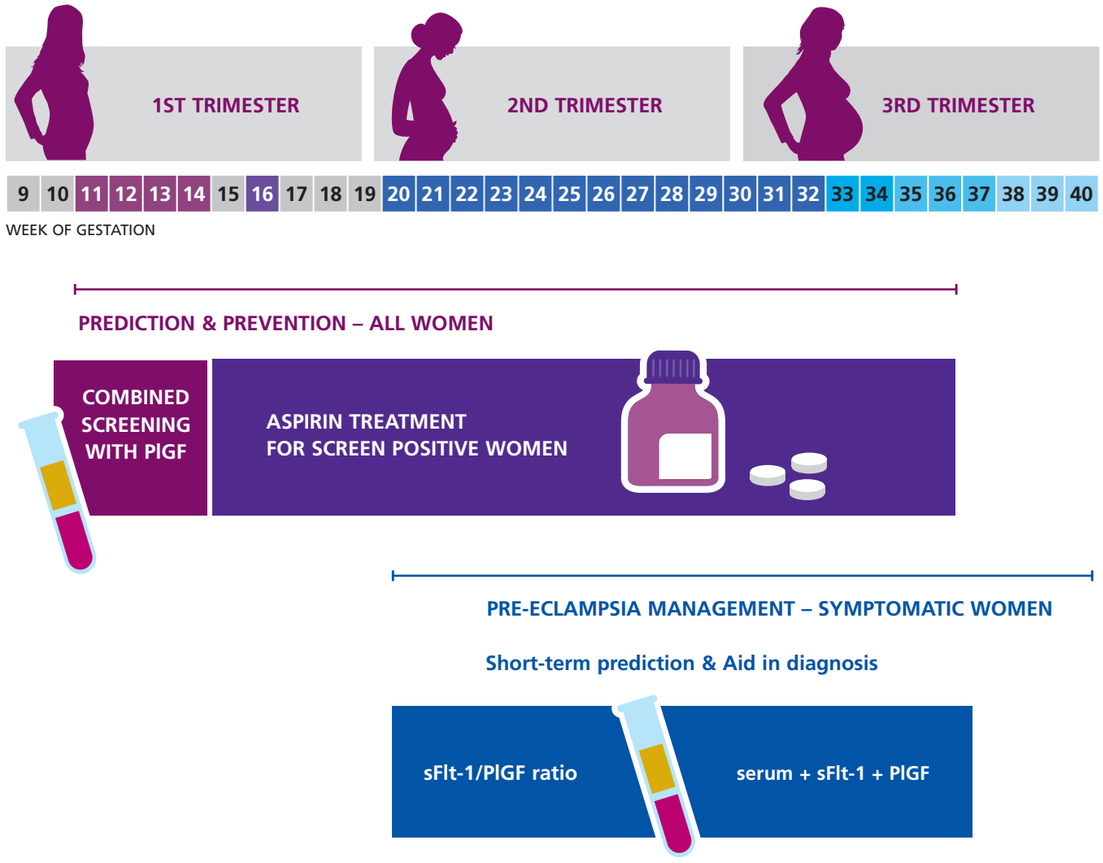
1T: screening and prevention of preterm pre-eclampsia

Traditional methods (Blood pressure and Proteinuria) have poor sensitivity and specificity to predict pre-eclampsia. Decreased PlGF levels predict future development of PE, especially early-onset and preterm pre-eclampsia, severe PE requiring delivery <34 gestational weeks and <37 gestational weeks, respectively. [13,27]

PlGF values are used together with other relevant clinical information (Maternal history, Mean Arterial blood pressure and uterine artery pulsatility index). The risk is calculated by using a software with a risk calculation algorithm (e.g. LifeCycle). During 1T sFlt-1 levels are not predictive for the onset of preterm pre- eclampsia. [32]

2T and 3T: Short term prediction and aid in diagnosis

During 2T and 3T sFlt-1 and PlGF are both predictive and diagnostic for pre-eclampsia. It has been shown that increased levels of sFlt-1 and decreased levels of PlGF in maternal serum can predict the subsequent onset of pre-eclampsia. Determining serum sFlt-1 and PlGF levels improves the clinical management and decision making (risk stratification) with women showing signs and symptoms of pre-eclampsia. [34]



COMBINED SCREENING PROTOCOL

FROM MATERNAL FACTORS TO EFFECTIVE 1T COMBINED SCREENING

The right combination

A combined screening program for pre-eclampsia is recommended by international guidelines.[22, 23] to identify women at high risk of pre-eclampsia in the early stages of pregnancy. The combined screening program consists of the PlGF 1-2-3™ blood test, maternal medical history assessment, mean arterial blood pressure measurement and, if available, uterine artery Doppler ultrasonography.

1st trimester – perfect timing

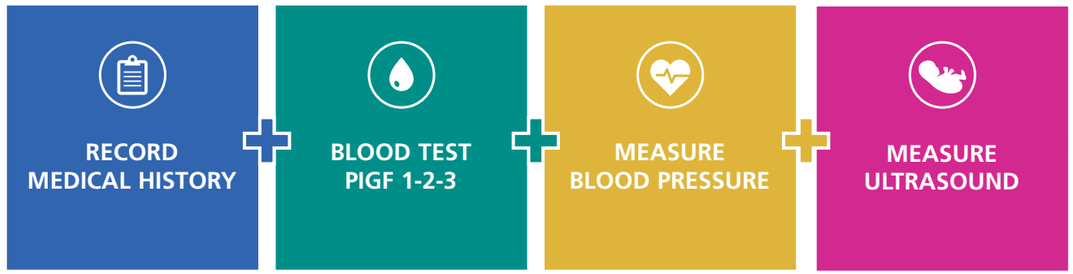
The timeframe for pre-eclampsia screening is the first trimester, when low-dose aspirin therapy shows the best results in the prevention of pre-eclampsia. To achieve maximum effectiveness, aspirin therapy should be started before 16 weeks of gestation among women at high risk of pre-eclampsia.[10]

Ideal solution - Four simple steps

The combined screening program is made up of four simple steps that require short training and minimal additional investment in equipment for screening programs.

1. Record medical history, weight and height.
2. Take blood sample for use with PlGF 1-2-3™ kit.
3. Measure blood pressure 2 times from both arms simultaneously.
4. If accessible, measure uterine artery Doppler pulsatility index.

Even if all four markers are not available, maternal history combined with additional markers is recommended. Highest detection rate can be achieved with all four markers. [23]



Medical history – a priori risk

The traditional method of screening for pre-eclampsia has been based on asking women a series of questions during their first pregnancy visit.[11,12] This method considers each risk factor as an independent and unrelated event. The more effective approach to defining maternal a priori risk uses an algorithm that determines the relative importance of each risk factor and their interrelationship.[13]

PlGF 1-2-3 blood test

The high-sensitivity PlGF 1-2-3™ assay can be performed as early as the first trimester, at 11–13^{+6} weeks. The blood sample is analysed using the same PerkinElmer instrument that is used for aneuploidy screening. No additional blood sample is required as the same sample can be used both to screen for pre-eclampsia and for aneuploidy screening. Women with an elevated risk of pre-eclampsia show a lower maternal serum level of placental growth factor (PlGF).

Mean arterial blood pressure – MAP

When mean arterial blood pressure (MAP) is used as a pre-eclampsia screening marker, it is important to use the standardised protocol for MAP measurement. The blood pressure (BP) should be measured two times from both arms simultaneously using two blood pressure monitors. The blood pressure should be recorded from both arms because of significant non-pathological inter-arm variations.[14]

Uterine artery Doppler pulsatility index (UTPI) ultrasound

The uterine artery Doppler pulsatility index (UTPI) can be measured between 11–13+6 weeks via a transvaginal or transabdominal ultrasound. Please refer to the Fetal Medicine Foundation's guidelines for the detailed protocol and certificates of competence.[15]

How to measure MAP

- Arms supported at the level of the heart
- Right cuff size: S, M, L
- Take 2 measurements in both arms
- Both feet on the floor

Approved blood pressure monitors for pre-eclampsia screening

Manufacturer	Model
Microlife®	WatchBP Home
Microlife®	BP A200
Microlife®	3AS1-2
Microlife®	CRADLE VSA
Omron®	MIT-Elite

Monitors that are not listed here can also be used if they have been validated for pre-eclampsia, or declared identical with a validated model.

PRE-ECLAMPSIA RISK CALCULATION WITH LIFECYCLE™ SOFTWARE

PREVENTING PRE-ECLAMPSIA

EASY CALCULATION OF RISK FROM COMBINED SCREENING MARKERS

Specialised software generates a unique patient risk profile and report based on combination of risk factors. Depending on access and availability, other marker combinations can also be used to screen for pre-eclampsia.

What do the results mean?

Low risk

Low risk means that there is minimal risk of developing pre-eclampsia later in pregnancy. While it is possible to develop pre-eclampsia regardless of low risk status, the pregnancy can continue as normal and the mother can rest assured that there is little or no reason for concern.

High risk

If the risk of developing pre-eclampsia later in pregnancy is high, the doctor may start treatment at the optimum time and monitor the pregnancy more closely. While not all women in the high-risk group develop pre-eclampsia, doctors can now consider whether preventive treatment is appropriate.

Combined pre-eclampsia screening – the first step to better detection

When it comes to effectively predicting pre-eclampsia, the combined screening program outperforms screening methods that rely only on maternal history. The effectiveness of pre-eclampsia screening also depends on marker combination.[13]

Parameters	Very Early PE	Preterm PE
Medical history with:	Detection rate	Detection rate
PlGF + PAPP-A	88 %	66 %
PlGF + MAP	88 %	69 %
PlGF + MAP + UTPI	100 %	75 %
PlGF + PAPP-A + MAP + UTPI	100 %	80 %

Medical history and blood test can help to identify 88% of very early pre-eclampsia cases and 66% of preterm pre-eclampsia cases. Similar detection rates can be achieved with medical history, PlGF 1-2-3™ and MAP. If UTPI is available, the detection rate is close to 100% for very early PE and between 75%–80% for preterm PE.[13] These are examples and other combinations are possible. FPR (False Positive Rate) = 10% in this example.

Flexible screening
- Multiple screening strategies are supported
- Software is able to combine demographics and biomarker data to produce risk with FMF algorithm

Tailored to population
- Optimize risk calculation to your population
- Ability to level or change MoM equations

Configurable
- High level of configurability and connectivity options

Who should be screened for pre-eclampsia?

All pregnant women should be assessed early on in their pregnancy to prevent the development of pre-eclampsia. [23] They should also have access to screening even if there are no maternal risk factors or history of pre-eclampsia. The benefit of detecting and treating pre-eclampsia early in the pregnancy always outweighs the conventional wait-and-see approach to pre-eclampsia management.[23]

Why should women be screened for pre-eclampsia?

While pre-eclampsia screening is critical to protecting the health of mother and child, many women are unaware of pre-eclampsia and that pre-eclampsia can affect any pregnancy. Some pregnancies are more at risk of developing pre-eclampsia than others. Combined pre-eclampsia screening with the PlGF 1-2-3™ assay is an effective way to assess this risk of this preventable condition.

Pre-eclampsia affects both the mother and the child also later in life. In fact, women with a history of pre-eclampsia have a three to four times greater risk of developing chronic hypertension than mothers with no history of pre-eclampsia and double the risk of ischemic heart disease, venous thromboembolism and stroke.[16] Pre-eclampsia can cause prematurity, which in turn subjects babies to additional risks, as well as cardiovascular diseases and diabetes later in life. [25, 26, 27]

While aspirin treatment is not a cure for pre-eclampsia, fewer women need to suffer from this serious disease if low-dose aspirin is administered early in the pregnancy.[5]

Low-dose aspirin in the prevention of pre-eclampsia

Aspirin

82% drop in the rate of early pre-eclampsia

62% drop in the rate of preterm pre-eclampsia

Dose	150 mg	A dose response effect of aspirin is demonstrated. A high proportion (1/3) of the population is non-responsive to aspirin at lower doses.[18,19]
Start	12 weeks	Aspirin is effective if given to high risk women before 16 weeks of gestation.[4,10]
Finish	36 weeks	Avoid potential hemorrhage for neonate.[20]
Time	Bed time	Lower incidence of PE when taken at bedtime compared to morning or afternoon.[21]

Aspirin treatment according to ASPRE study design[5]

PerkinElmer does not endorse or make recommendations with respect to research, medication, or treatments. All information presented is for informational purposes only and is not intended as medical advice. For country-specific recommendations please consult your local health care professional.

2ND & 3RD TRIMESTER

SHORT TERM PREDICTION & AID IN DIAGNOSIS

sFlt-1/PlGF ratio - Short term prediction and aid in diagnosis

During 2T and 3T sFlt-1 and PlGF are both predictive and diagnostic for PE. It has been shown that increased levels of sFlt-1 and decreased levels of PlGF in maternal serum can predict the subsequent onset of pre-eclampsia. [33, 34]

Determining serum sFlt-1 and PlGF levels, used as a ratio, improves the clinical management and decision making (risk stratification) with women showing signs and symptoms of pre-eclampsia. [33, 34]

When should I determine the sFlt-1/PlGF ratio?

- Testing is applicable to women with signs and symptoms of pre-eclampsia after week 20 of gestation
- To confirm clinical suspection of pre-eclampsia with symptomatic women and/or to confirm unclear diagnosis of pre-eclampsia
- To monitor women that are at high risk for pre-eclampsia

What is the sFlt-1/PlGF ratio used for?

Confirming or excluding diagnosis of pre-eclampsia:

- Measuring maternal serum concentrations of sFlt-1 and PlGF can differentiate healthy women from women with pre-eclampsia. Changes in sFlt-1 and PlGF levels reflect the severity of the disease. [33, 34]
- To avoid unnecessary hospitalization
- For improved diagnosis and prognosis

Decisions regarding delivery are not based solely on the sFlt-1/PlGF ratio, but are always made in context of other clinical signs and symptoms

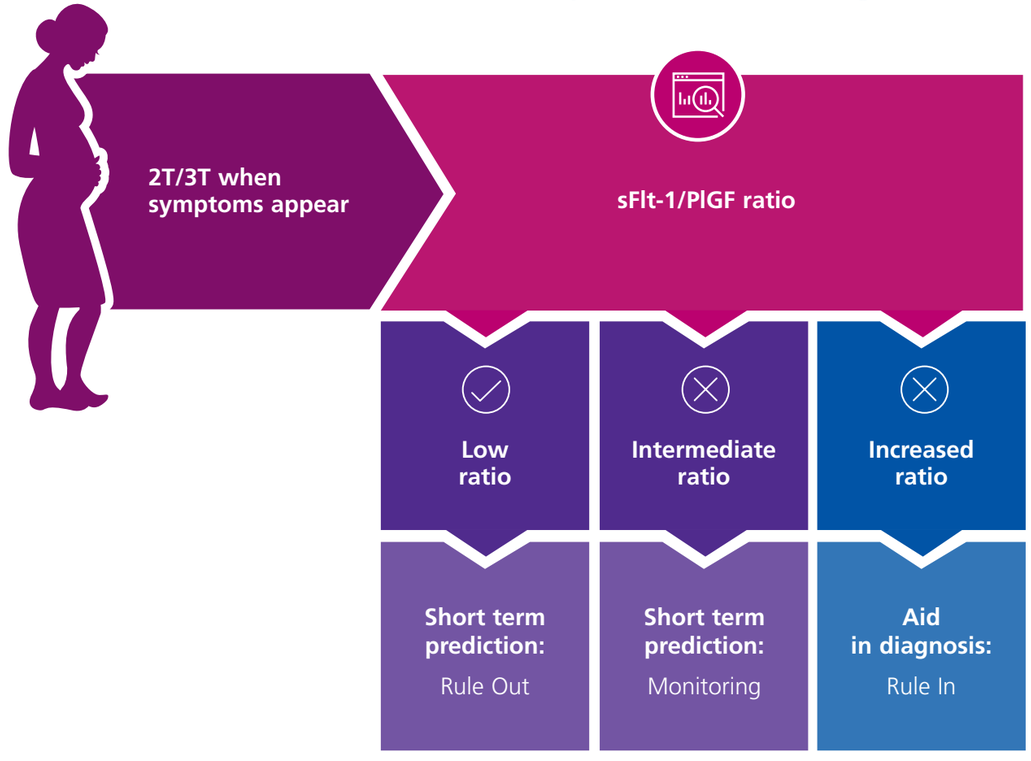
sFlt-1/PlGF Ratio calculation with LifeCycle™ software*

With LifeCycle™ software you can follow up the patient from 1T pre-eclampsia risk assessment to 2T/3T pre-eclampsia management. sFlt-1 and PlGF concentrations are transferred automatically from the DELFIA® Xpress platform to the LifeCycle™ software, so there is no need for manual typing.

LifeCycle™ software enables monitoring pre-eclampsia status with the sFlt-1/PlGF ratio and the ratio results can be linked to the same patients' other results in LifeCycle™software. For ratio calculations the cut-offs for PE management are adjustable.

PRE-ECLAMPSIA MANAGEMENT

FOR LABORATORY: Short term prediction and aid in diagnosis



COMPREHENSIVE OFFERING COVERING ALL TRIMESTERS

PlGF 1-2-3™ kit for different platforms

PerkinElmer's high-sensitivity PlGF 1-2-3™ kit is the only assay that can offer the level of accuracy and precision that was required by the ground-breaking ASPRE trial.

The kit is used as an aid in screening pregnant women for pre-eclampsia in all pregnancy trimesters. The kit is available in two package sizes for three different platforms to accommi-date different throughput needs.

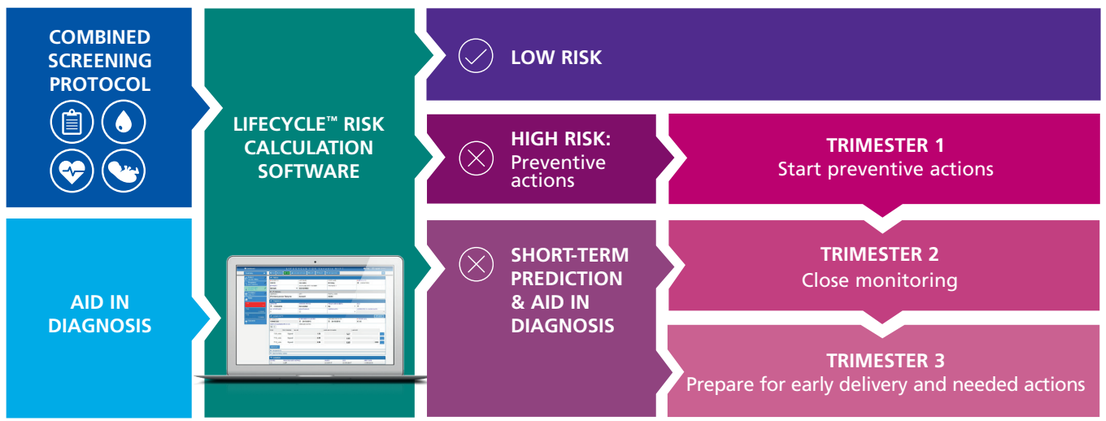
DELFIA® Xpress sFlt-1 kit

This kit is intended for the quantitative determination of soluble Fms-like tyrosine kinase-1 (sFlt-1) in maternal serum using the 6000 DELFIA® Xpress random access immunoanalyzer. The ratio of sFlt-1/PlGF may be used as an aid in diagnosis of pre-eclampsia and for short term prediction of suspected pre-eclampsia together with other biochemical and clinical information. The kit is available in two package sizes.

Native Serum Controls

Lyophilized human serum controls are intended for use as an assayed quality control serum to monitor precision of laboratory measurement procedures for the DELFIA® assays.

Two levels of controls are sold as separate products for both PlGF and SFlt-1 assays to allow performance monitoring within the clinical range.



PRE-ECLAMPSIA OFFERING

Sample collection	Analysis and measurement			Reagents	Result and interpretation
Laboratory	Instrumentation for different laboratory needs			1st trimester assays	Software
Serum samples	**Small** Victor2D • PlGF 1-2-3™	**Medium** DELFIA® Xpress • PlGF 1-2-3™ • sFlt-1	**High** AutoDELFIA® • PlGF 1-2-3™	• PlGF controls **2nd/3rd trimester assays** • PlGF & sFlt-1 controls	• LifeCycle™ • Statistical Services™ • Astraia® link, ViewPoint® link

For more infomation about our prenatal screening offering including aneuplody screening with biochemical markers and NIPT, please visit

www.prenataltesting.perkinelmer.com

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PerkinElmer is committed to advancing maternal-fetal health

With more than 10 million prenatal screens performed annually on our solutions, PerkinElmer is the globally recognized leader in maternal fetal health. Our complete screening and diagnostic solutions, combining clinically proven assays, equipment and informatics, are devoted to supporting the needs of all women worldwide. PerkinElmer is committed to leveraging this knowledge to advance the science of maternal fetal health and expand the capabilities of laboratory specialists and clinicians now, and in the future.

PERKINELMER – YOUR COMPLETE SCREENING SOLUTION PROVIDER

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