



# Pre-eclampsia screening in 1<sup>st</sup> trimester of pregnancy

Early screening for pre-eclampsia with PIGF and PAPP-A  
for timely intervention and optimal patient care

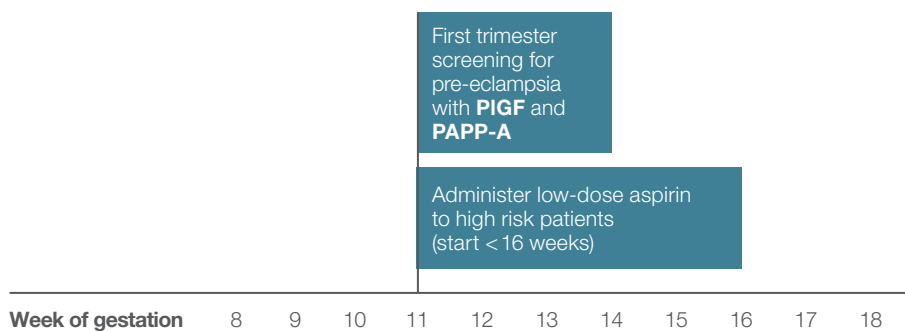
# Early screening – early intervention

## Pre-eclampsia screening in 1<sup>st</sup> trimester for improved patient care

### Serum PIGF determination in combination with other factors allows early risk assessment for pre-eclampsia

Pre-eclampsia is a leading cause of maternal morbidity and mortality.<sup>1</sup> A combined first trimester screening approach including measurement of PIGF (Placental Growth Factor) and PAPP-A (Pregnancy-Associated Plasma Protein A) can identify women at high risk for pre-term pre-eclampsia. Early identification of women at high risk allows for intensified maternal and fetal monitoring and timely intervention with low-dose aspirin to significantly reduce the prevalence for pre-eclampsia.

The high sensitivity assays Thermo Scientific™ B·R·A·H·M·S™ PIGF plus KRYPTOR™ and B·R·A·H·M·S PAPP-A KRYPTOR can reliably detect PIGF and PAPP-A in maternal serum already at weeks 11–13+6 of gestation to support a high quality first trimester pre-eclampsia screening.



### First trimester screening for pre-eclampsia

A combination of

- maternal characteristics
- uterine artery pulsatility index (UtA-PI)
- mean arterial pressure (MAP) and
- maternal serum PAPP-A and PIGF

at 11–13+6 weeks' gestation can identify a high proportion of pregnancies at high-risk for pre-term pre-eclampsia.<sup>2</sup>

## Low-dose aspirin can reduce the risk for pre-eclampsia

A meta-analysis showed that the use of low-dose aspirin (<150 mg/day) can reduce the incidence of pre-term pre-eclampsia by about 50% if started before 16 weeks of gestation in high risk women.<sup>3,4</sup>

These findings have been confirmed by a multi-centre randomized controlled trial. In the ASPRE trial > 25 000 women were screened between weeks 11 and 13–6 according FMF. Women identified at high risk either received placebo or 150 mg aspirin and outcomes of both arms were compared.<sup>5</sup>

**Pre-eclampsia < 34 weeks** occurred in 1.8% of patients in the placebo group vs. 0.4% in the aspirin group

→ **82%** reduction of early-onset pre-eclampsia

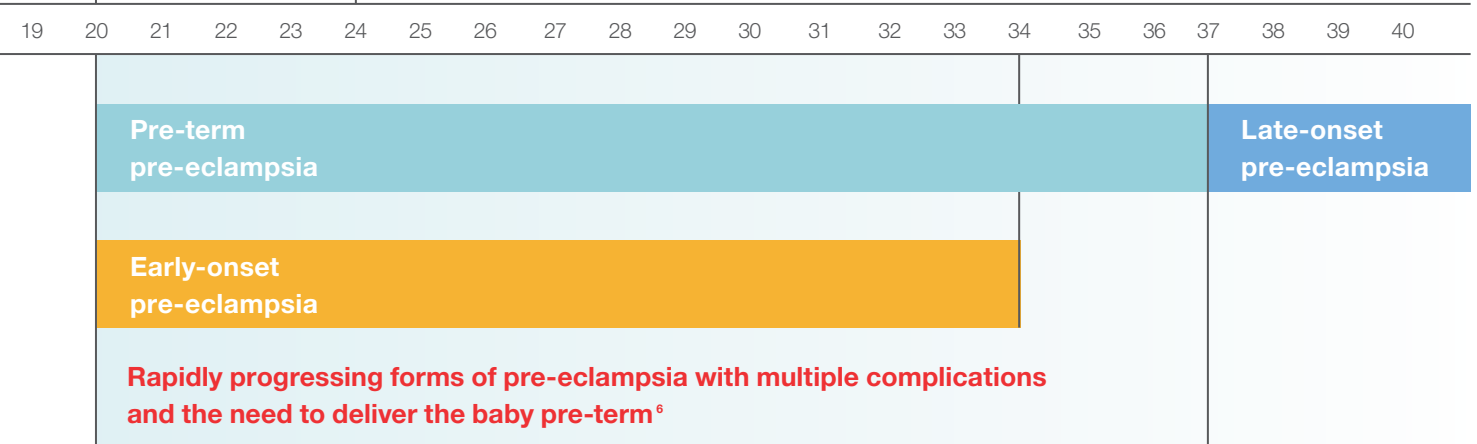
**Pre-eclampsia < 37 weeks** occurred in 4.3% of patients in the placebo group vs. 1.6% in the aspirin group

→ **62%** reduction of pre-term pre-eclampsia

### First onset of clinical symptoms of pre-eclampsia (hypertension, proteinuria)

Confirm or exclude diagnosis of pre-eclampsia with sFlt-1/PIGF ratio

Prognosis of adverse outcome using sFlt-1/PIGF ratio



**Figure 1** First clinical symptoms of pre-eclampsia are observed > 20 weeks of gestation. The gestational age at onset correlates with the severity of maternal and fetal consequences.<sup>7</sup>

# Pre-eclampsia: a leading cause of maternal morbidity and mortality

## Severe complications for the mother

With an incidence between 2–8%, pre-eclampsia is a frequent pregnancy disorder<sup>8</sup> affecting more than 4.1 million women per year worldwide.<sup>1</sup>

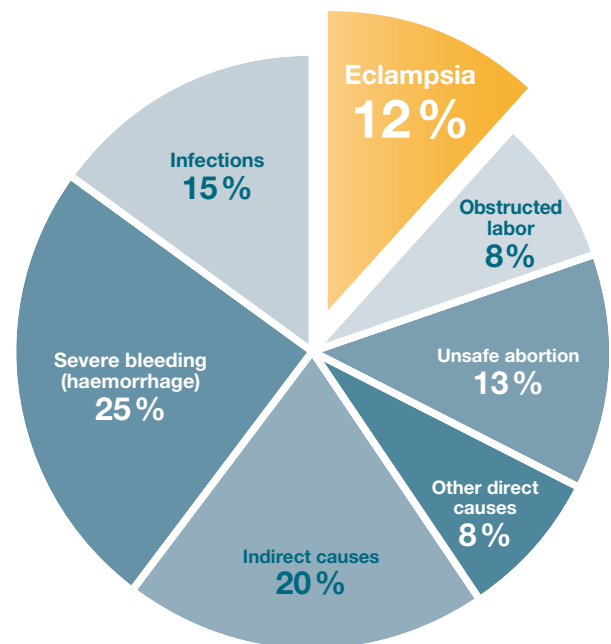
The severe pre-eclampsia form HELLP syndrome (**H**emolysis, **E**levated **L**iver enzymes, **L**ow **P**latelets) occurs in about 20% of the affected women. It is defined by additional complications of the liver and the coagulation system resulting in symptoms such as abdominal pain, hemorrhage, placental abruption, hepatic infarction and rupture, intra-abdominal bleeding and edema. Eclampsia is the final and most feared stage of the disease, associated with severe tonic-clonic seizures and coma as well as brain injury, cerebral edema and stroke.<sup>9</sup>

**HELLP syndrome and eclampsia account for more than 50 000 maternal deaths each year worldwide.<sup>8</sup>**

## Severe complications for the fetus

Due to an insufficient supply of oxygen and nutrients, pre-eclampsia causes severe complications for the fetus, such as prematurity, intra uterine growth restriction, bronchopulmonary dysplasia and sometimes even death.<sup>9</sup>

**About 15–20% of pre-term deliveries are due to pre-eclampsia.<sup>9</sup>**



**Figure 2** Causes of maternal death worldwide (Total is more than 100% due to rounding)<sup>1</sup>



## Long-term complications for the women

Pre-eclampsia is responsible for long-term complications later in life. Large retrospective epidemiological studies have shown that women with a previous pre-eclampsia have a 3–4 times higher risk for cardiovascular disorders later in life than non pre-eclamptic women. The risk is even higher (4–8 fold) if the onset of pre-eclampsia was before 34 weeks of gestation or pre-eclampsia was combined with a pre-term birth.<sup>9</sup>

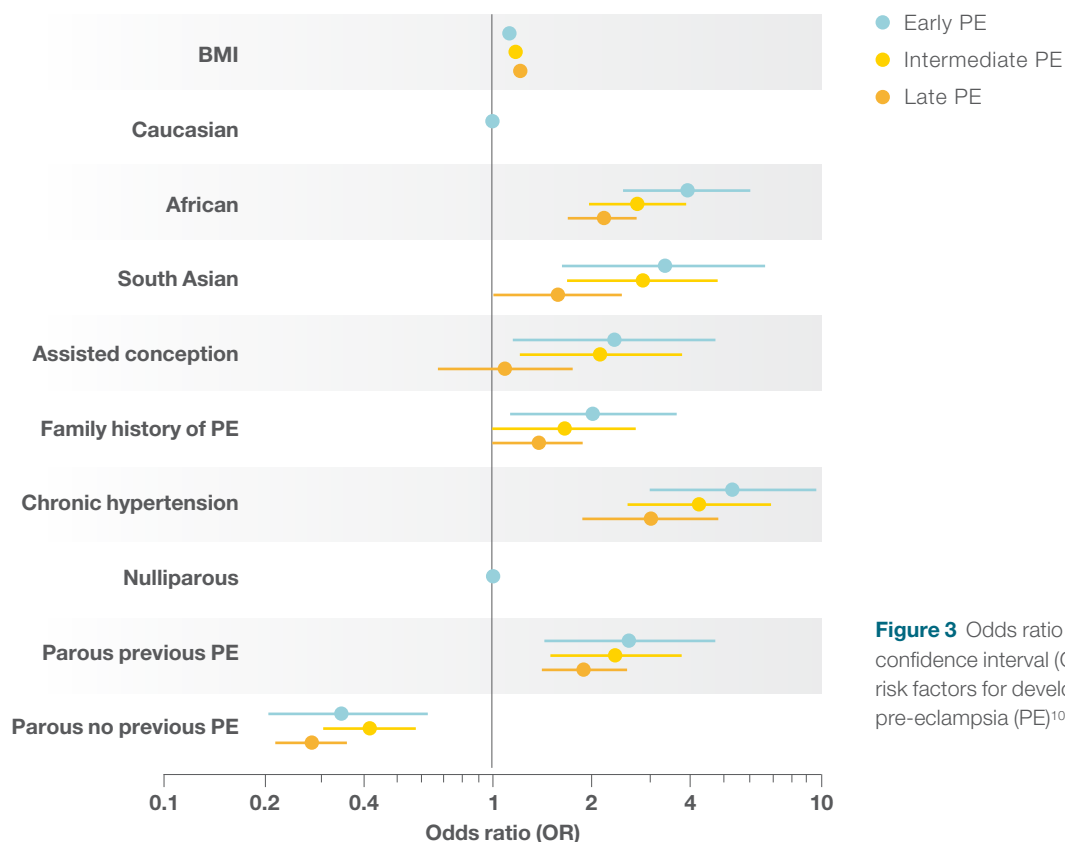
### The risk of death from cardiovascular and cerebrovascular disease is 50% higher in women with a history of pre-eclampsia.<sup>9</sup>

The underlying mechanism accounting for the elevated risk is not yet well understood, but it was shown that endothelial dysfunction persists for many years in women with a former pre-eclampsia episode.<sup>9</sup>

## Risk factors

There are many risk factors for pre-eclampsia including

- Maternal and paternal family history
- Previous pregnancy with pre-eclampsia
- Multiple pregnancy (triplets > twins)
- Maternal Age (>40 years)
- Body Mass Index (BMI >30)
- Pre-existing hypertension, Diabetes mellitus or renal disease
- Systemic inflammation
- Ethnic origin



**Figure 3** Odds ratio and 95% confidence interval (CI) of risk factors for development of pre-eclampsia (PE)<sup>10</sup>



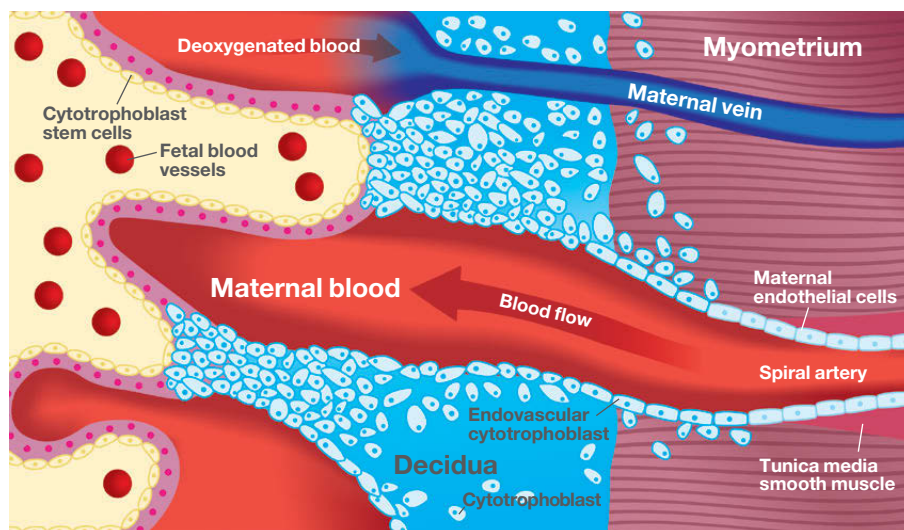
# Imbalance of pro- and antiangiogenic factors

A key factor for developing pre-eclampsia

## Normal pregnancy

Placenta and developing fetus are provided with sufficient maternal oxygen and nutrients<sup>11</sup>

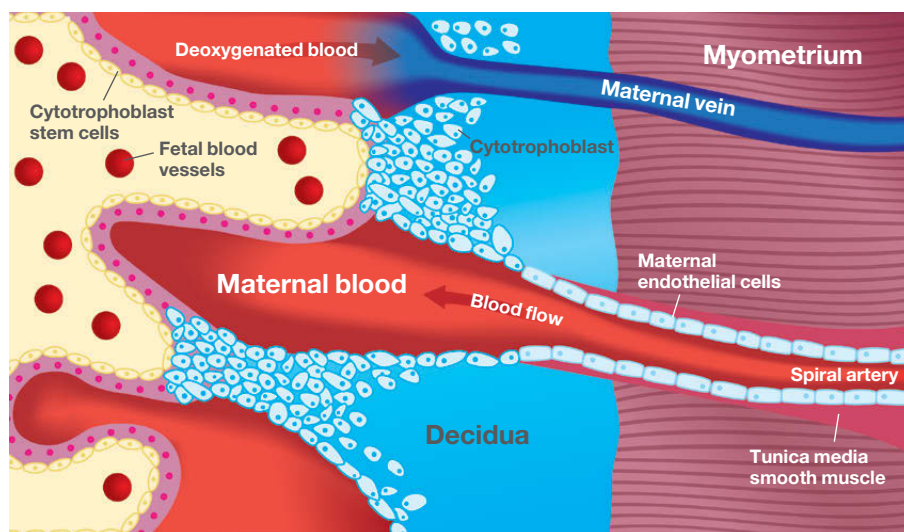
- Fetal cytotrophoblast cells invade maternal uterine wall (into smooth muscle and endothelial layer)
- Maternal spiral arteries are remodeled into large vessels with high capacity and low resistance



## Pre-eclamptic pregnancy

Inadequate circulation between placenta and uterus<sup>11</sup>

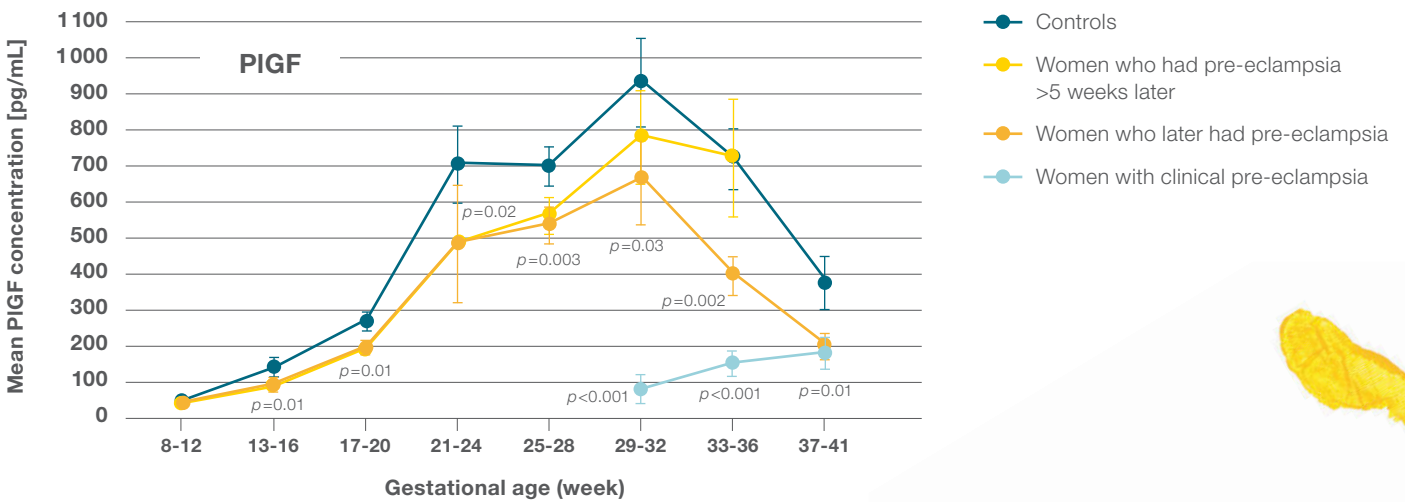
- Invasion of cytotrophoblasts is incomplete, they can only be found in superficial layers of decidua
- Maternal spiral arteries fail to be invaded/remodeled, resulting in vessels with a decreased capacity and increased resistance.
- As a consequence of the decreased blood flow the fetus is not supplied sufficiently with oxygen and nutrients.



## Maternal PIGF serum concentration is significantly decreased in pre-eclampsia in the first trimester

The cause of pre-eclampsia is still not well understood, but the placenta has been identified as the central organ in pathogenesis.<sup>9</sup>

Studies suggest that an imbalance of angiogenic proteins secreted by the placenta account for many complications with respect to pre-eclampsia. **PIGF** is a proangiogenic factor, belonging to the Vascular Endothelial Growth Factors (VEGF) family, which are promoting proliferation and survival of endothelial cells and inducing vascular permeability.<sup>12</sup> **sFlt-1** is an antiangiogenic factor, binding PIGF and VEGF with high affinity, therefore antagonizing their effects.<sup>13</sup> In contrast to a healthy pregnancy, PIGF levels are significantly lower in pre-eclamptic patients (Figure 4). This difference is measurable in the first trimester.<sup>14</sup> sFlt-1 levels in pre-eclamptic women are significantly higher compared to normal, but this difference is only notable after week 20.



**Figure 4** Mean PIGF concentrations of healthy women and those women who later developed pre-eclampsia<sup>14</sup>



# 1<sup>st</sup> trimester screening for pre-eclampsia

Identification of women at risk for pre-eclampsia before clinical symptoms appear

Combined first trimester screening for pre-eclampsia can be easily integrated into clinical routine pregnancy assessments in weeks 11+0 – 13+6.



1 Maternal characteristics including medical and obstetric history



2 Serum Biomarkers PAPP-A and PIGF



3 Mean arterial blood pressure (MAP)



4 Uterine artery pulsatility index (UtA-PI)



5 Risk assessment with appropriate PNS software to calculate individual risk to develop pre-eclampsia

Risk assessment for **fetal trisomies** and **maternal pre-eclampsia** can be performed at the **same time**





## Combined screening achieves highest detection rates

Using the traditional screening method, based on maternal history only, the detection rate for women who are at risk for developing pre-term pre-eclampsia is about 30%. Detection rates become more accurate when maternal factors are combined with PIGF measurement as well as other biomarkers such as serum PAPP-A (both measured in weeks 11–13+6), mean arterial pressure (MAP), and uterine artery Doppler (UtA-PI), resulting in a detection rate of >90% for cases of early pre-eclampsia for a fixed false positive rate of 5%. **Therefore, an effective prediction of pre-eclampsia can be achieved already in first trimester.**<sup>6,7,15,18</sup>

Screening test	FPR (%)	Detection rate (%)		
		PE < 34 wks	PE < 37 wks	PE ≥ 37 wks
Maternal factors	10	41	29	18
Maternal factors plus				
• PIGF	10	88	63	37
• UtA-PI	10	82	61	39
• MAP	10	71	47	37
• PAPP-A	10	59	47	37
• UtA-PI, PIGF	10	100	75	39
• MAP, PIGF	10	88	69	43
• PIGF, PAPP-A	10	88	66	39
• MAP, UtA-PI, PIGF	10	100	75	43
• MAP, UtA-PI, PAPP-A	10	94	69	42
• MAP, PAPP-A, PIGF	10	88	69	43
• MAP, UtA-PI, PAPP-A, PIGF	10	100	80	43

**Table 1** Screening performance for early-, intermediate- and late-onset pre-eclampsia by combining different factors<sup>18</sup>

**Highly sensitive PIGF and PAPP-A assays are needed to reliably detect these biomarkers in weeks 11–13+6.**

# Thermo Fisher Scientific B·R·A·H·M·S pre-eclampsia biomarkers

High sensitivity and exceptional precision

## Thermo Scientific B·R·A·H·M·S PIGF plus KRYPTOR

Automated immunofluorescent assay for the quantitative determination of the concentration of PIGF (Placental Growth Factor) in human serum. The assay is specific for the measurement of human free PIGF-1.

- 75 determinations per kit
- 29 min incubation time
- Monoparametric control kit, 3 levels
- Wide measuring range: 3.6–7 000 pg/mL
- Excellent precision

With a detection limit of 3.6 pg/mL and an upper limit of 7 000 pg/mL B·R·A·H·M·S PIGF plus KRYPTOR provides the high sensitivity needed for **measuring PIGF levels in first trimester** as well as a wide measuring range to **reliably measure clinical values throughout pregnancy**.

## Thermo Scientific B·R·A·H·M·S PAPP-A KRYPTOR

Automated immunofluorescent assay for the determination of pregnancy associated plasma protein-A (PAPP-A) in human serum and heparin plasma.

- 75 determinations per kit
- 19 min incubation time
- FAS: 10 mIU/L
- Wide measuring range: 0.004–90 IU/L
- Excellent precision

B·R·A·H·M·S PAPP-A KRYPTOR provides an outstanding precision with a mean CV of only 3.1%, proven by UK NEQAS data 2003-2019.<sup>17</sup>



# Exceptionally precise, fast and easy

## B·R·A·H·M·S KRYPTOR analyzers



- All KRYPTOR platforms FMF approved
- In routine use by FMF since 1999
- Excellent precision and proven median stability
- OSCAR compatible



Thermo Scientific  
B·R·A·H·M·S KRYPTOR GOLD

Thermo Scientific  
B·R·A·H·M·S KRYPTOR compact PLUS



## Your **BENEFITS** performing a 1<sup>st</sup> trimester pre-eclampsia screening

- ▶ **Early identification** of high risk pregnancies for pre-eclampsia weeks before first clinical symptoms appear
- ▶ **Early risk assessment** allows for closer surveillance and in time administration of low dose aspirin (<16 weeks) to significantly reduce the incidence of pre-eclampsia

## Your **ACCESS** to our interactive e-detail

Get more information on pre-eclampsia management throughout pregnancy:



<http://prenatal.world-of-biomarkers.com>

Pin code: **plgf01**



### Thermo Scientific B·R·A·H·M·S Biomarkers Prenatal Screening Portfolio on B·R·A·H·M·S KRYPTOR Systems

B·R·A·H·M·S <b>AFP</b> KRYPTOR	Art. no.: 816.075
B·R·A·H·M·S <b>Free <math>\beta</math>hCG</b> KRYPTOR	Art. no.: 809.075
B·R·A·H·M·S <b>hCG+<math>\beta</math></b> KRYPTOR	Art. no.: 841.050
B·R·A·H·M·S <b>Inhibin A</b> KRYPTOR*	Art. no.: 850.075
B·R·A·H·M·S <b>PAPP-A</b> KRYPTOR	Art. no.: 866.075
B·R·A·H·M·S <b>PIGF plus</b> KRYPTOR**	Art. no.: 859.075
B·R·A·H·M·S <b>sFit-1</b> KRYPTOR**	Art. no.: 845.075
B·R·A·H·M·S <b>uE3</b> KRYPTOR***	Art. no.: 803.075
B·R·A·H·M·S <b>Fast Screen pre I plus Software</b>	Art. no.: 105750

\* Available on B·R·A·H·M·S KRYPTOR GOLD

\*\* Available on B·R·A·H·M·S KRYPTOR compact PLUS and B·R·A·H·M·S KRYPTOR GOLD

\*\*\* Available on B·R·A·H·M·S KRYPTOR, B·R·A·H·M·S KRYPTOR compact PLUS and B·R·A·H·M·S KRYPTOR GOLD

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