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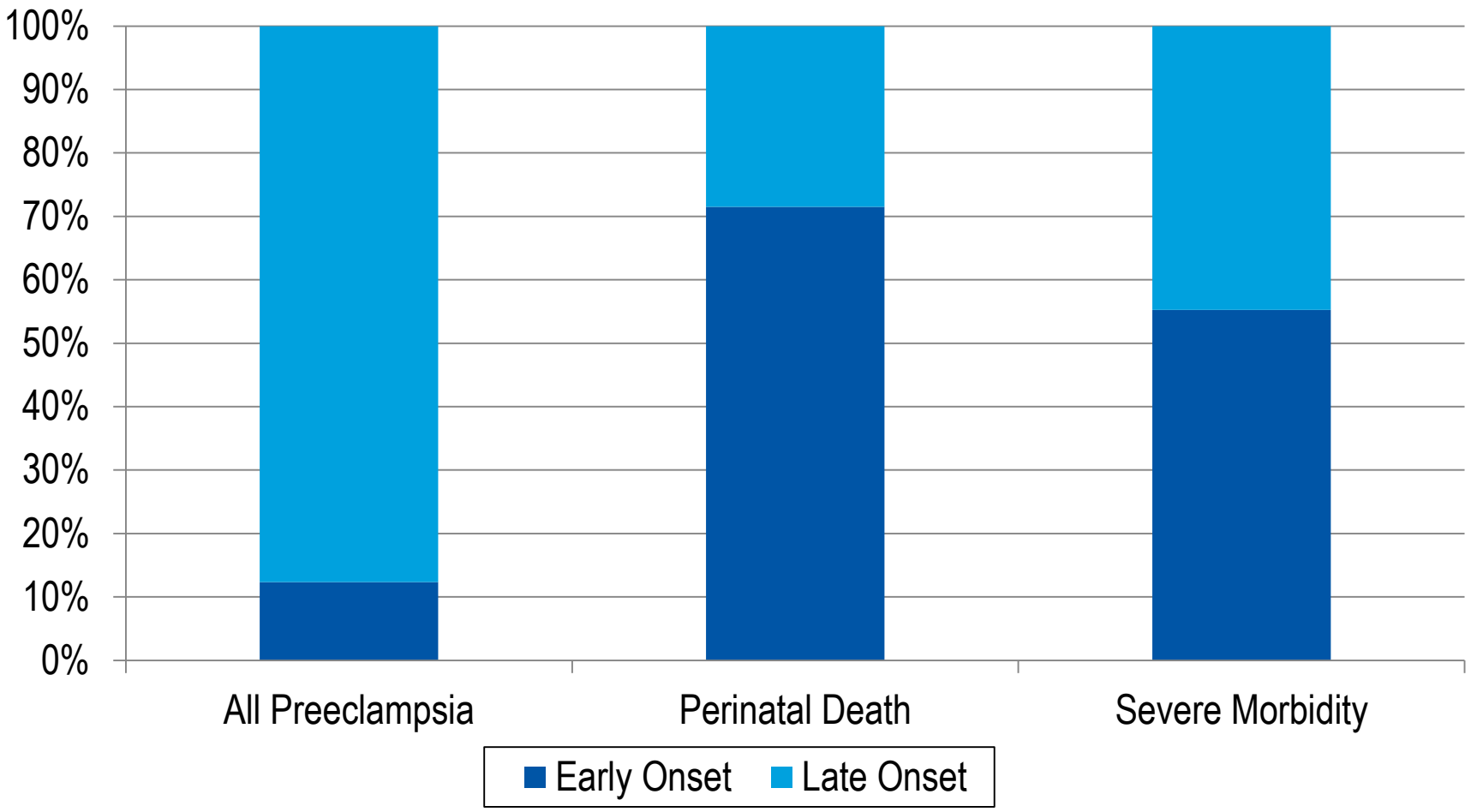
HUMAN HEALTH | ENVIRONMENTAL HEALTH

First Trimester Screening for Early Onset Preeclampsia

Terrence W. Hallahan, Ph.D.
Laboratory Director
PerkinElmer Labs | NTD

Early Onset Preeclampsia – Less Common – More Severe



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PreeclampsiaScreen™ | T1

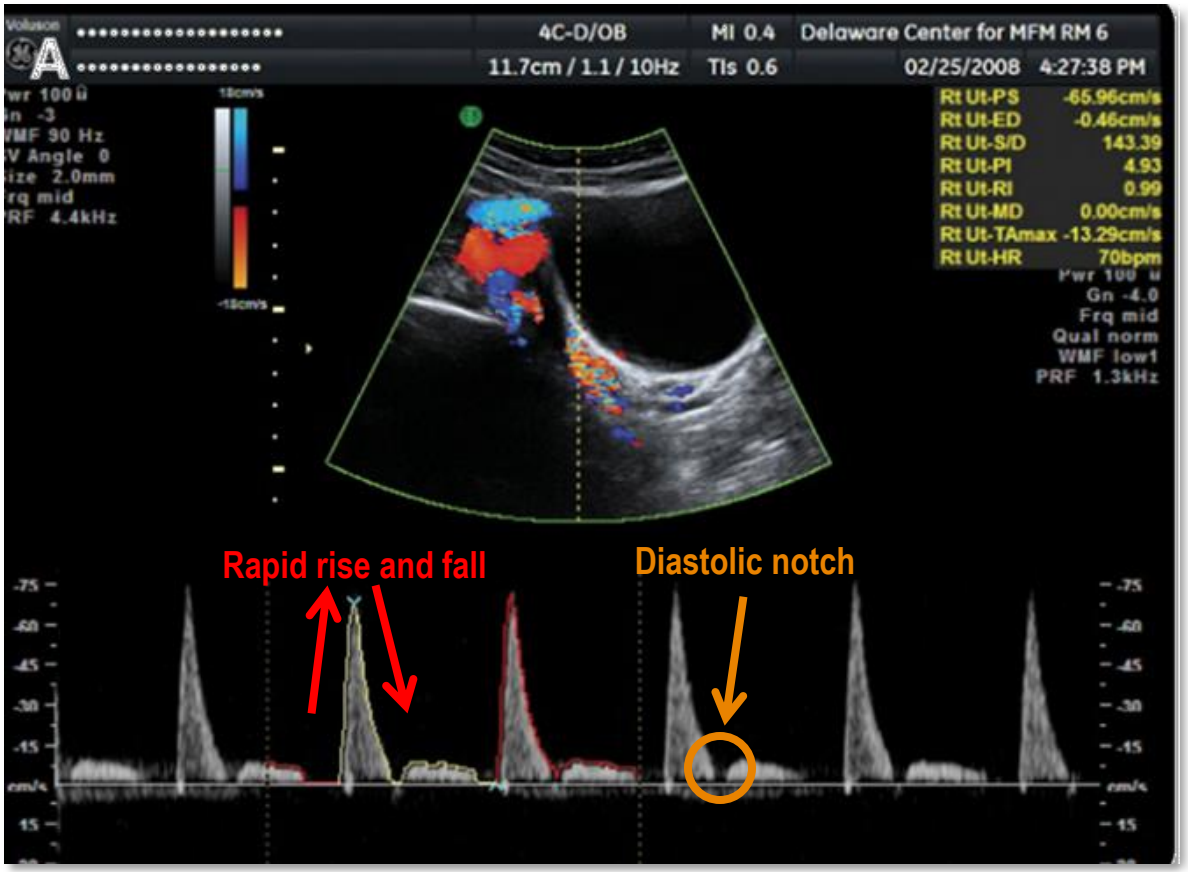
- First of its kind serum screening test for **early onset preeclampsia**
- Quantitates demographic and historical factors in a risk algorithm
  - Body mass index (BMI)
  - Ethnicity
  - Patient history, including
    - Previous delivery >=24 weeks
    - Maternal and personal history of preeclampsia
    - History of chronic hypertension
- Measures three biochemical markers in maternal serum
  - PAPP-A (pregnancy-associated plasma protein-A)
  - PIGF (placental growth factor)
  - AFP (alpha fetoprotein)
- Two biophysical markers
  - MAP
  - UtAD-PI

Uterine Artery Doppler (UtAD) Helps Demonstrate Vascular Resistance in Uterine Arteries in Women With Preeclampsia

Nonpregnancy

- Rapid rise and fall in uterine artery flow velocity during systole and a “notch” in the descending waveform in early diastole

Uterine Artery Doppler in the Nonpregnant Patient[1]



Reproduced from: Sciscione AC, et al. *Am J Obstet Gynecol*. 2009 Aug;201(2):121-6 with permission from Elsevier

Evolving UtAD in Nonpregnant and Pregnant Women

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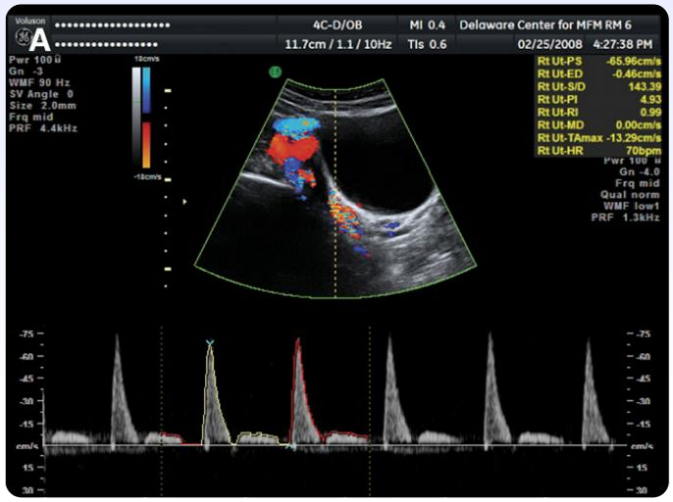
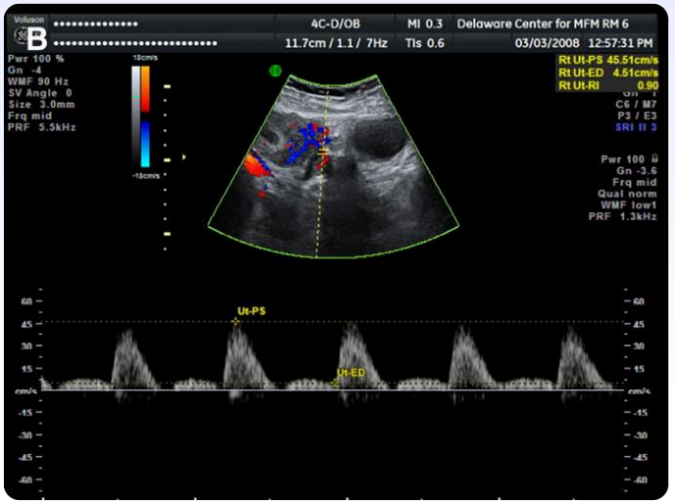
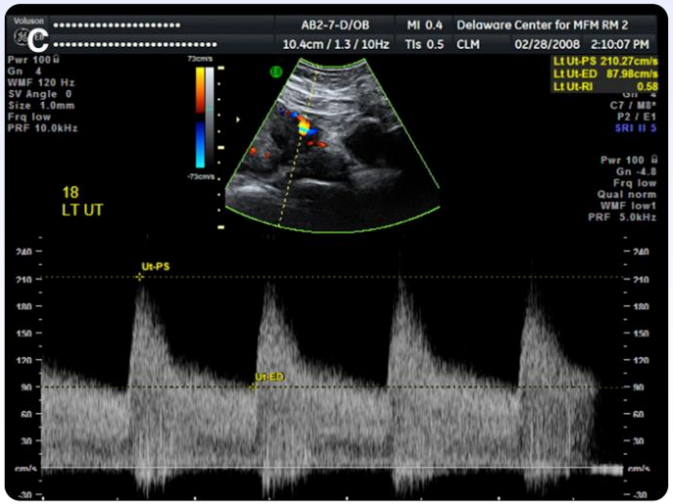
Nonpregnant Patient



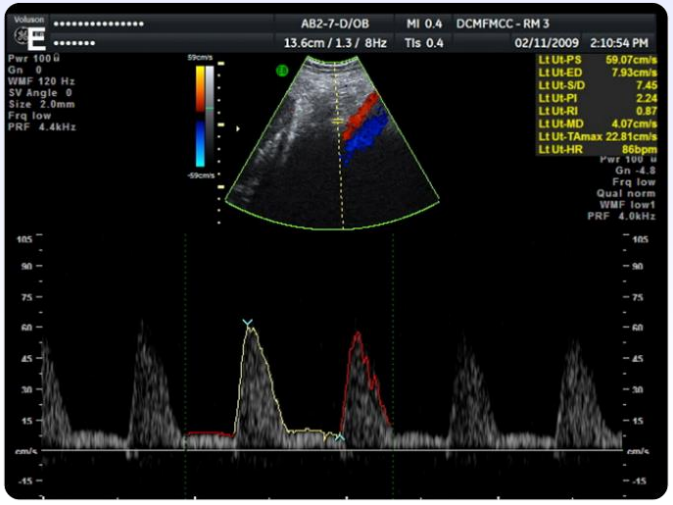
Normal First Trimester



Normal Second Trimester



Abnormal UtAD Demonstrating High Resistance



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Mean Arterial Pressure

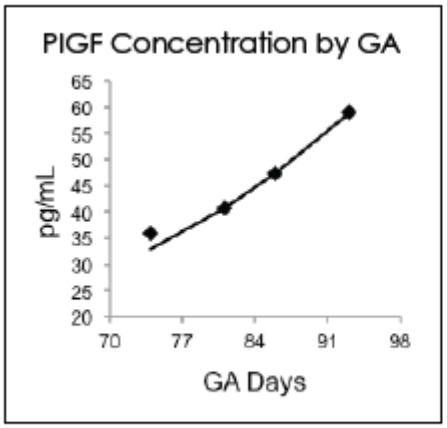
- The blood pressure (BP) should be measured in both arms simultaneously.
- Series of recordings at 1-minute intervals should be taken until readings become stable.
- The measurement from the arm with the higher final pressure should be used for risk assessment.

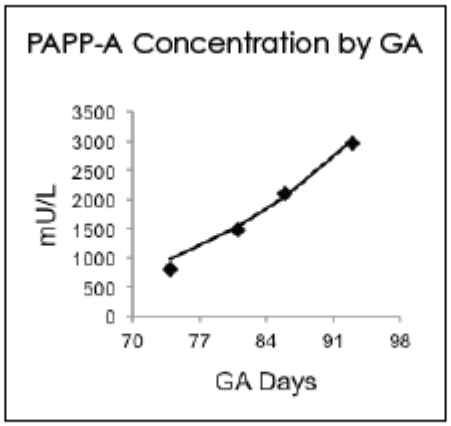
MAP = Diastolic BP + (Systolic BP – Diastolic BP) / 3

There is evidence that in a high proportion of pregnancies predisposed to develop pre-eclampsia the maternal mean arterial pressure (MAP) is increased at 11 to 13 weeks.

Poon LC et al. (2008) Hypertension. 51(4):1027-33.

PerkinElmer | NTD Validation Data Set





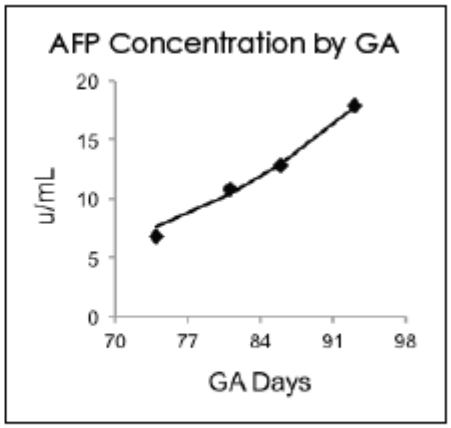
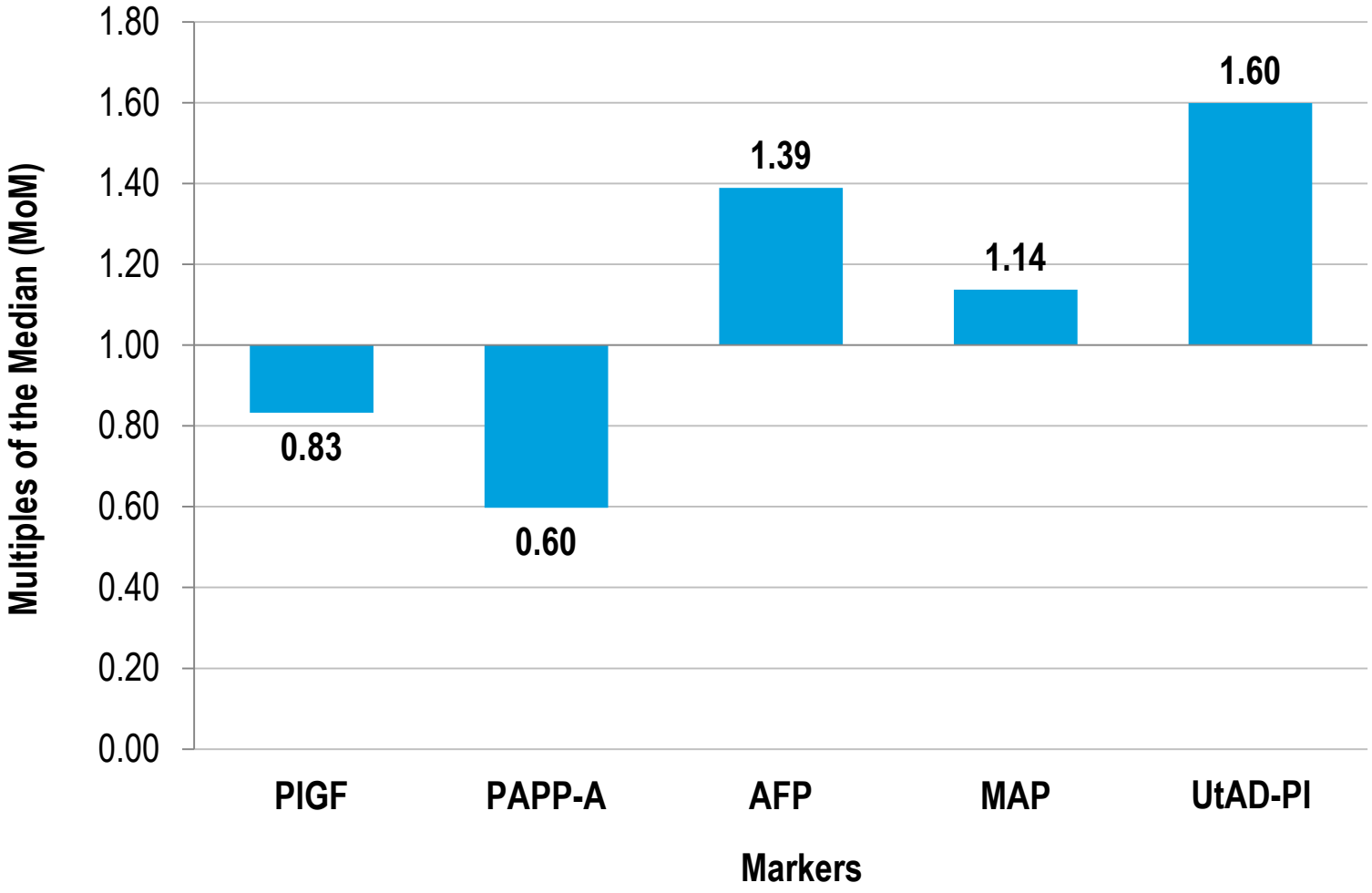


Figure 1: Squares are observed medians. Solid lines show regressed values by GA.

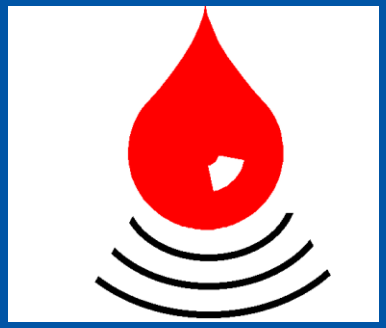
Regression Formula Coefficients			
	PIGF	PAPP-A	AFP
Method	ln-linear	ln-ln	ln-linear
Slope	0.2144	4.9164	0.3096
Intercept	1.2236	-4.7076	-1.2407

1048 Unaffected Cases

Biomarker MoM Values Found in PerkinElmer Labs/NTD Validation Studies for Early Onset Preeclampsia



31 EOPE Cases



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Quantitative Risk Assessment of Early Onset Preeclampsia:

Combined Biochemical and Biophysical Markers

Test Specifications for PreeclampsiaScreen™ | T1

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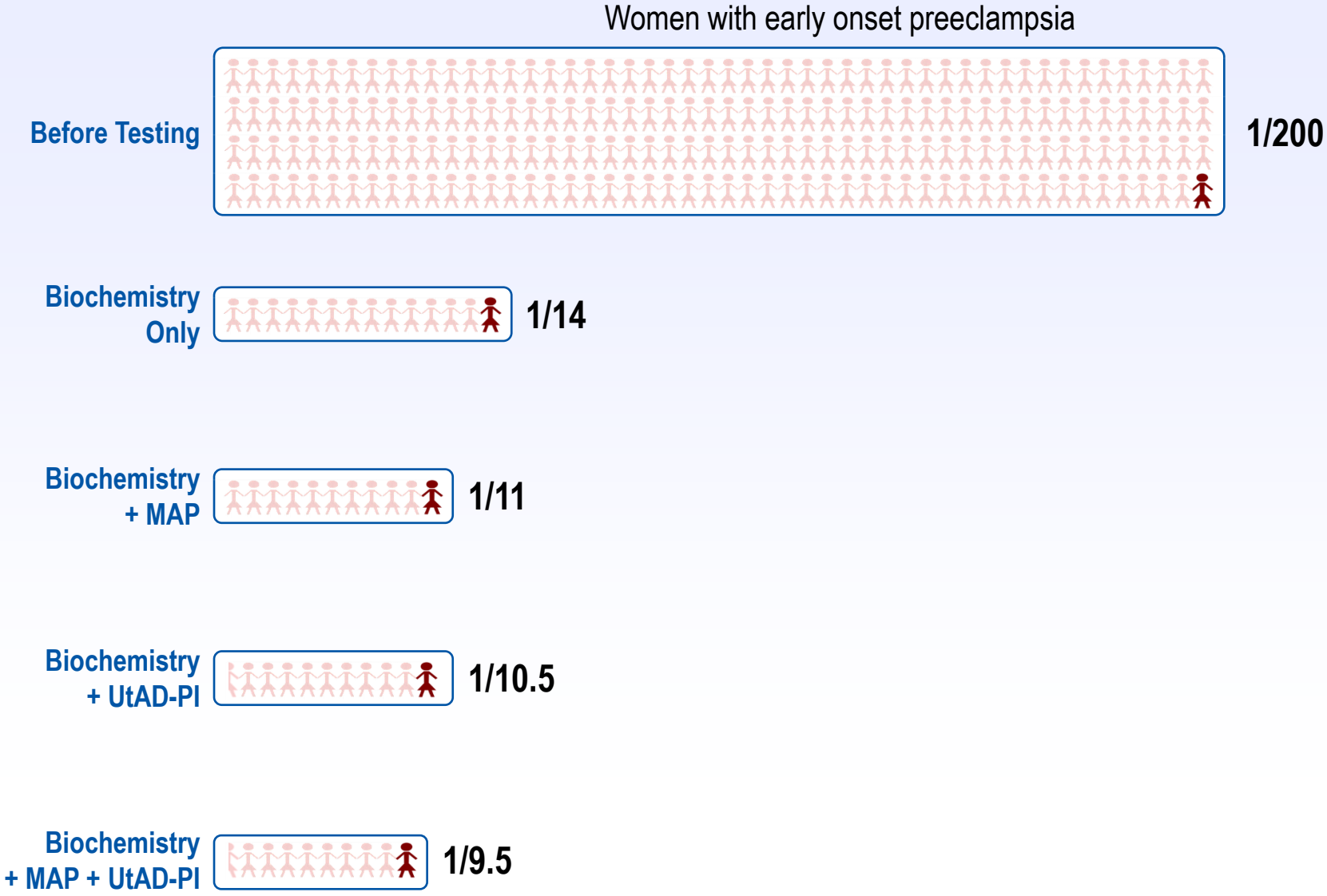
	Biochemistry + History	Biochemistry + History + MAP	Biochemistry + History + UtAD-PI	Biochemistry + History +MAP + UtAD-PI
Markers	PIGF, PAPP-A, AFP	PIGF, PAPP-A, AFP, MAP	PIGF, PAPP-A, AFP, UtAD-PI	PIGF, PAPP-A, AFP, MAP, UtAD-PI
Gestational Age (ultrasound dated)	10 weeks, 0 days – 13 weeks, 6 days	11 weeks, 1 day – 13 weeks, 6 days	11 weeks, 1 day – 13 weeks, 6 days	11 weeks, 1 day – 13 weeks, 6 days
Detection rate at 5% FPR	**60%**	**77%**	**82%**	**91%**
Requirements	• 5 ml maternal serum in SST (red/grey speckled or gold) tube or red top tube	• 5 ml maternal serum in SST tube or red top tube • MAP measurement	• 5 ml maternal serum in SST tube or red top tube • UtAD-PI measurement	• 5 ml maternal serum in SST tube, or red top tube • MAP • UtAD-PI measurement

Early Preeclampsia Screening Improves Clinical Focus



Positive Predictive Value and Negative Predictive Value of PreeclampsiaScreen™ | T1

Protocol	PPV (1 in…)	PPV (%)	NPV (%)
Biochemistry only	14	7.0	99.73
Biochemistry + MAP	11	9.0	99.84
Biochemistry + UtAD-PI	10.5	9.5	99.88
Biochemistry + MAP + UtAD-PI	9.5	10.5	99.94

Sample Report: Increased Risk for Early Onset Preeclampsia

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Identifying Information

PerkinElmer Labs NTD

80 Ruland Rd, Suite 1 • Melville, NY • 11747 • (631) 425-0800 • Fax (631) 425-0811 • Email: ntdlabs@perkinelmer.com

Preeclampsia Screen ™ | T1 Report

Physician ID #: 24328
Physician Tel #: (000) 000-0000
OB SPECIALISTS
100 ANYWHERE ST
MELVILLE, NY 11747

Patient Name:	INCRISK, MAPPI		
Patient ID #:	13PE0001084	**U/S Date:**	02/04/13
Client ID #:		**GA @ U/S:**	11w4d
Date of Birth:	06/10/83 (age at EDC: 30)	**Draw Date:**	02/04/13
CRL (mm):	50	**GA @ Draw:**	11w4d (CRL)
Multi. Preg:	No	**MAP Date:**	02/04/13
Smoker:	No	**GA @ MAP:**	11w4d
		Date Received:	02/06/13
		Report Date:	02/07/13

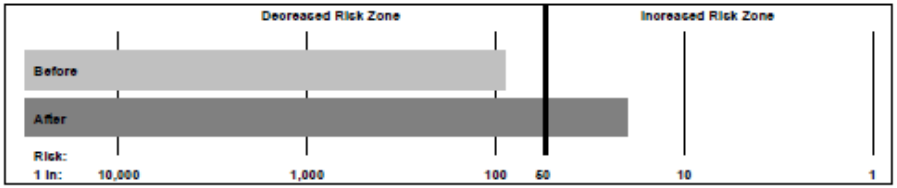
Interpretation: ** INCREASED RIS

Prior Risk Factors	
Ethnicity	Afr. Am
Previous delivery >24 weeks	No
Fam Hx Preeclampsia	No
Previous Preeclampsia	No
Chronic Hypertension	No
Weight	138 lbs
Height	5' 2"
BMI	25.24

Mean Arterial Pressure (MAP)	110 mm Hg	1.24	99
Uterine Artery Doppler PI (UtAD-PI)	3.2	1.09	60

Risk Table	Cut-Off	Risk Before Screening	Risk After Screening	Result
Early Onset Preeclampsia	1 in 50	1 in 87	1 in 18	**INCREASED RISK**

Early Onset Preeclampsia Risk



Comments:
- Recommend immediate follow-up with increased monitoring.

Jonathan B. Carmichael, Ph.D
Laboratory Director,
PerkinElmer Labs/NTD

Terrence W. Hallahan, Ph.D
Laboratory Director,
PerkinElmer Labs/NTD

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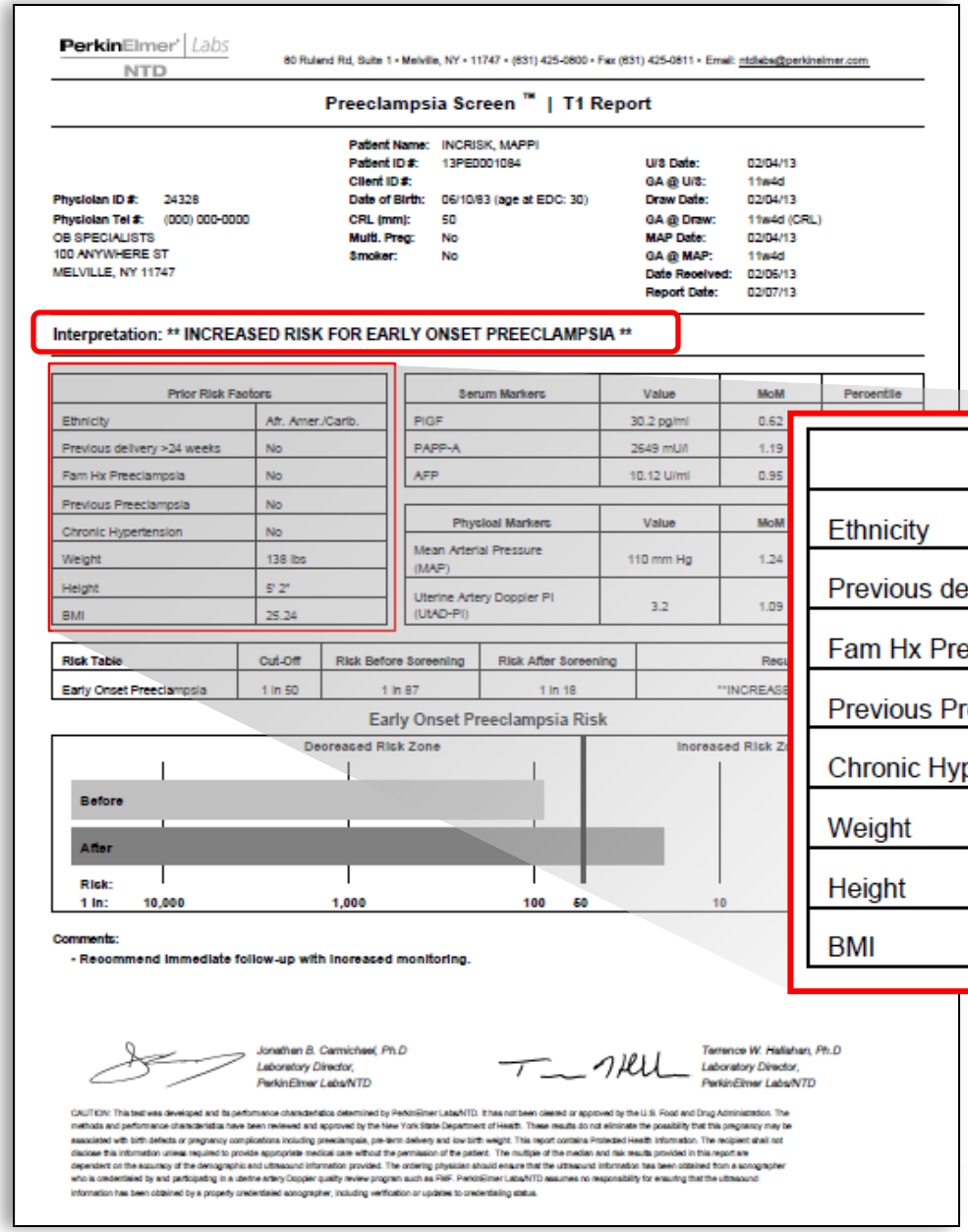
Sample Report: Increased Risk for Early Onset Preeclampsia



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Preeclampsia Screen ™ | T1 Report

Patient Name: INCRISK, MAPPI
Patient ID #: 13PE0001084
Client ID #:
Date of Birth: 06/10/83 (age at EDC: 30)
CRL (mm): 50
Multi. Preg: No
Smoker: No

U/S Date: 02/04/13
GA @ U/S: 11w4d
Draw Date: 02/04/13
GA @ Draw: 11w4d (CRL)
MAP Date: 02/04/13
GA @ MAP: 11w4d
Date Received: 02/05/13
Report Date: 02/07/13

Physician ID #: 24328
Physician Tel #: (000) 000-0000
OB SPECIALISTS
100 ANYWHERE ST
MELVILLE, NY 11747

Interpretation: ** INCREASED RISK FOR EARLY ONSET PREECLAMPSIA **

Prior Risk Factors	
Ethnicity	Afr. Amer./Carib.
Previous delivery >24 weeks	No
Fam Hx Preeclampsia	No
Previous Preeclampsia	No
Chronic Hypertension	No
Weight	138 lbs
Height	5' 2"
BMI	25.24

Serum Markers	Value	MoM	Percentile
PlGF	30.2 pg/ml	0.62	
PAPP-A	2649 mU/l	1.19	
AFP	10.12 U/ml	0.95	

Physical Markers	Value	MoM
Mean Arterial Pressure (MAP)	110 mm Hg	1.24
Uterine Artery Doppler PI (UtAD-PI)	3.2	1.09

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Early Onset Preeclampsia	1 in 50	1 in 87	1 in 18	**INCREASE

Early Onset Preeclampsia Risk

Comments:
- Recommend immediate follow-up with increased monitoring.

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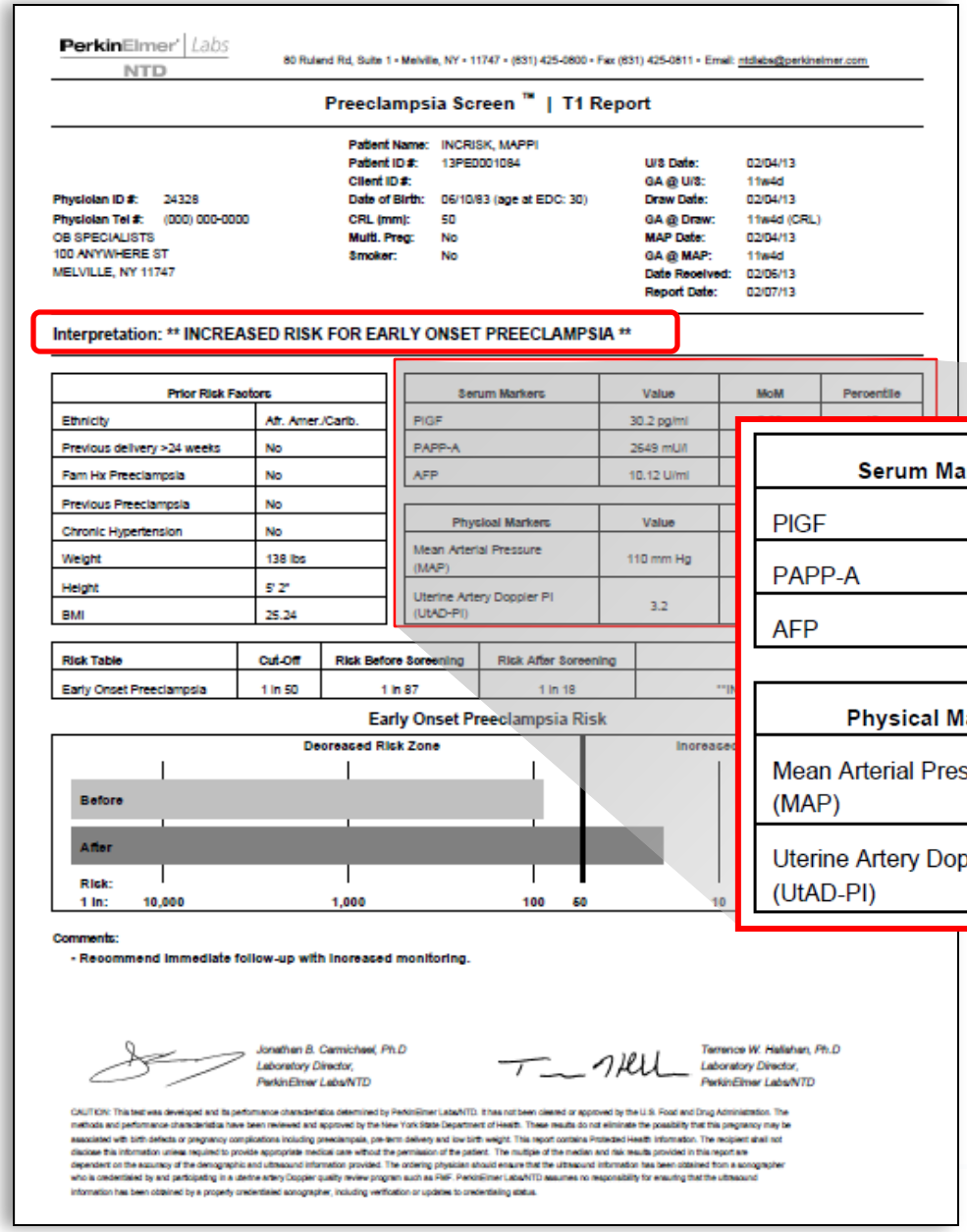

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Preeclampsia Screen ™ | T1 Report

Patient Name: INCRISK, MAPPI
Patient ID #: 13PE0001084
Client ID #:
Date of Birth: 06/10/83 (age at EDC: 30)
CRL (mm): 50
Multi. Preg: No
Smoker: No

U/S Date: 02/04/13
GA @ U/S: 11w4d
Draw Date: 02/04/13
GA @ Draw: 11w4d (CRL)
MAP Date: 02/04/13
GA @ MAP: 11w4d
Date Received: 02/05/13
Report Date: 02/07/13

Physician ID #: 24328
Physician Tel #: (000) 000-0000
OB SPECIALISTS
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PAPP-A	2649 mU/l		
AFP	10.12 U/ml		

Physical Markers	Value
Mean Arterial Pressure (MAP)	110 mm Hg
Uterine Artery Doppler PI (UtAD-PI)	3.2

Risk Table	Cut-Off	Risk Before Screening	Risk After Screening
Early Onset Preeclampsia	1 in 50	1 in 87	1 in 18

Early Onset Preeclampsia Risk

Comments:
- Recommend immediate follow-up with increased monitoring.

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Test Parameters

Serum Markers	Value	MoM	Percentile
PlGF	30.2 pg/ml	0.62	10
PAPP-A	2649 mU/l	1.19	60
AFP	10.12 U/ml	0.95	50

Physical Markers	Value	MoM	Percentile
Mean Arterial Pressure (MAP)	110 mm Hg	1.24	99
Uterine Artery Doppler PI (UtAD-PI)	3.2	1.09	60

Sample Report: Increased Risk for Early Onset Preeclampsia

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Preeclampsia Screen ™ | T1 Report

Physician ID #: 24328
Physician Tel #: (000) 000-0000
OB SPECIALISTS
100 ANYWHERE ST
MELVILLE, NY 11747

Patient Name: INCRISK, MAPPI
Patient ID #: 13PED001084
Client ID #:
Date of Birth: 06/10/83 (age at EDC: 30)
CRL (mm): 50
Multi. Preg: No
Smoker: No

U/S Date: 02/04/13
GA @ U/S: 11w4d
Draw Date: 02/04/13
GA @ Draw: 11w4d (CRL)
MAP Date: 02/04/13
GA @ MAP: 11w4d
Date Received: 02/05/13
Report Date: 02/07/13

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Physical Markers	Value	MoM	Percentile
Mean Arterial Pressure (MAP)	110 mm Hg	1.24	99
Uterine Artery Doppler PI (UtAD-PI)	3.2	1.09	60

Risk Table
Early Onset Preeclampsia

Before
After
Risk:
1 in: 10,000

Comments:
- Recommend Immedi

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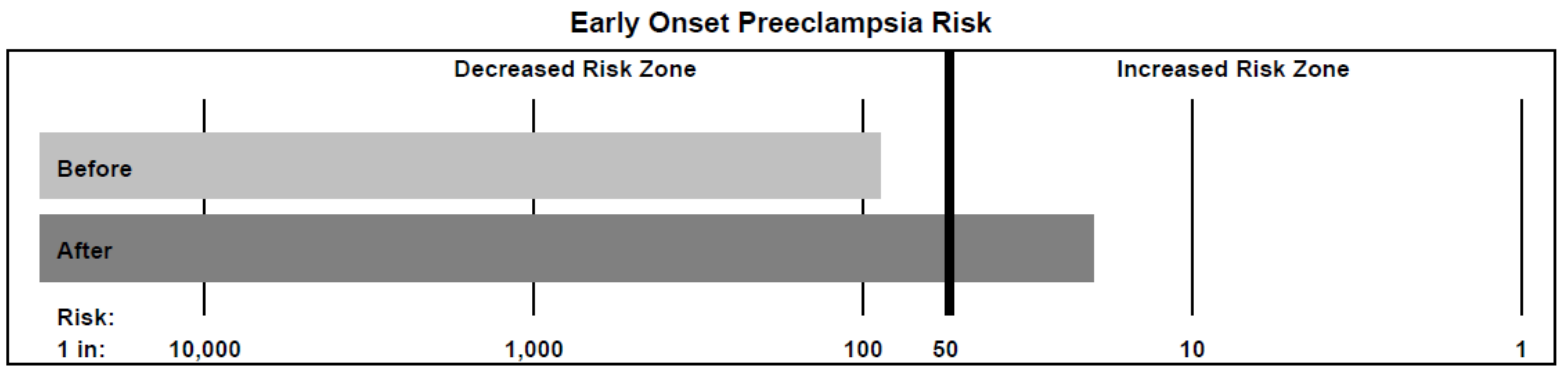
Risk Assessment

Risk Table	Cut-Off	Risk Before Screening	Risk After Screening	Result
Early Onset Preeclampsia	1 in 50	1 in 87	1 in 18	**INCREASED RISK**



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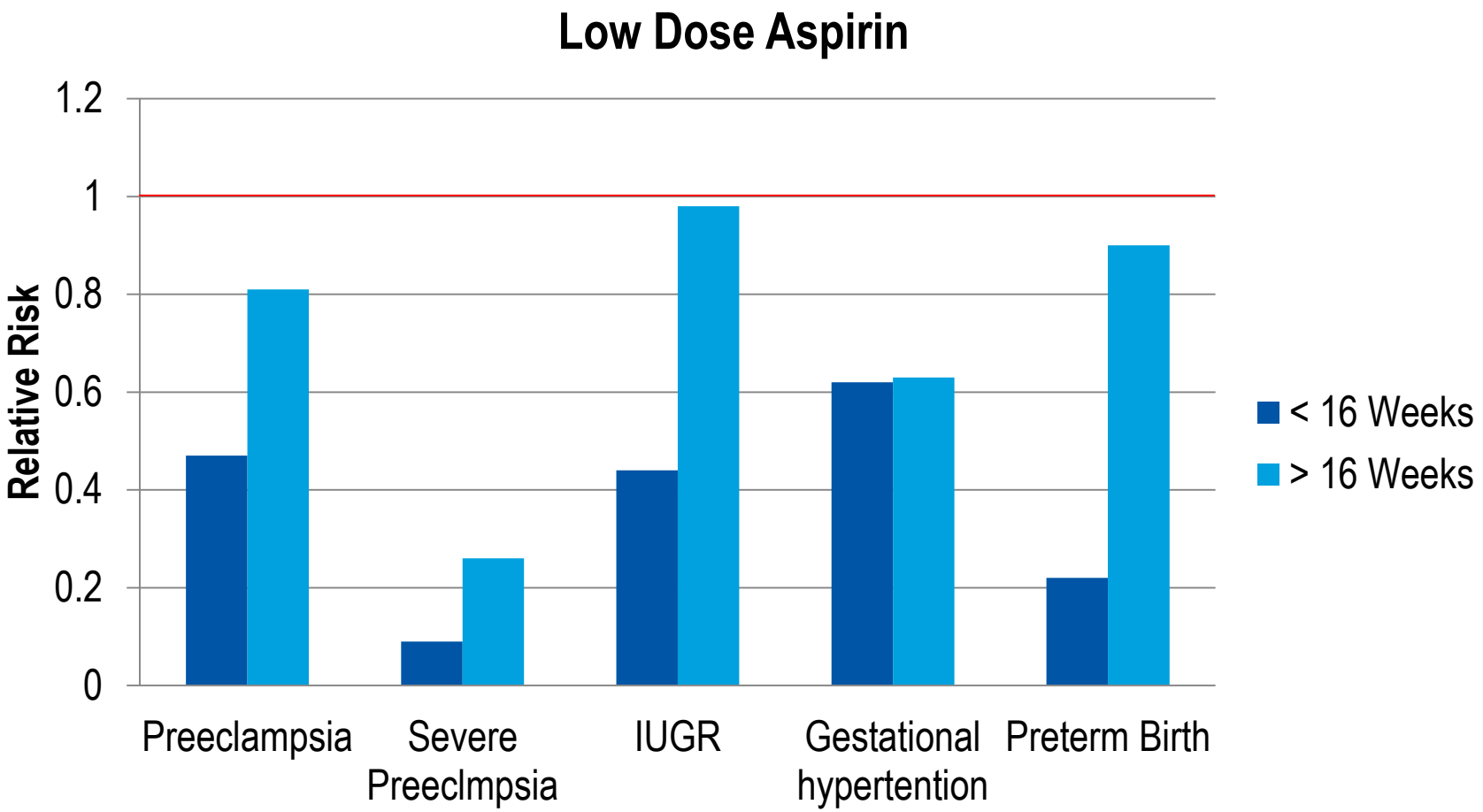
What Do You Do With Patients Identified As Increased Risk for Early Onset Preeclampsia?

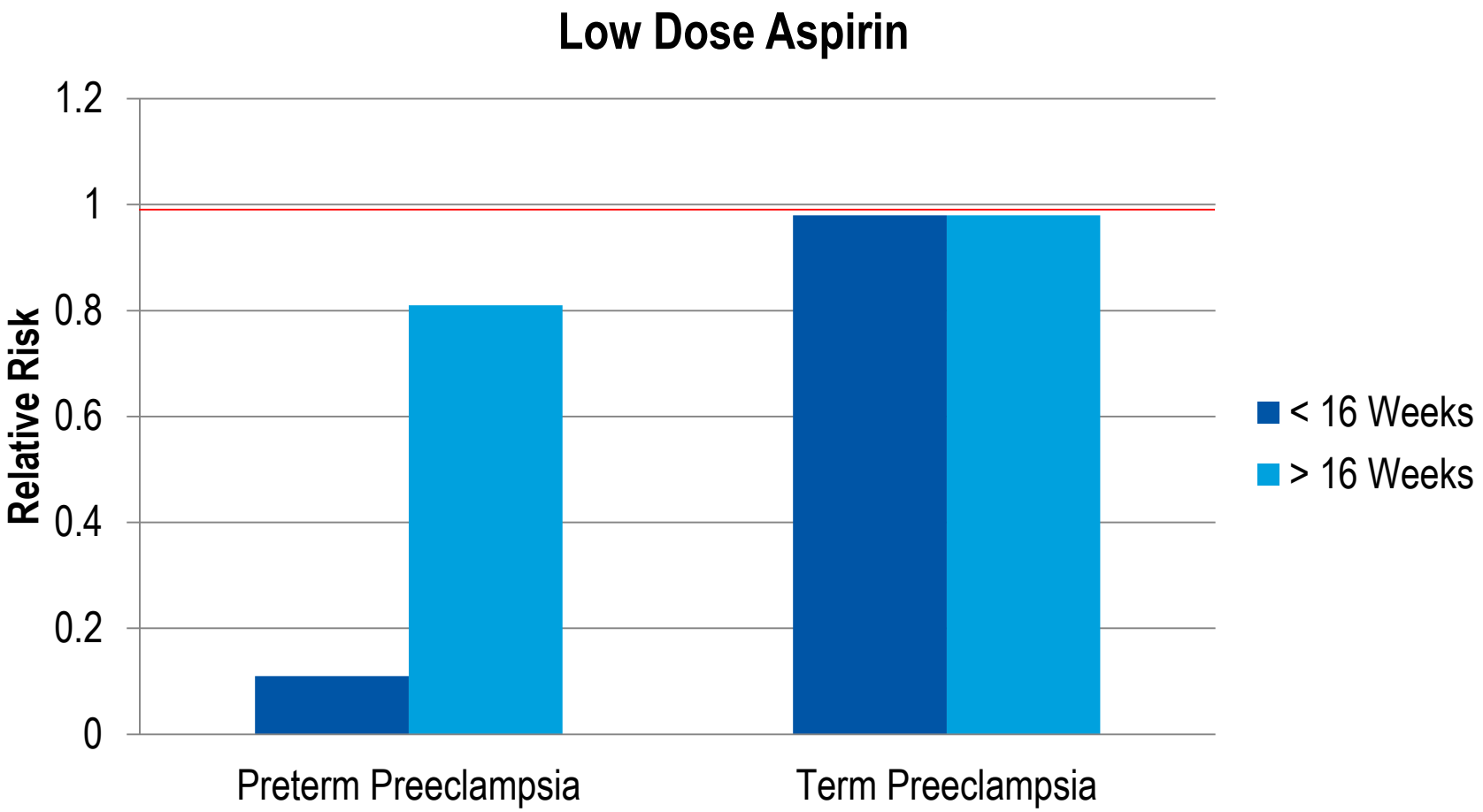
Aspirin Reduced Relative Risk of Adverse Outcomes



Severe Preeclamsia - severe hypertension (BP of at least 160 mmHg systolic or 110 mmHg diastolic or 105 mmHg diastolic), severe proteinuria (at least 2, 3, or 5 g of protein in 24 h or 3 on dipstick), reduced urinary volume (less than 400 to 500 mL in 24 h), neurologic disturbances such as headache and visual perturbations, upper abdominal pain, pulmonary edema, impaired liver function tests, high serum creatinine, low platelet count

Bujold E, et al. *Obstet Gynecol*. 2010 Aug;116(2 Pt 1):402-14

Aspirin in Term vs. Preterm Preeclampsia



Low-dose aspirin was defined as 50–150 mg of acetylsalicylic acid (ASA) daily, alone or in combination with < 300 mg of dipyridamole, another antiplatelet agent.
Preterm preeclampsia is defined by delivery of women with preeclampsia before 37 completed weeks of gestation

Roberge S, et.al *Fetal Diagn Ther* 2012;31:141–146

U.S. Preventative Services Task Force

- For asymptomatic pregnant women who are at high risk for preeclampsia prescribe low-dose (81 mg/d) aspirin after 12 weeks gestation

TABLE 2. CLINICAL RISK ASSESSMENT FOR PREECLAMPSIA*

Risk Level	Risk Factors	Recommendation
High†	History of preeclampsia, especially when accompanied by an adverse outcome Multifetal gestation Chronic hypertension Type 1 or 2 diabetes Renal disease Autoimmune disease (i.e., systemic lupus erythematous, antiphospholipid syndrome)	Recommend low-dose aspirin if the patient has ≥1 of these high-risk factors
Moderate‡	Nulliparity Obesity (body mass index >30 kg/m^2) Family history of preeclampsia (mother or sister) Sociodemographic characteristics (African American race, low socioeconomic status) Age ≥35 y Personal history factors (e.g., low birthweight or small for gestational age, previous adverse pregnancy outcome, >10-y pregnancy interval)	Consider low-dose aspirin if the patient has several of these moderate-risk factors§
Low	Previous uncomplicated full-term delivery	Do not recommend low-dose aspirin

* Includes only risk factors that can be obtained from the patient medical history. Clinical measures, such as uterine artery Doppler ultrasonography, are not included.

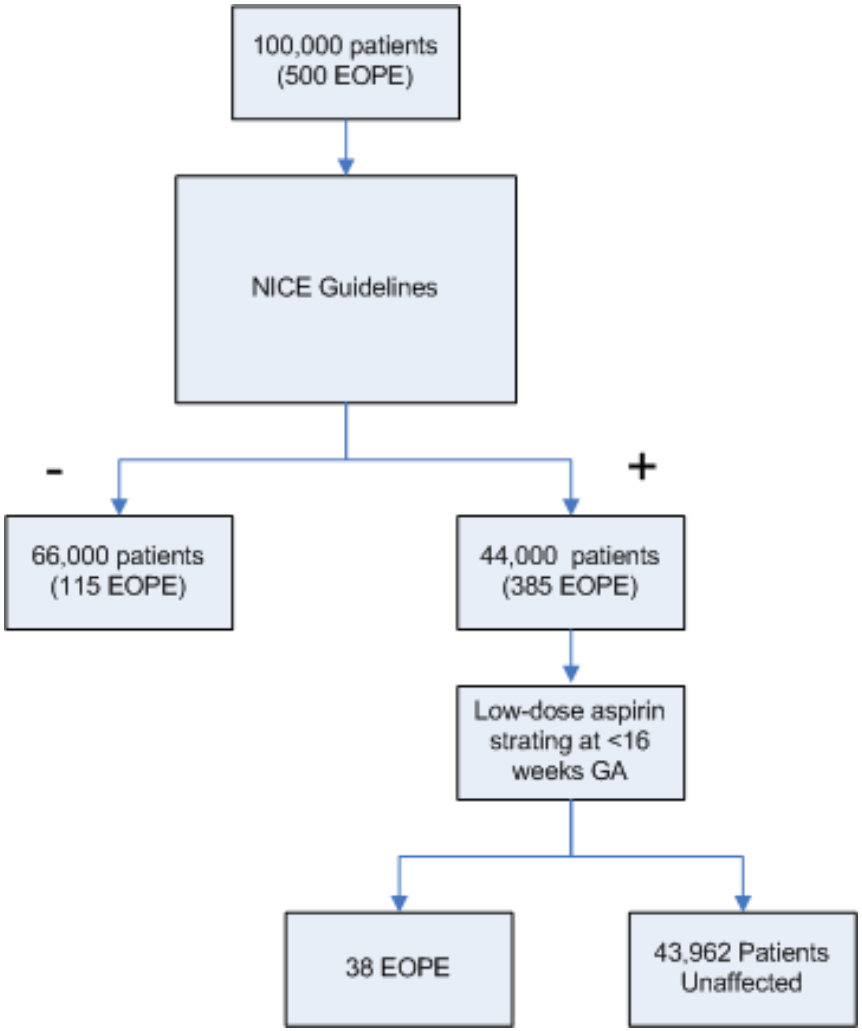
† Single risk factors that are consistently associated with the greatest risk for preeclampsia. The preeclampsia incidence rate would be approximately 8% in a pregnant woman with 1 of these risk factors (1, 5).

‡ A combination of multiple moderate-risk factors may be used by clinicians to identify women at high risk for preeclampsia. These risk factors are independently associated with moderate risk for preeclampsia, some more consistently than others (1).

§ Moderate-risk factors vary in their association with increased risk for preeclampsia.

1. LeFevre M Low Dose Aspirin Use for the Prevention of Morbidity and mortality from Preeclampsia. U.S. Preventative Services Task Force recommendation statement. *Ann. Intern. Med.* Doi.10.7326/M14-1884.

Preeclampsia Screening Based on Previous History and Clinical Risk Factors



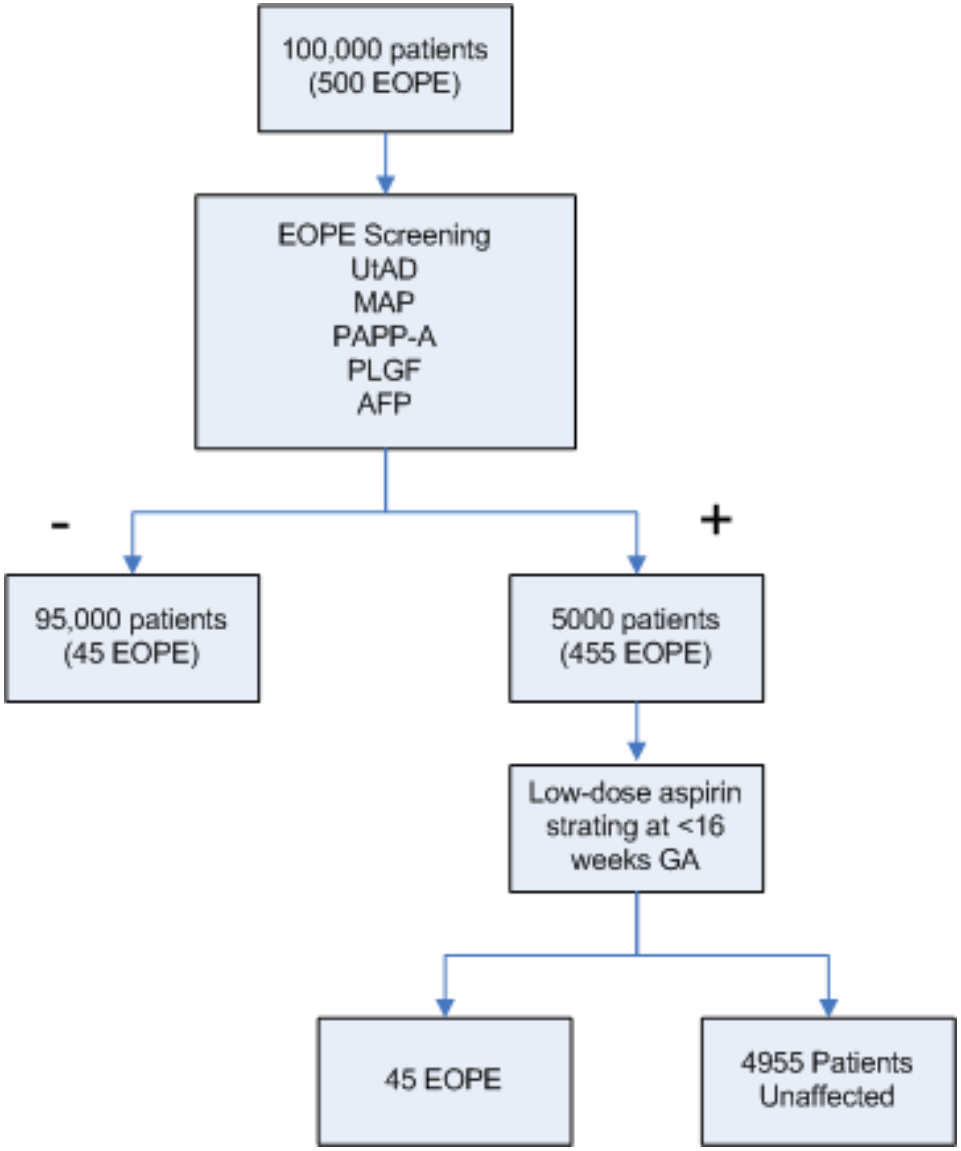
Screening/Treatment Parameters based on NICE Parameters

- 0.5% Incidence of EOPE
- 44% Screen Positive Rate
- 77% Detection Rate
- 90% Reduction in EOPE w/ LDA

69% Theoretical Reduction in Incidence of EOPE

347/500 EOPE cases prevented

Screening for Early Onset Preeclampsia in 100,000 Patients



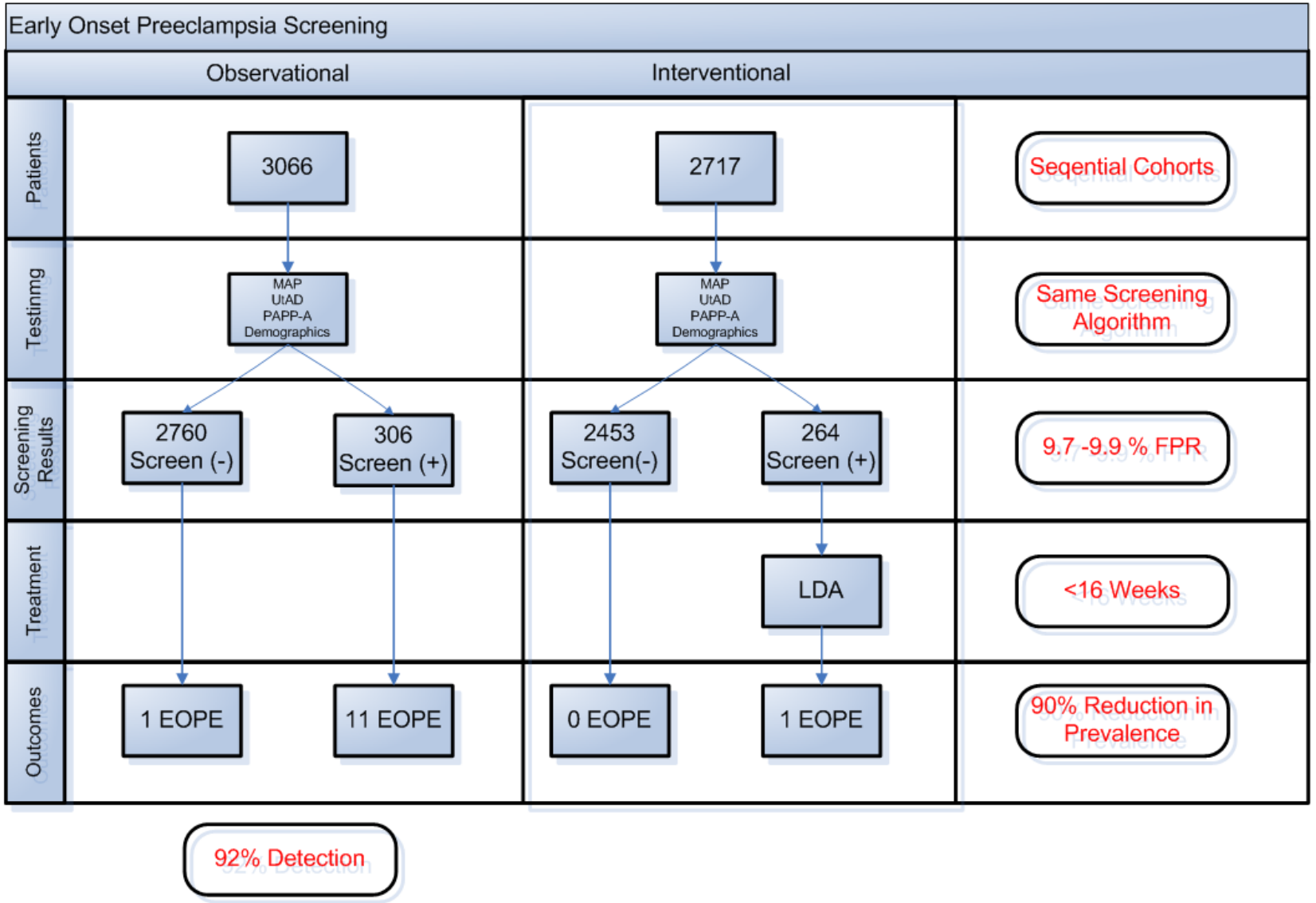
EOPE Screening/Treatment Parameters

- 0.5% Incidence of EOPE
- 5% Screen Positive Rate
- 91% Detection Rate
- 90% Reduction in EOPE w/ LDA

82% Theoretical Reduction in Incidence of EOPE

410/500 EOPE cases prevented)

Prediction and prevention of early onset pre-eclampsia: The impact of aspirin after first trimester screening



Park, F et. al. Obstet. Gynecol. doi: 10.1002/uog.14819

Conclusions

- **Early onset preeclampsia** is a serious complication of pregnancy
  - Multifactorial etiology beginning with abnormal placental implantation and shallow or absent trophoblast invasion of the spiral arteries
  - Associated with significant morbidity and mortality
- Number of therapeutic options for prevention of preeclampsia in high-risk women under investigation
  - Low-dose aspirin leading choice right now; should be administered <16 weeks gestation
- A variety of risk factors for preeclampsia are recognized
  - Screening strategies may assess maternal history, family history, pregnancy-related chemical biomarkers, changes in mean arterial pressure, and abnormalities on UtAD
  - Combination approaches most sensitive
- Opportunity to change treatment paradigms with an effective screening protocol for early onset PE
  - Better tailor treatment and allocate resources

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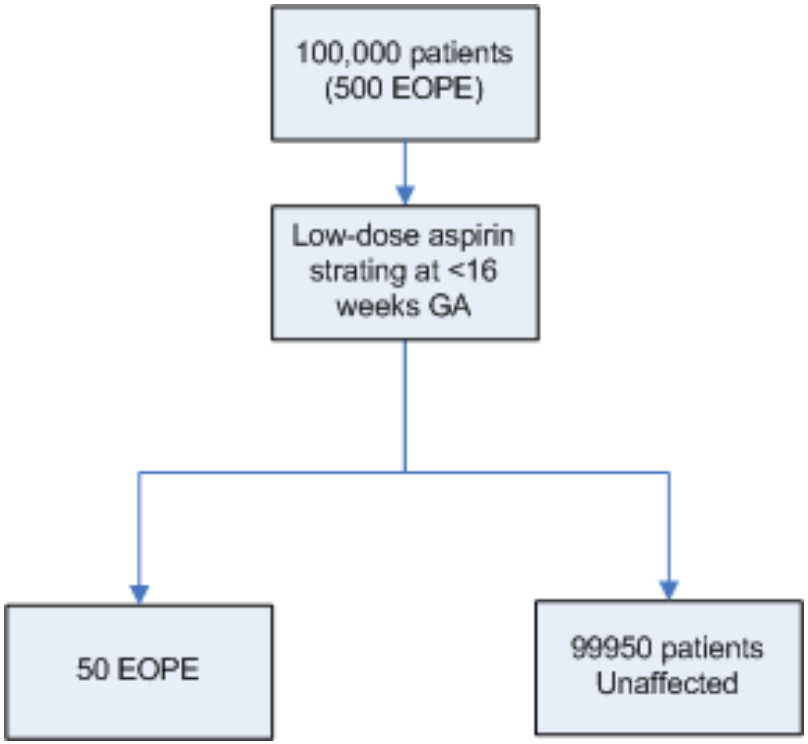
First Trimester Screening for Early Onset Preeclampsia

Thank You

Why Not Just Give Aspirin to All Pregnant Women?



- 90% Reduction in EOPE
- However, although aspirin is considered generally safe during pregnancy potentials risks include;
- Aspirin has not been formally assigned to pregnancy category by the FDA. However, aspirin is considered to be in pregnancy category D by the FDA if full dose aspirin is taken in the third trimester.