FIRST TRIMESTER PREDICTION OF PRE-ECLAMPSIA
Earlier identification of women at high risk for pre-eclampsia

**Prediction before symptoms appear**

DELFIA® Xpress PlGF is the first placental growth factor (PlGF) assay designed for use as an aid in screening pregnant women for pre-eclampsia in the first trimester. Pregnancies destined to develop pre-eclampsia are typically associated with reduced levels of PlGF in maternal serum samples. Since this reduction is already visible in the first trimester, PlGF assay helps to identify women at high risk for pre-eclampsia at an early stage of pregnancy.

**Early screening makes prediction of early-onset pre-eclampsia possible**

Early-onset pre-eclampsia means that the delivery of the baby is needed before 34 weeks of pregnancy because the disorder is having an adverse effect on the mother’s or the baby’s condition. Although less common than the late form of the disorder, early-onset pre-eclampsia contributes most to the mortality and morbidity statistics. PlGF is predictive of both early and late pre-eclampsia, but is most sensitive and specific as a marker of the early-onset form.

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**What is PlGF?**

Protein produced by the placenta*

Growth factor active in angiogenesis and endothelial cell growth

Reduced maternal serum concentration of PlGF has been shown in a high proportion of pregnancies destined to develop pre-eclampsia.

*Also detected in heart, lung, muscle and adipose tissue.
Although there is no proven effective method for the prevention of pre-eclampsia, identification of affected pregnancies in the first trimester opens up a time window that is potentially very valuable and can ultimately lead to improved pregnancy outcome. Identification at the end of the first trimester allows:

- Increased surveillance of high risk pregnancies
- Earlier diagnosis of the clinical signs of the disease
- Earlier identification of the associated intrauterine growth restriction (IUGR)
- Wider ranging intervention possibilities

Aspirin treatment before 16 weeks effective in preventing pre-eclampsia

Treatment with low doses of aspirin (acetylsalicylic acid, ASA) during pregnancy has been shown to reduce the risk of pre-eclampsia. As a therapy, low dose aspirin has a number of attractions, among them the low cost and free availability of the drug throughout the world. By identifying pregnant women at risk for pre-eclampsia and starting them on low-dose aspirin before 16 weeks of gestation physicians can more than halve the risk of pre-eclampsia, preterm birth and intrauterine growth retardation (IUGR).
A complete package for pre-eclampsia prediction

**Pre-eclampsia screening at 11 to 13+6 weeks is now a practical proposition**

PerkinElmer is the first company to provide a complete, practical solution for pre-eclampsia prediction.

PerkinElmer leads the way in biochemistry assays and instrumentation, providing essential items such as native controls to assure the integrity of results before they are used in risk calculation.

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**DELFIA XPRESS INSTRUMENT**

Both aneuploidy screening and pre-eclampsia screening with the same instrument

**PLGF ASSAY KIT**

The only validated 1st trimester assay for prediction of pre-eclampsia

**PLGF CONTROLS**

The only native pregnancy serum IVD PLGF controls

**RISK CALCULATION SERVICE**

Professor H. Cuckle’s web based risk calculation service on https://www.screeninfo.co.uk/
DELFIA® Xpress has been developed to streamline workflows in laboratories and clinics providing prenatal screening services. The instrument is already in use for aneuploidy screening in more than 40 countries.

DELFIA Xpress is a compact table-top instrument offering a range of benefits critical for operational efficiency.

- The speed and convenience of random access
- The security associated with barcoded reagents and samples to ensure positive identification
- The reassurance from using reliable, proven DELFIA chemistry

DELFIA Xpress reagents for Maternal Health screening

- PIGF
- PAPP-A
- Free hCGβ
- hAFP
- uE3
- hCG

The PAPP-A and Free hCGβ assays and the DELFIA Xpress instrument are approved by the FMF for first trimester aneuploidy screening.

Confirmed stability of PIGF

Sample PIGF remains within 5% of the initial level for the following periods.

<table>
<thead>
<tr>
<th>Storage at</th>
<th>PIGF in serum (tested over 30 days)</th>
<th>PIGF in whole blood (tested over 3 days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>+30°C</td>
<td>up to 1 day</td>
<td>up to 21 hours</td>
</tr>
<tr>
<td>Room temperature</td>
<td>up to 2 days</td>
<td>up to 1 day</td>
</tr>
<tr>
<td>+4°C</td>
<td>at least 30 days</td>
<td>at least 3 days</td>
</tr>
</tbody>
</table>

Human pregnancy serum PIGF Controls

The CE marked PIGF Controls product is now available for IVD use. PerkinElmer has worked from first principles with the aim of creating the best possible product because excellence in the QC materials used is critical to ensuring the integrity of results. Whenever controls are run, the objective should be to compare like with like. In the PIGF Controls product human pregnancy serum is used, hence the controls behave exactly like the unknown samples to provide your best guarantee of reliable results.

Controls at optimal levels

The product includes two PIGF controls at optimally chosen levels for use in monitoring precision of laboratory measurement procedures for DELFIA® PIGF assays

- PIGF CL 5 vials, lyophilized
- PIGF CH 5 vials, lyophilized

The package includes controls for one month’s use if the controls are run twice per working day (=20 days). The volume in each vial after reconstitution is 1.5 mL.
The traditional method of screening for pre-eclampsia is maternal history, for example, as recommended in the U.K.’s National Institute for Clinical Excellence (NICE) guidelines. However, screening as suggested by NICE would result in false positive rates of more than 64% in order to achieve a detection rate of around 90% for early pre-eclampsia. This result is compatible with the detection rate of less than 40% at a 5% false positive level suggested in earlier works. A recent update on these guidelines suggests categorizing women into those with moderate or with high risk factors. This approach would lower the false positive rate to some extent.

Best detection rates for early-onset pre-eclampsia are achieved by combining PlGF with other markers

Far better performance in early-onset pre-eclampsia detection is attainable by combining maternal history with other serum and ultrasound marker results. According to recent studies, appropriate choice of markers can yield detection rates of 78% or higher for a false positive rate of 5%. The utility of maternal serum PlGF measurement in pre-eclampsia prediction has been confirmed in many studies, and it has been shown to be a more discriminating marker than PAPP-A. However, a number of studies confirm the benefit of including both of these serum markers.

<table>
<thead>
<tr>
<th>DR% at 5% FPR</th>
<th>History</th>
<th>MAP</th>
<th>uA-PI</th>
<th>PAPP-A</th>
<th>PlGF</th>
<th>Reference</th>
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<tbody>
<tr>
<td>33</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Yu [ref 11] Akolekar [ref 2]</td>
</tr>
<tr>
<td>38</td>
<td></td>
<td>x</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>47</td>
<td>x</td>
<td></td>
<td></td>
<td>x</td>
<td></td>
<td>Akolekar [ref 2]</td>
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<tr>
<td>54</td>
<td>x</td>
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<td>x</td>
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<tr>
<td>60</td>
<td>x</td>
<td>x</td>
<td></td>
<td>x</td>
<td></td>
<td>Foidart [ref 4]</td>
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<td>78</td>
<td>x</td>
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<td>78</td>
<td>x</td>
<td>x</td>
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<td>x</td>
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<td>84</td>
<td>x</td>
<td>x</td>
<td></td>
<td>x</td>
<td></td>
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<td>x</td>
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<td>x</td>
<td>x</td>
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<td>x</td>
<td>x</td>
<td></td>
<td>x</td>
<td>x</td>
<td>Poon [ref 7]</td>
</tr>
</tbody>
</table>

Detection rates for early-onset pre-eclampsia as estimated for various combinations of markers.

History = body mass index, family history of PE, previous PE, ethnicity, smoking
MAP = mean arterial blood pressure
uA-PI = uterine artery pulsatility index
Pre-eclampsia prediction using risk calculation engine

Using the web based pre-eclampsia risk calculation service offered by Prof Howard Cuckle, you can transform your DELFIA Xpress PIGF results into risk figures for both early-onset and late-onset pre-eclampsia. Besides PIGF, crown-rump length (for establishing gestational age) is the only mandatory input, but you can refine your risk estimates by inputting any other marker information that is available, for example, PAPP-A, MAP and/or uaDoppler.

The application generates both the prior risk and the risk based on all markers for both early-onset (<34 weeks) and late-onset (≥34 weeks) pre-eclampsia.

An example of a result screen generated by Howard Cuckle's pre-eclampsia risk calculation

<table>
<thead>
<tr>
<th>Prior Risk Factors only:</th>
<th>1 in 51</th>
<th>1 in 28</th>
</tr>
</thead>
<tbody>
<tr>
<td>After Blood Pressure, Doppler &amp; Blood Test:</td>
<td>1 in 143</td>
<td>1 in 39</td>
</tr>
<tr>
<td>Cut-off:</td>
<td>1 in 10</td>
<td>1 in 50</td>
</tr>
<tr>
<td>Interpretation:</td>
<td>Screen Negative</td>
<td>Screen Positive</td>
</tr>
</tbody>
</table>

For more information on his Screen Info service please contact Prof Cuckle on hscuckle@screeninfo.co.uk.
REFERENCES

1 Akolekar et al. (2008)  
Maternal serum placental growth factor at 11+0 to 13+6 weeks of gestation in the prediction of pre-eclampsia.  
*Ultrasound Obstet Gynecol 32:732-9*

2 Akolekar et al. (2011)  
Prediction of early, intermediate and late pre-eclampsia from maternal factors, biophysical and biochemical markers at 11–13 weeks.  
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3 Bujold et al. (2010)  
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*Obstet Gynecol. 116:402-14*

4 Foidart et al. (2010)  
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*Ultrasound Obstet Gynecol. 35: 680-7.*

5 Levine and Lindheimer (2009)  
First trimester prediction of early pre-eclampsia: a possibility at last!  
*Hypertension 53:747-748*

6 Poon et al. (2009)  
First-trimester maternal serum pregnancy-associated plasma protein-A and pre-eclampsia.  
*Ultrasound Obstet Gynecol 33:23-33.*

7 Poon et al. (2009)  
First-trimester prediction of hypertensive disorders in pregnancy.  
*Hypertension 53:812-8*

8 Poon et al. (2010)  
*J Hum Hypertens 24:104-10.*

9 Poon et al. (2010)  
Hypertensive disorders in pregnancy: screening by biophysical and biochemical markers at 11-13 weeks.  
*Ultrasound Obstet Gynecol 35:662-70.*

10 Poon et al. (2010)  
Hypertensive disorders in pregnancy: combined screening by uterine artery Doppler, blood pressure and serum PAPP-A at 11-13 weeks.  
*Prenat Diagn 30:216-223.*

11 Yu et al. (2005)  
An integrated model for the prediction of preeclampsia using maternal factors and uterine artery Doppler velocimetry in unselected low-risk women.  

ORDERING INFORMATION

<table>
<thead>
<tr>
<th>6007-0010/6007-001C</th>
<th>DELFIA Xpress PlGF kit</th>
</tr>
</thead>
<tbody>
<tr>
<td>B055-101</td>
<td>AutoDELFIA/DELFIA PlGF*</td>
</tr>
<tr>
<td>3090-0010</td>
<td>PI GF Controls</td>
</tr>
<tr>
<td>6000-0010</td>
<td>DELFIA Xpress instrument</td>
</tr>
</tbody>
</table>

* CE-marked during 2011

All products mentioned may not be available in every country.  
Please check the availability with your local representative.