



Pre-eclampsia screening in 1st trimester of pregnancy

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

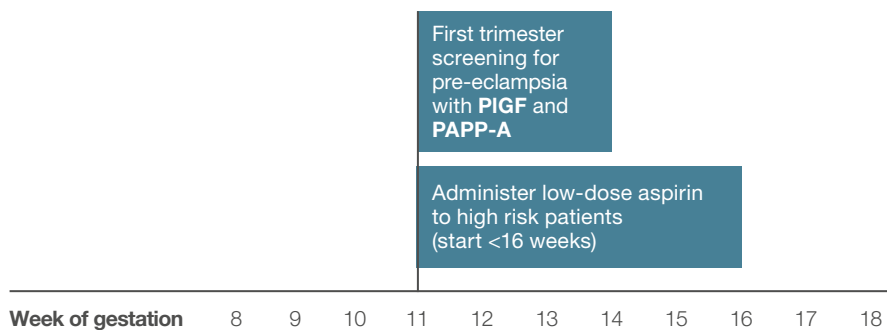
Early screening – early intervention

Pre-eclampsia screening in 1st trimester for optimal 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.¹ A combined first trimester screening approach including measurement of Placental Growth Factor (PIGF) and Pregnancy-Associated Plasma Protein A (PAPP-A) can reliably identify women at high risk for early-onset pre-eclampsia. Early identification of women at high risk allows for intensified maternal and fetal monitoring and timely intervention 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 (UAPI)
- 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-eclampsia.²



Low-dose aspirin can reduce the risk of pre-eclampsia

A meta-analysis has shown that the application of low-dose aspirin (<150 mg/day) started before week 16 of gestation caused a significant reduction in pre-eclampsia and intrauterine fetal growth restriction (IUGR) compared to controls, while aspirin started after 16 weeks of gestation did not.^{3,4}

Recent prospective studies proved the efficacy of low-dose aspirin in reducing pre-eclampsia. Women identified at high risk for pre-eclampsia after first trimester screening either received low-dose aspirin or nothing. In the aspirin group the prevalence of pre-eclampsia was reduced by 90%.⁵

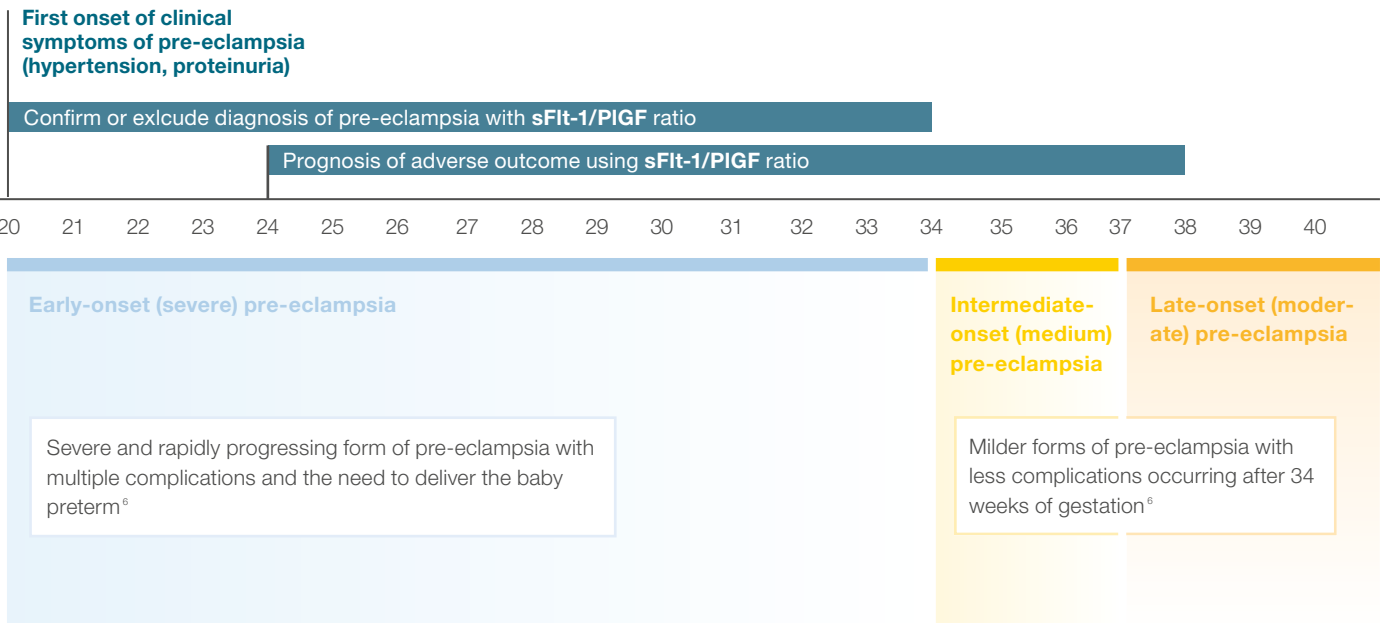


Figure 1 First clinical symptoms of pre-eclampsia are observed >20 weeks of gestation. The gestational age at onset correlates with the severity of maternal and fetal consequences.⁷

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 disorder⁸ affecting more than 4.1 million women per year worldwide.¹

The severe pre-eclampsia variant HELLP syndrome (**H**emolysis, **E**levated **L**iver enzymes, **L**ow **P**latelets) occurs in about 20% of the affected women and 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.⁹

HELLP syndrome and eclampsia account for more than 50 000 maternal deaths each year.⁸

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, IGUR, bronchopulmonary dysplasia and sometimes even death.⁹

About 15-20% of preterm deliveries are due to pre-eclampsia.⁹

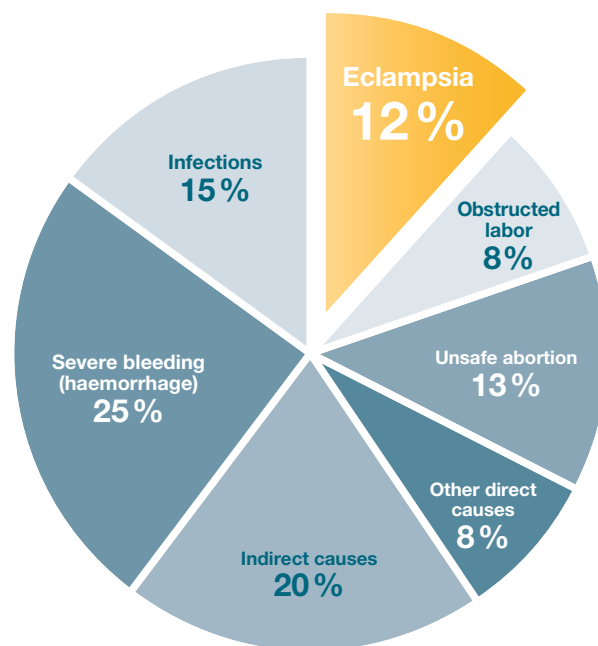


Figure 2 Causes of maternal death worldwide (Total is more than 100% due to rounding)¹



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 preterm birth.⁹

The risk of death from cardiovascular and cerebrovascular disease is 50% greater in women with a history of pre-eclampsia.⁹

The underlying mechanism that accounts 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.⁹

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
- Ethnical origin

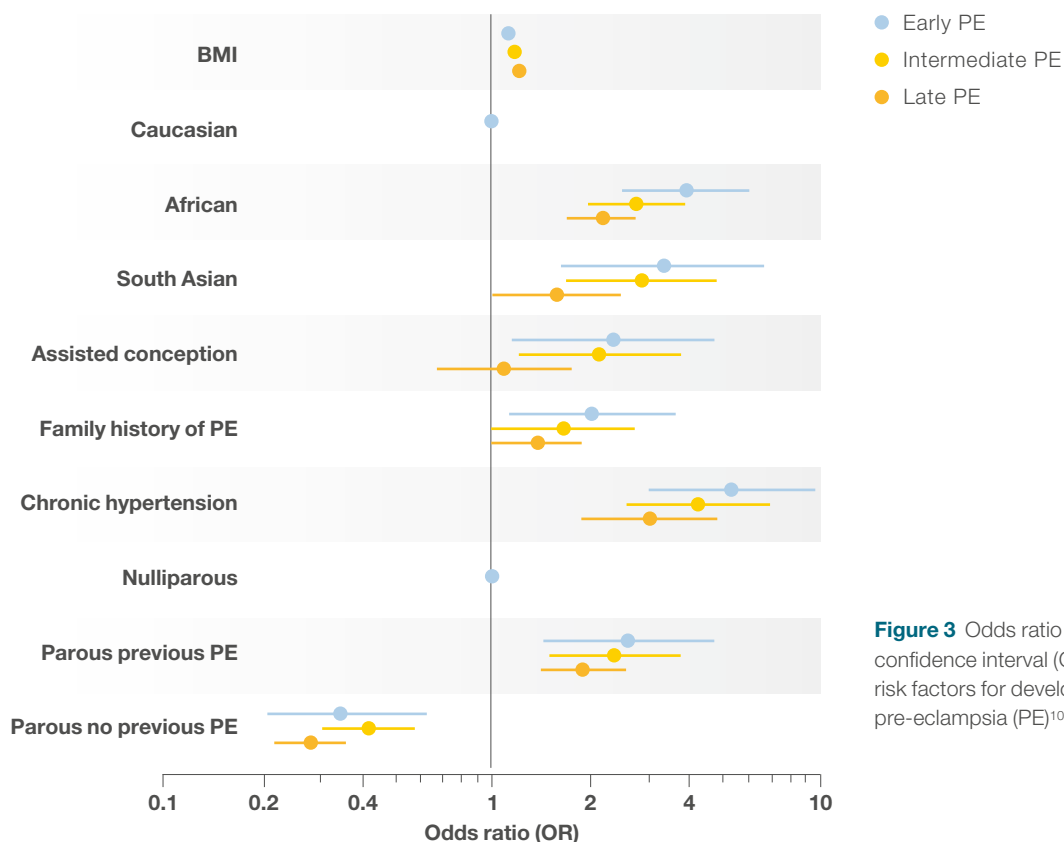


Figure 3 Odds ratio and 95% confidence interval (CI) of risk factors for development of pre-eclampsia (PE)¹⁰

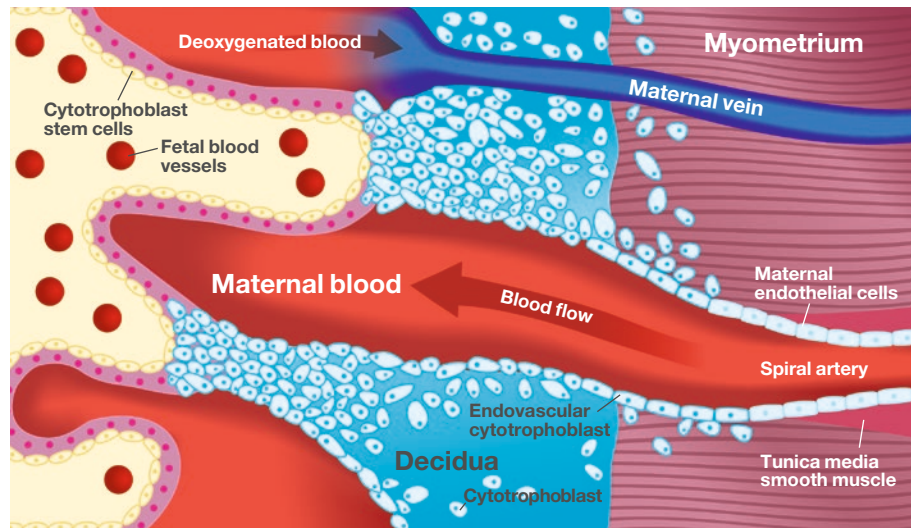
Imbalance of pro- and antiangiogenic proteins

A key factor for developing pre-eclampsia

Normal pregnancy

Placenta and developing fetus are provided with sufficient maternal oxygen and nutrients¹¹

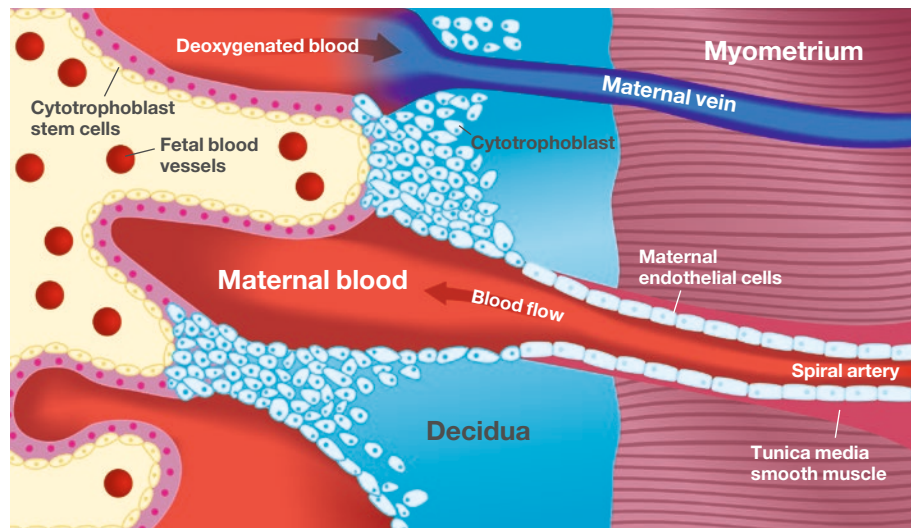
- Fetal cytotrophoblast cells invade maternal uterine wall (into smooth muscle and endothelial layer)
- Maternal spiral arteries are remodeled into large vessels with high capacity and low resistance



Pre-eclamptic pregnancy

Inadequate circulation between placenta and uterus¹¹

- 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.⁹

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.¹² **sFlt-1** (soluble FMS-like tyrosine kinase) is an antiangiogenic factor, binding PIGF and VEGF with high affinity, therefore antagonizing their effects.¹³ 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.¹⁴ sFlt-1 levels in pre-eclamptic women are significantly higher compared to normal, but this difference is only notable after week 20.

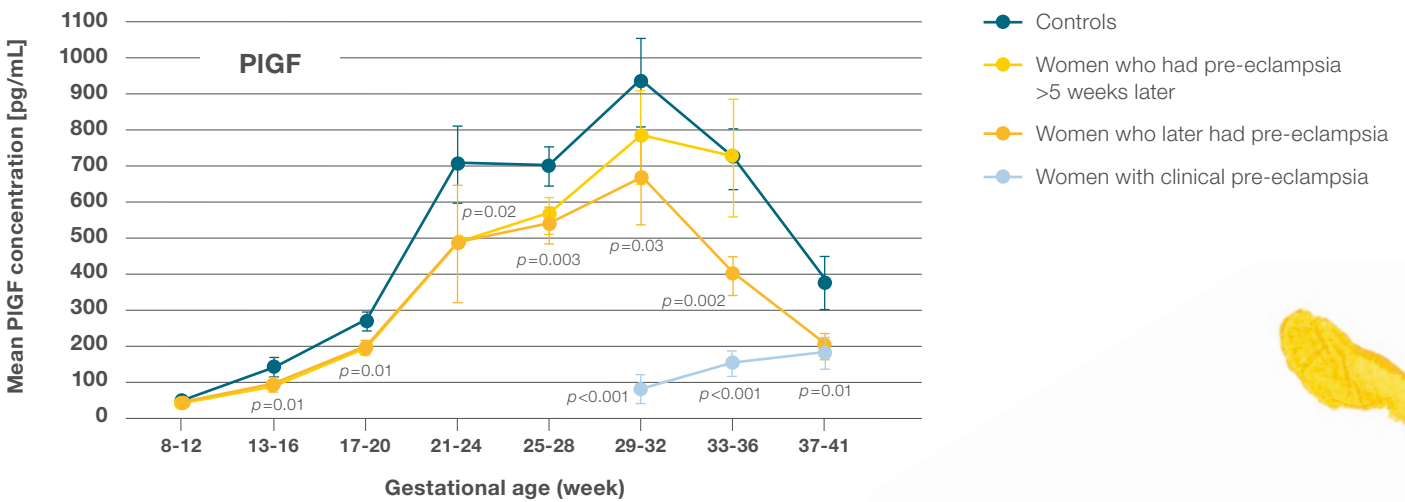


Figure 4 Mean PIGF concentrations of healthy women and those women who later developed pre-eclampsia¹⁴



1st trimester screening for pre-eclampsia

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

Combined first trimester screening for pre-eclampsia

Pre-eclampsia screening 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 (UAPI)



- 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, detection rate for women who are at risk for developing pre-eclampsia is about 30%. Detection rates become more accurate when maternal characteristics are combined with PIGF measurement as well as other factors such as serum PAPP-A (both measured in weeks 11–13+6), mean arterial pressure (MAP), and uterine artery Doppler (uA-PI), resulting in a detection rate of >90% for cases of early pre-eclampsia for a fixed false positive rate of 5% before any clinical symptoms appear.⁷ **Therefore, an effective prediction of pre-eclampsia can be achieved already in first trimester.**^{6, 15}

Screening test	FPR (%)	Detection rate (%)		
		PE < 34 wks	PE < 37 wks	PE < 42 wks
Maternal characteristics	5	36	33	29
PAPP-A	5	44	37	32
PIGF	5	59	41	29
PAPP-A and PIGF	5	60	43	30
MAP	5	58	44	37
UAPI	5	59	40	31
MAP and UAPI	5	80	55	35
MAP, UAPI and PAPP-A	5	82	53	36
MAP, UAPI and PIGF	5	87	61	38
MAP, UAPI, PAPP-A and PIGF	5	93	61	38

Table 1 Screening performance for early-, intermediate- and late-onset pre-eclampsia by combining different factors¹⁵

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

Thermo 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.

- **CE mark for trisomy and pre-eclampsia first trimester screening**
- **75 determinations per kit**
- **29 min incubation time**
- **FAS: 6.7 pg/mL**
- **Single-point calibration**
- **Wide measuring range: 3.6-7000 pg/mL**
- **Lowest cross reactivity to PIGF-2 and PIGF-3**

With the lowest FAS and lowest cross-reactivity to other PIGF isoforms B·R·A·H·M·S PIGF plus KRYPTOR provides the **highest sensitivity** needed for reliably measuring low PIGF levels in the first trimester of pregnancy.¹⁶





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.

- **CE mark for trisomy and pre-eclampsia first trimester screening**
- **75 determinations per kit**
- **19 min incubation time**
- **FAS: 10 mIU/L**
- **Single-point calibration**
- **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 2003-2016.¹⁷



Exceptionally precise, fast and easy

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

18 Years Reliable Results
18 Years Confident Decisions

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



Your **BENEFITS** performing a 1st 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 KRYPTOR Systems

B·R·A·H·M·S AFP KRYPTOR	Art. no.: 816.075
B·R·A·H·M·S Free βhCG KRYPTOR	Art. no.: 809.075
B·R·A·H·M·S hCG+β KRYPTOR	Art. no.: 841.050
B·R·A·H·M·S Inhibin A KRYPTOR	(under development)
B·R·A·H·M·S PAPP-A KRYPTOR	Art. no.: 866.075
B·R·A·H·M·S PIGF plus KRYPTOR*	Art. no.: 859.075
B·R·A·H·M·S sFit-1 KRYPTOR*	Art. no.: 845.075
B·R·A·H·M·S uE3 KRYPTOR**	Art. no.: 803.075
B·R·A·H·M·S Fast Screen pre I plus Software	Art. no.: 105750

* Available on KRYPTOR compact PLUS

** Available on KRYPTOR and KRYPTOR compact PLUS

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