Biomarkers for Adverse Pregnancy Outcomes

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Pitfalls

- Noisy outcomes
- Two-step process
- Dynamic gestation
- Comparator
- Mechanisms

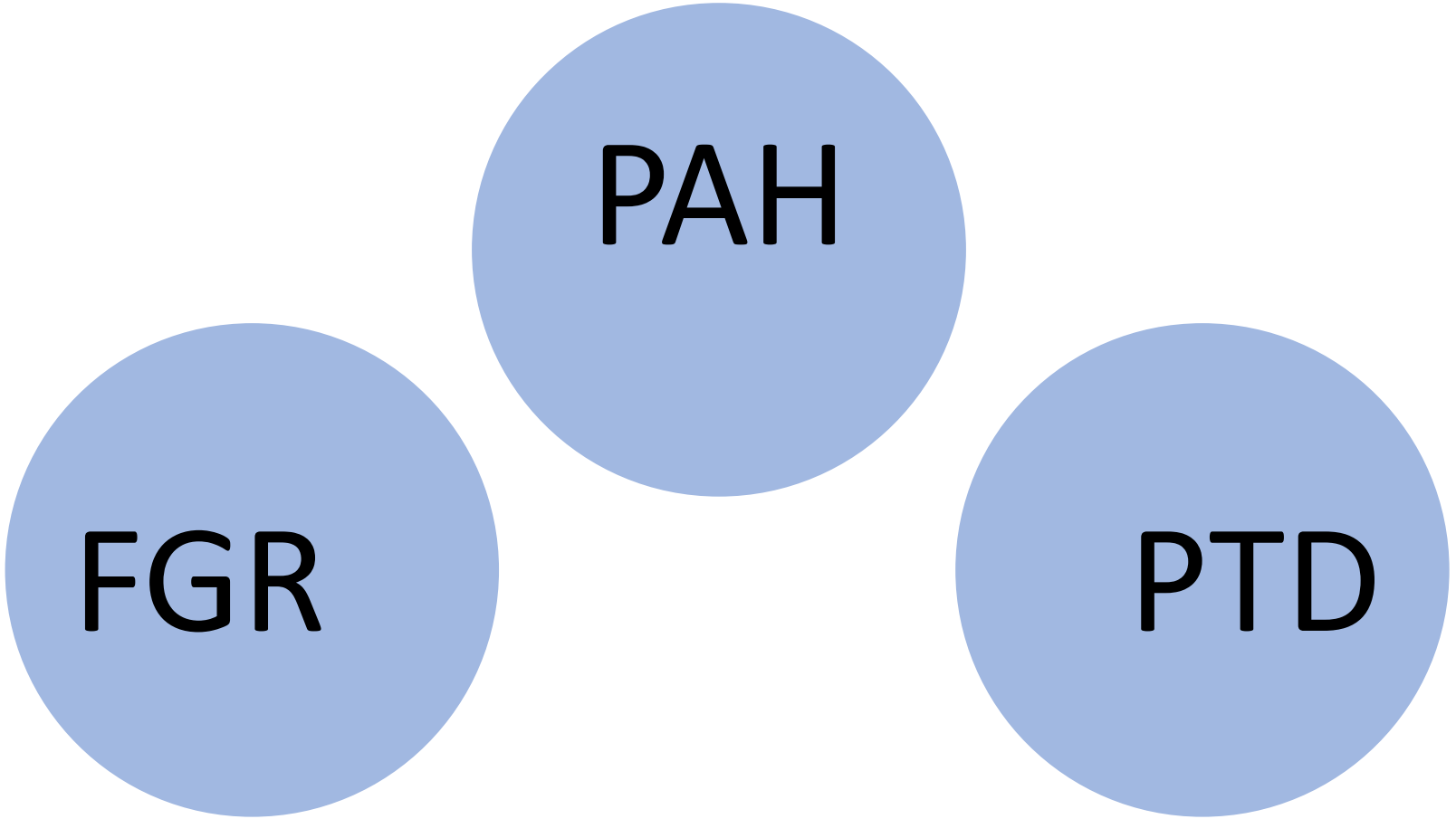
Challenges

- Noisy outcomes
- Two-step process
- Dynamic gestation
- Comparator
- Mechanisms

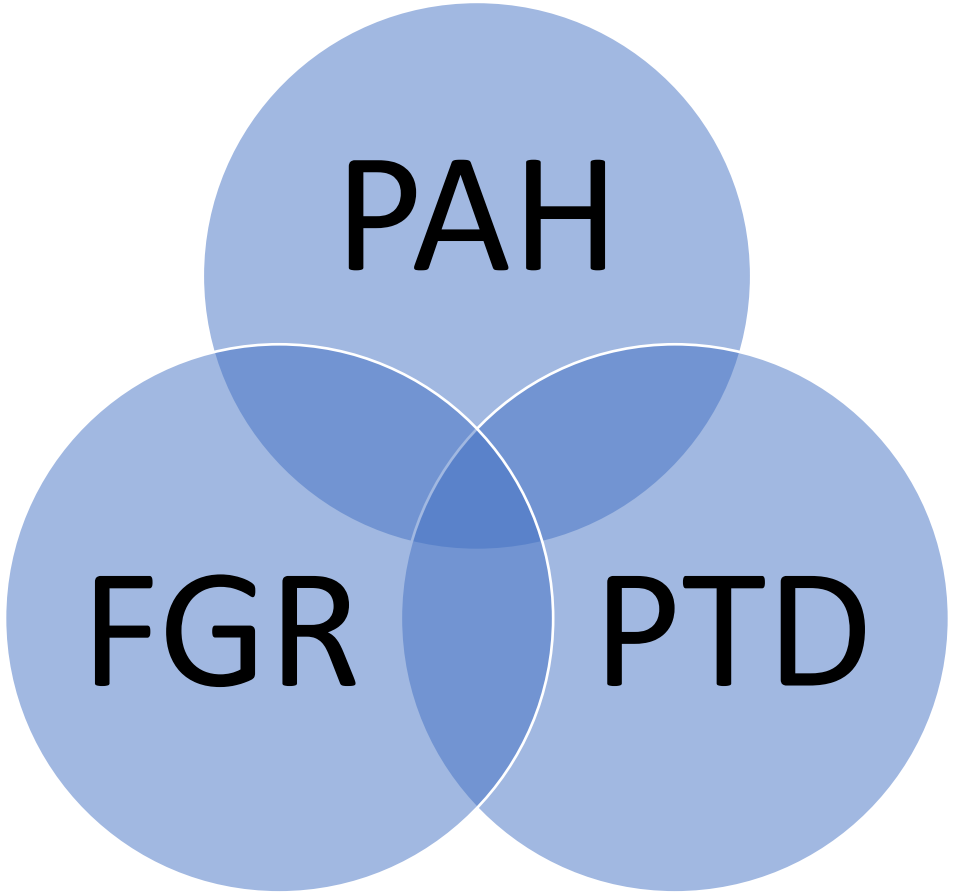
Noisy Outcomes

- Clinical judgment
  - Preeclampsia vs gestational hypertension vs superimposed preeclampsia
  - Preeclampsia with severe features
  - Spontaneous preterm labor vs indicated preterm delivery
  - PPROM vs preterm contractions
  - Nomogram for fetal growth restriction
- Frequently combination of APOs

Combination of APOs



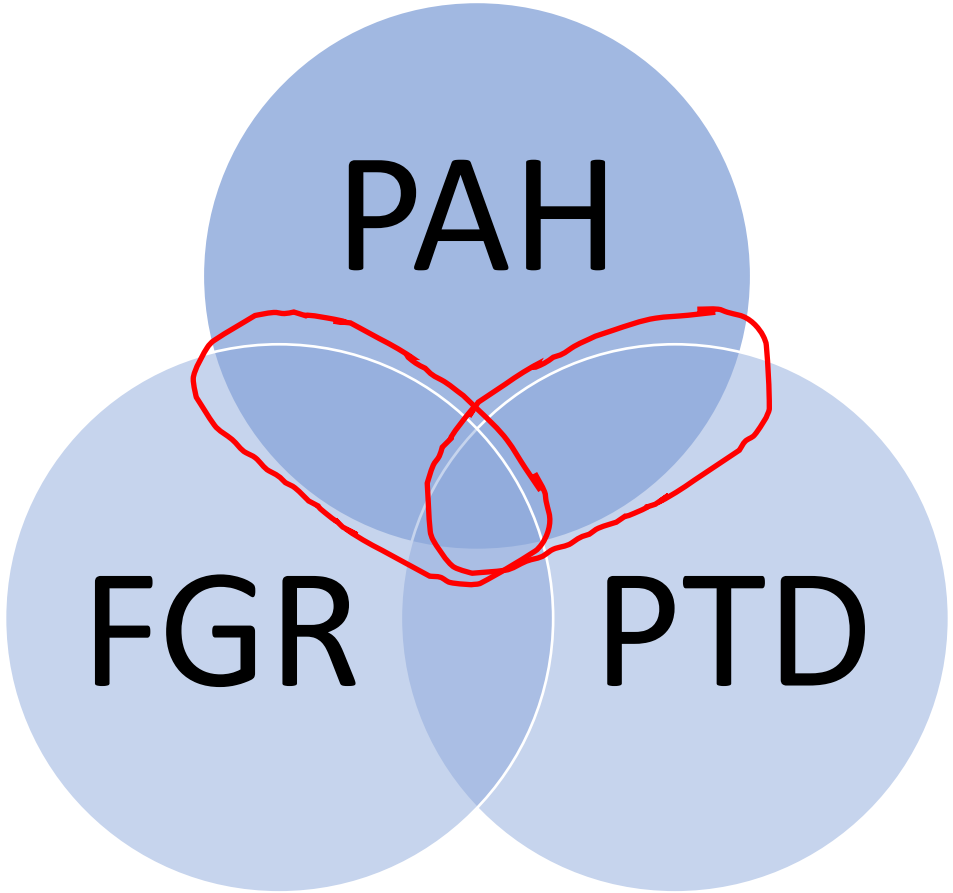
Combination of APOs



Combination of APOs

FGR PTD

Combination of APOs

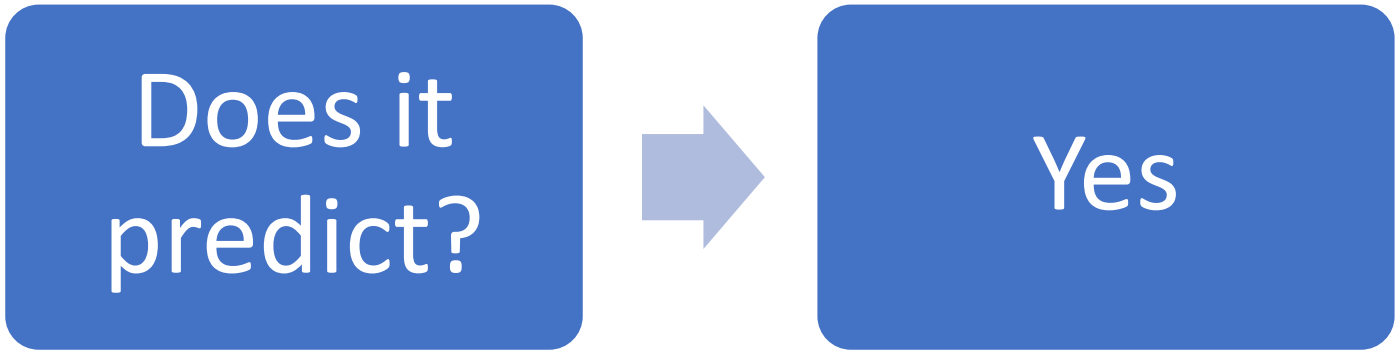


Two-Step Process

Two-Step Process

Does it predict?

Two-Step Process



Two-Step Process

Two-Step Process

Clinical Utility

- Benefit
  - Prevent adverse outcome
  - Decrease cost
  - Improve satisfaction
- Unintended consequences
  - Increased resource utilization
  - Preterm delivery
  - Increased cost

Unintended Consequences

MONITORING WOMEN AT RISK FOR PRETERM LABOR

DONALD C. DYSON, M.D., KAREN H. DANBE, M.S.N., JUDITH A. BAMBER, M.S.N., YVONNE M. CRITES, M.D., D. ROBIN FIELD, M.D., JEFFREY A. MAIER, M.D., LAWRENCE A. NEWMAN, M.D., DEBORAH A. RAY, M.D., DAVID L. WALTON, M.D., AND MARY ANNE ARMSTRONG, M.A.

OUTCOME	ALL WOMEN (N=2422)			WOMEN WITH TWIN PREGNANCIES (N=844)		
	WEEKLY CONTACT (N=798)	DAILY CONTACT (N=796)	HOME MONITORING (N=828)	WEEKLY CONTACT (N=280)	DAILY CONTACT (N=277)	HOME MONITORING (N=287)
Preterm birth (%)						
<37 wk	30	31	30	49	54	51
<35 wk	14	13	14	22	24	24
<32 wk	4	5	4	7	9	6
Birth weight						
<1500 g	4	4	4	6	8	9
<2500 g	26	26	28	52	55	59
No. of unscheduled visits*†	1.2±1.5	1.8±2.0	2.3±2.3	1.3±1.5	1.9±2.0	2.5±2.4
Prophylactic tocolytic-drug therapy (%)†	12‡	14‡	19‡	8‡	11	16‡
Preterm labor <35 wk (%)	23	22	27	35	34	40

(N Engl J Med 1998;338:15-9.)

Unintended Consequences

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Development and validation of a spontaneous preterm delivery predictor in asymptomatic women

George R. Saade, MD; Kim A. Boggess, MD; Scott A. Sullivan, MD; Glenn R. Markenson, MD; Jay D. Iams, MD; Dean V. Coonrod, MD; Leonardo M. Pereira, MD; M. Sean Esplin, MD; Larry M. Cousins, MD; Garrett K. Lam, MD; Matthew K. Hoffman, MD; Robert D. Severinsen, BS; Trina Pugmire, BS; Jeff S. Flick, PhD; Angela C. Fox, MS; Amir J. Lueth, MPH; Sharon R. Rust, BS; Emanuele Mazzola, PhD; ChienTing Hsu, MS; Max T. Dufford, BS; Chad L. Bradford, MS; Ilia E. Ichetovkin, PhD; Tracey C. Fleischer, PhD; Ashoka D. Polpitiya, DSc; Gregory C. Critchfield, MD; Paul E. Kearney, PhD; J. Jay Boniface, PhD; Durlin E. Hickok, MD

Performance of IBP4/SHBG predictor

GA boundary	AUC (95% CI)	Sensitivity	Specificity	OR (95% CI)
<37 vs ≥ 37	0.75 (0.56–0.91)	0.75	0.74	5.04 (1.4–18)
<36 vs ≥ 36	0.79 (0.53–0.99)	0.83	0.83	17.33 (2.2–138)
<35 vs ≥ 35	0.93 (0.81–1.00)	1	0.83	34.47 (1.7–699)

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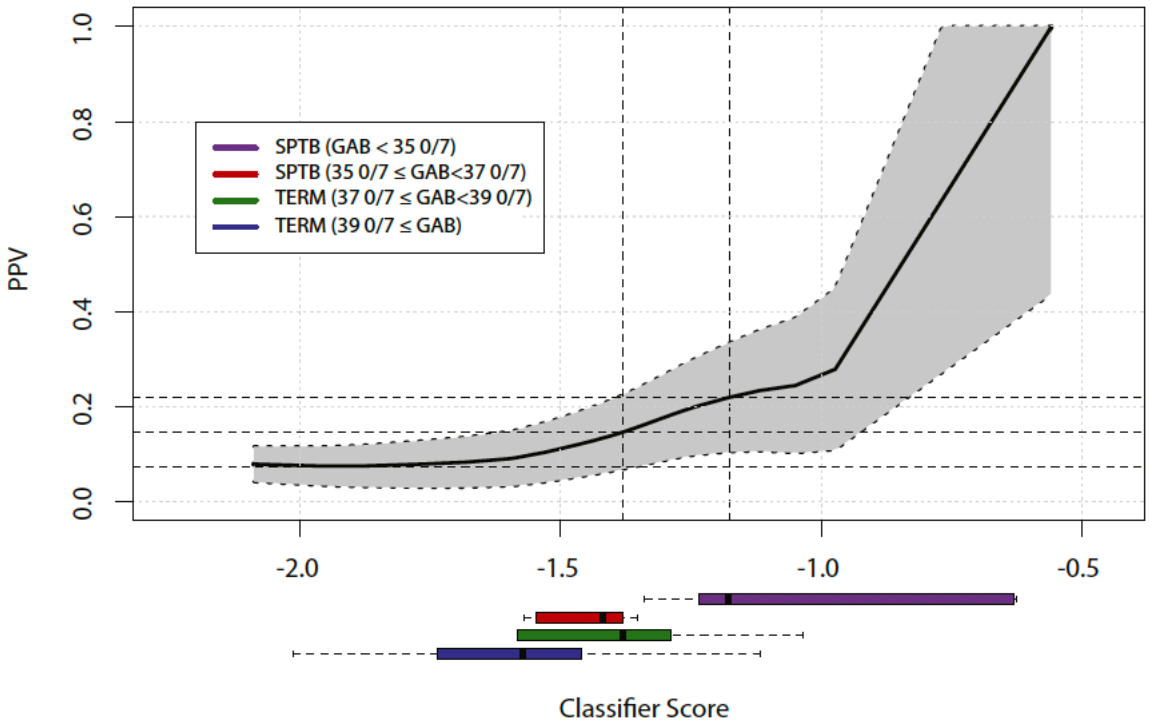

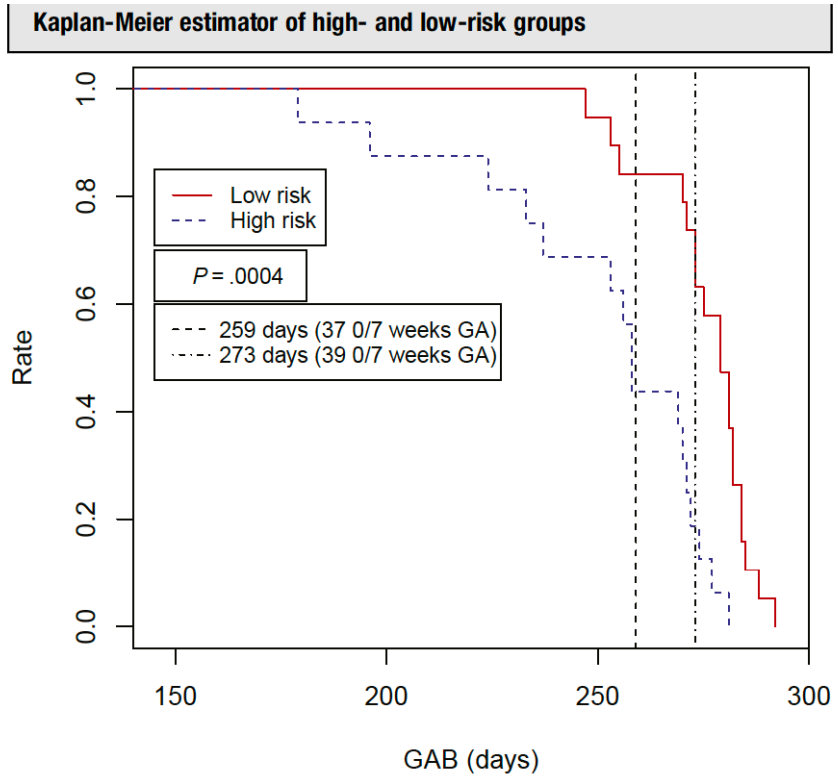

Prediction and Prevention of Preterm Birth: A Prospective, Randomized Intervention Trial

D. Ware Branch, MD[1] John M. VanBuren, PhD[2] T. Flint Porter, MD[1] Calla Holmgren, MD[1]
Richard Holubkov, PhD[2] Kent Page, MStat[2] Julja Burchard, MS[3] Garrett K. Lam, MD[4]
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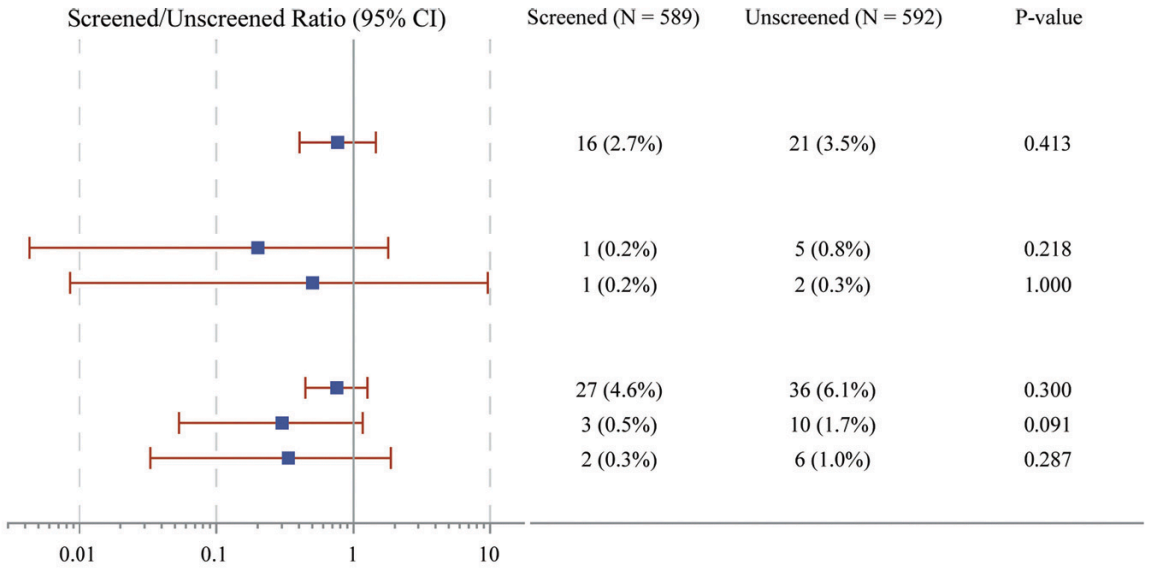
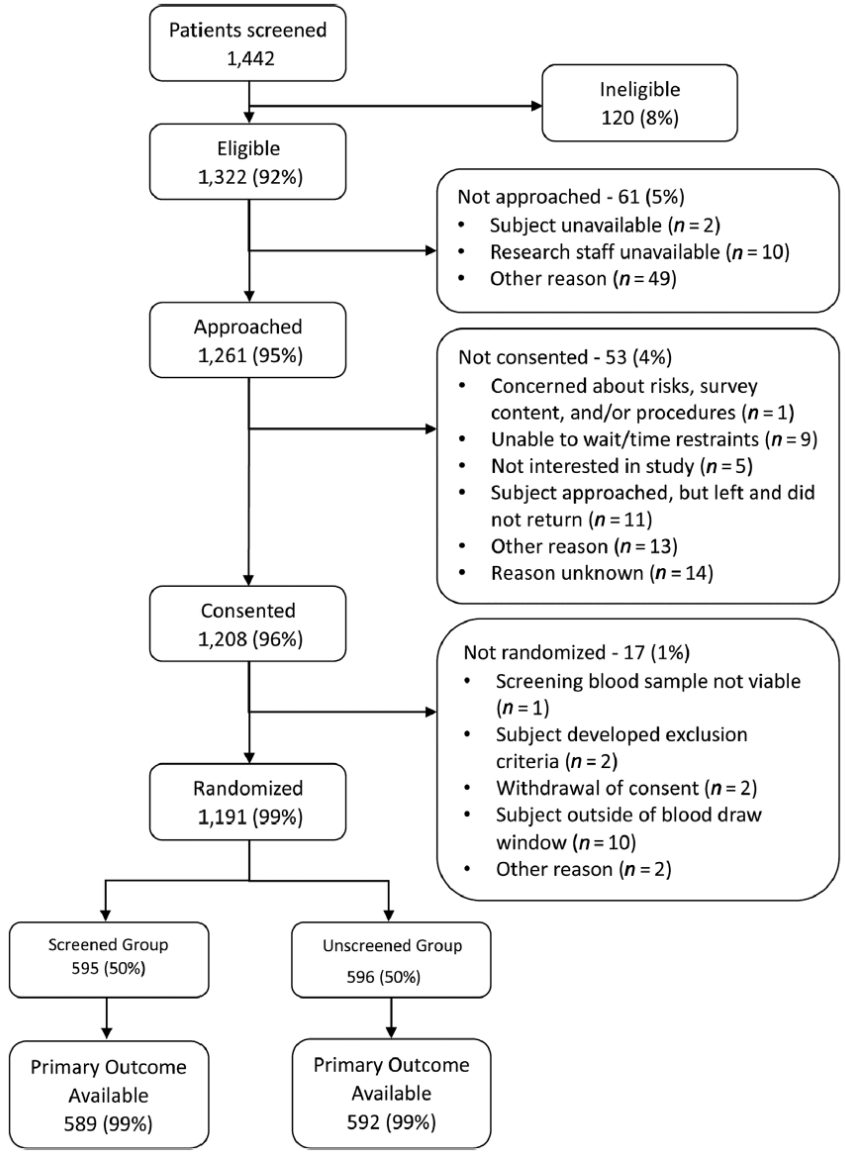


	Screened (N = 589)	Unscreened (N = 592)	P-value
Primary Efficacy Outcome:			
Spontaneous preterm birth (sPTB)			
< 37 weeks[1]	16 (2.7%)	21 (3.5%)	0.413
Exploratory Assessments:			
sPTB using Alternate Cutoffs			
< 35 weeks[2]	1 (0.2%)	5 (0.8%)	0.218
< 32 weeks[2]	1 (0.2%)	2 (0.3%)	1.000
Exploratory Assessments:			
Any preterm birth (PTB) using Various Cutoffs			
< 37 weeks[2]	27 (4.6%)	36 (6.1%)	0.300
< 35 weeks[2]	3 (0.5%)	10 (1.7%)	0.091
< 32 weeks[2]	2 (0.3%)	6 (1.0%)	0.287



Am J Perinatol 2023;40:1071–1080.

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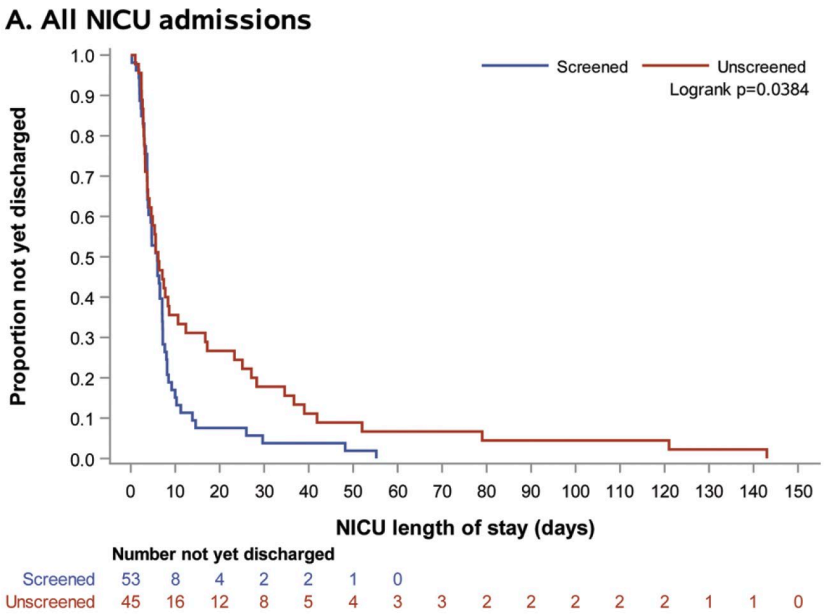

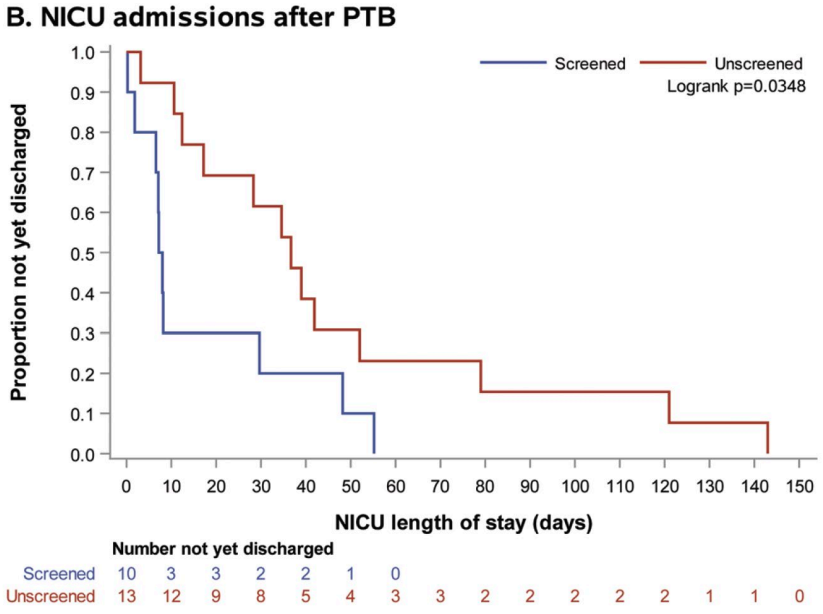

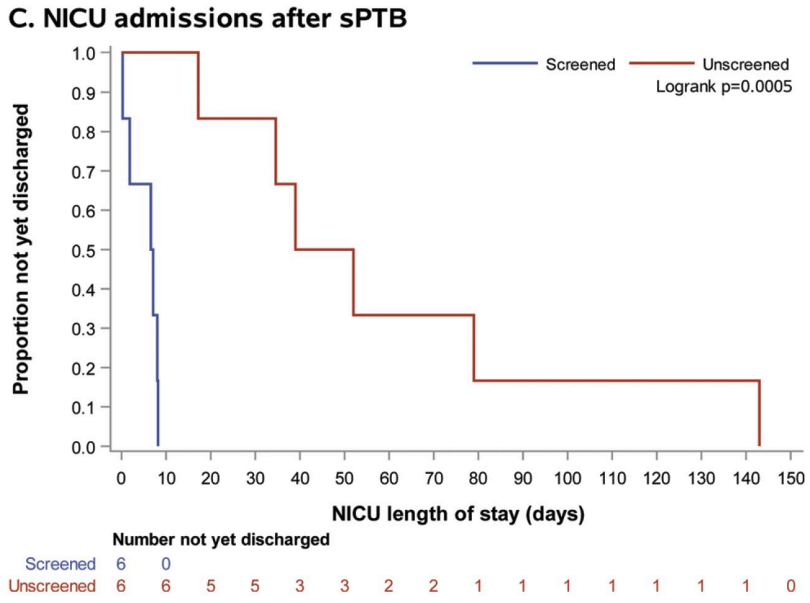

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Clinical Utility

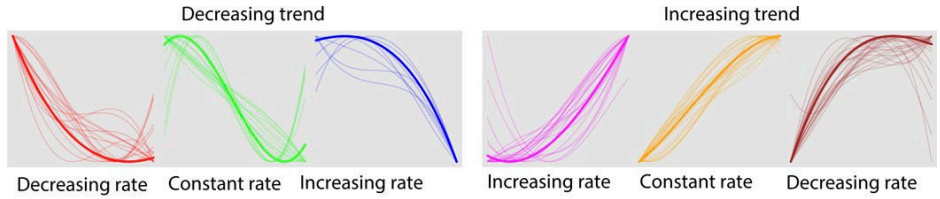
- Costly trials and limited resources
- No intervention proven to prevent outcome
- Balance benefit vs risk
  - Positive finding may lead to unnecessary interventions
  - Negative finding may lead to complacency
- Indication creep

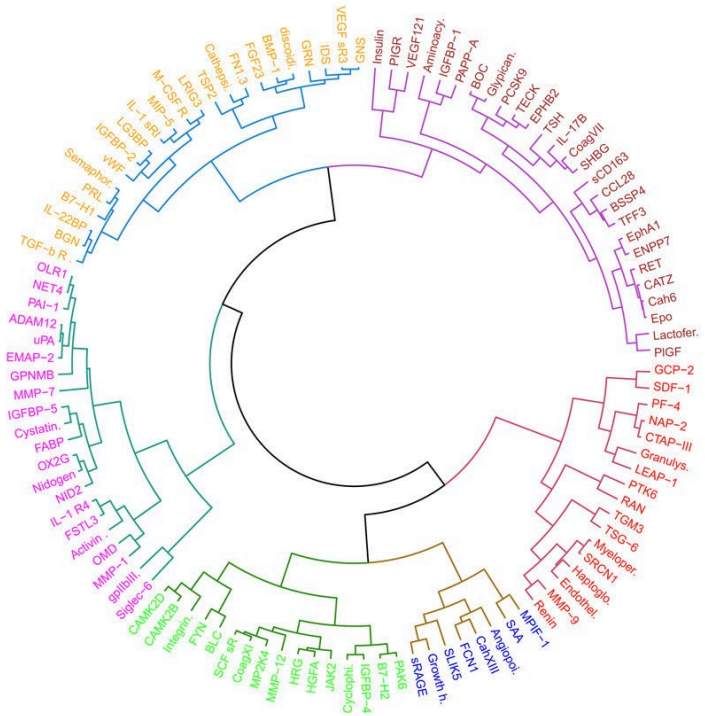
Dynamic Gestation

- Gestational changes in the biomarker
- Symptomatic versus asymptomatic
- Impact of clinical management
- Gestational dating
  - Affects interpretation of the results
  - Affects outcome

The Maternal Plasma Proteome Changes as a Function of Gestational Age in Normal Pregnancy: a Longitudinal Study

Roberto Romero, MD, D.Med.Sci.[1,2,3,4], **Offer Erez, MD**[1,5], **Eli Maymon, MD**[1,5], **Piya Chaemsaithong, MD**[1,5], **Zhonghui Xu, MSc**[1], **Percy Pacora, MD**[1,5], **Tinnakorn Chaiworapongsa, MD**[1,5], **Bogdan Done, MD**[1], **Sonia S. Hassan, MD**[1,5], and **Adi L. Tarca, PhD**[1,5]





Am J Obstet Gynecol 2017; 217:67.e1–67.e21.

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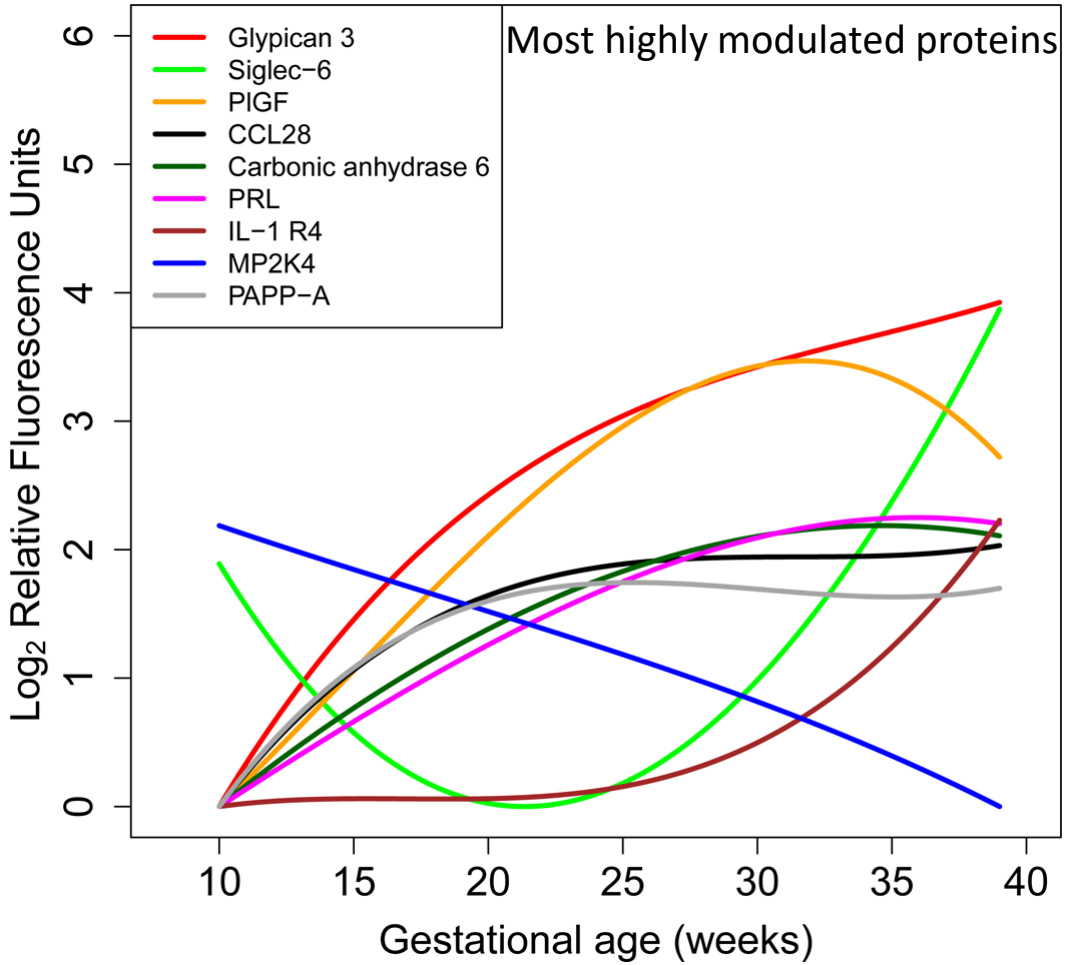

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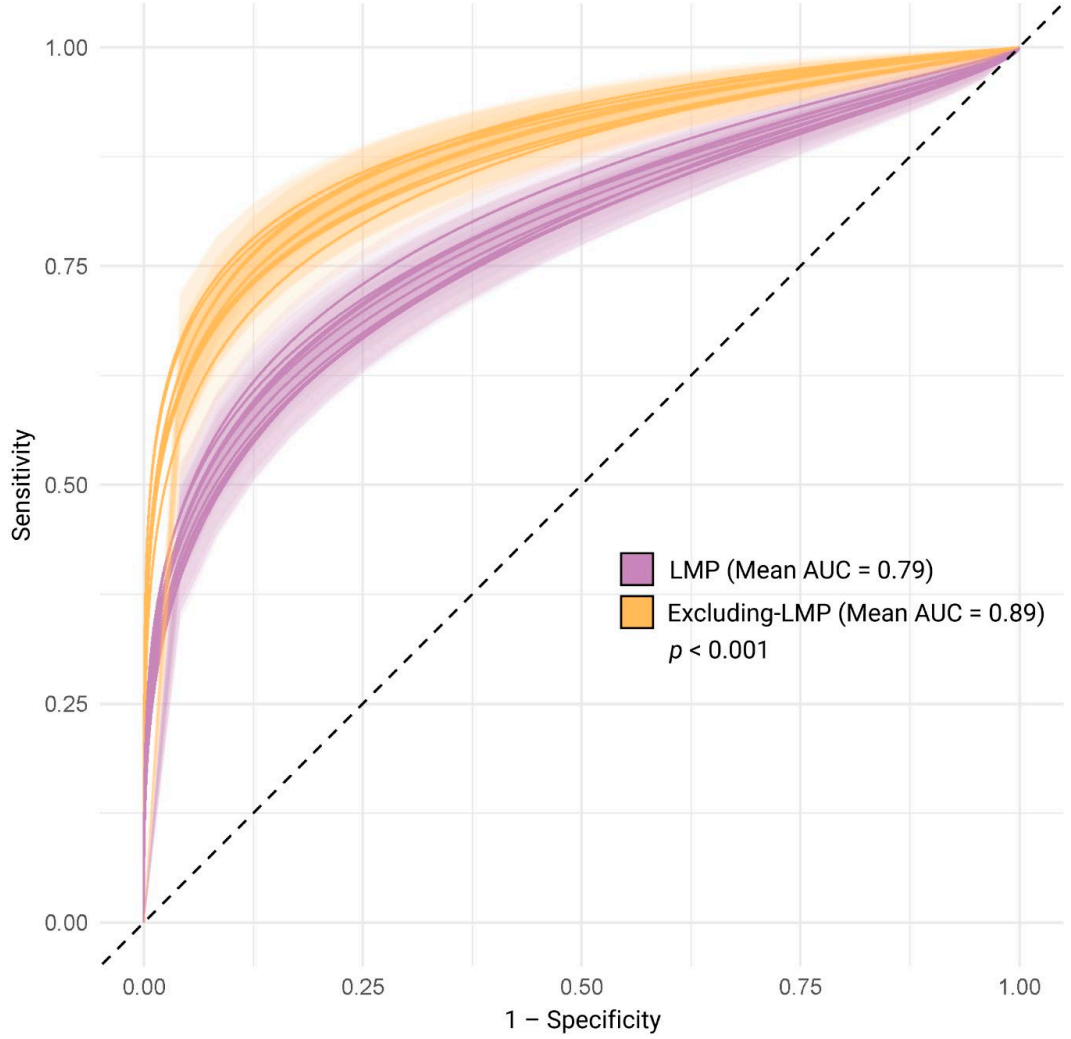
Better Estimation of Spontaneous Preterm Birth Prediction Performance through Improved Gestational Age Dating

Julja Burchard [1,*], George R. Saade [2], Kim A. Boggess [3], Glenn R. Markenson [4], Jay D. Iams [5], Dean V. Coonrod [6], Leonardo M. Pereira [7], Matthew K. Hoffman [8], Ashoka D. Polpitiya [1], Ryan Treacy [1], Angela C. Fox [1], Todd L. Randolph [1], Tracey C. Fleischer [1], Max T. Dufford [1], Thomas J. Garite [1], Gregory C. Critchfield [1], J. Jay Boniface [1] and Paul E. Kearney [1]



J. Clin. Med. 2022, 11, 2885

Comparator

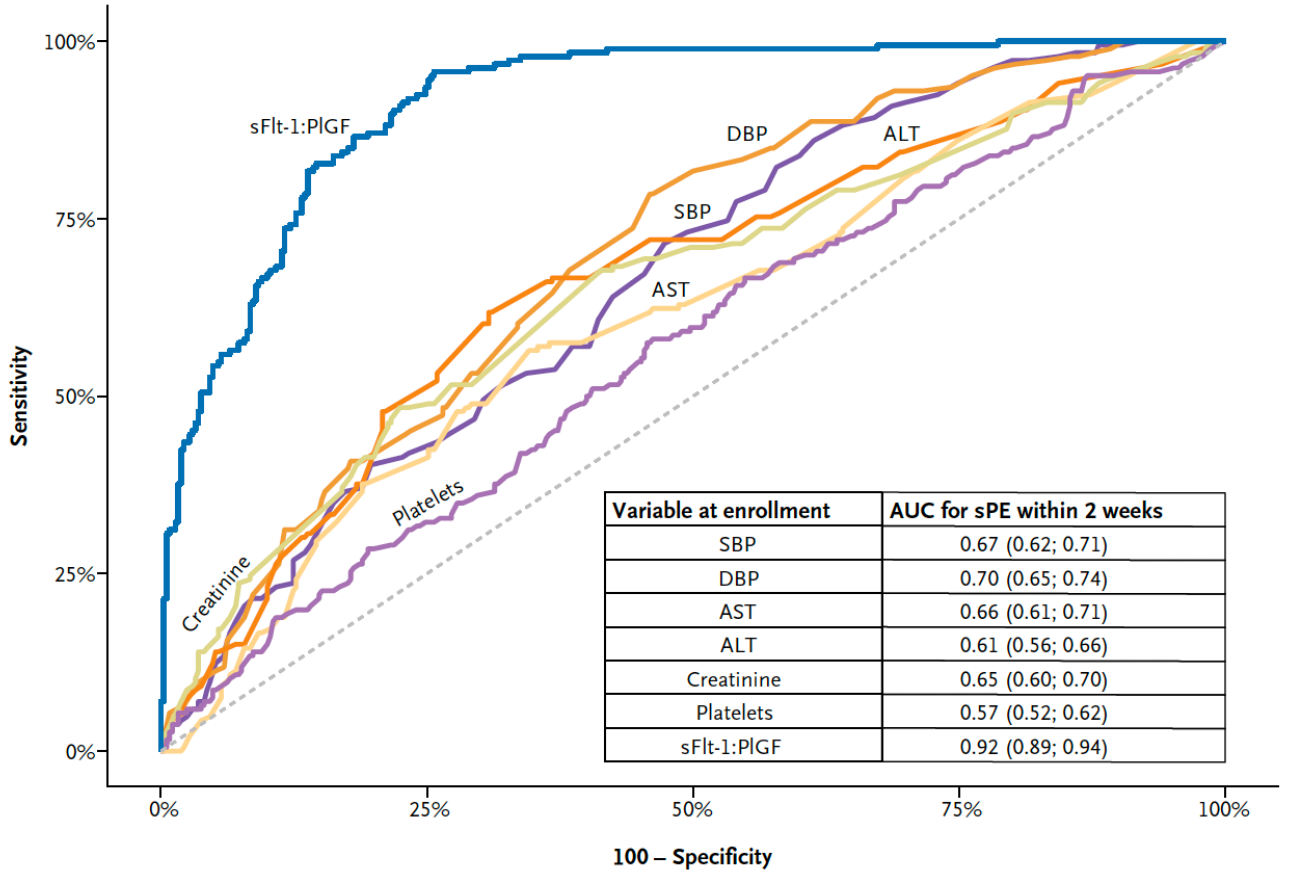
- Clinical factors most common
- Variability in comparator
  - Generalizability
  - Definitions
- When is comparator applied

NEJM Evidence

Circulating Angiogenic Factor Levels in Hypertensive Disorders of Pregnancy

Published November 9, 2022
NEJM Evid 2022; 1 (12)
DOI: 10.1056/EVIDoa2200161

Ravi Thadhani, M.D., M.P.H.,[1,2] Elizabeth Lemoine, M.D.,[1,3] Sarosh Rana, M.D., M.P.H.,[4] Maged M. Costantine, M.D.,[5] Vinicius F. Calsavara, Ph.D.,[1] Kim Boggess, M.D.,[3] Blair J. Wylie, M.D., M.P.H.,[6] Tiffany A. Moore Simas, M.D., M.P.H., M.Ed.,[7] Judette M. Louis, M.D., M.P.H.,[8] Jimmy Espinoza, M.D., M.Sc.,[9] Stephanie L. Gaw, M.D., Ph.D.,[10] Amy Murtha, M.D.,[10] Samantha Wiegand, M.D.,[11] Yvonne Gollin, M.D.,[12] Deepjot Singh, M.D., M.M.M.,[13] Robert M. Silver, M.D.,[14] Danielle E. Durie, M.D., M.P.H.,[15] Britta Panda, M.D.,[16] Errol R. Norwitz, M.D., Ph.D.,[16,17] Irina Burd, M.D., Ph.D.,[18] Beth Plunkett, M.D., M.P.H.,[19] Rachel K. Scott, M.D., M.P.H.,[20] Anna Gaden, B.S.,[1] Martha Bautista, B.S.,[1] Yuchiao Chang, Ph.D.,[2] Marcio A. Diniz, Ph.D.,[1] S. Ananth Karumanchi, M.D.,[1] and Sarah Kilpatrick, M.D., Ph.D.[1]



Variable at enrollment	AUC for sPE within 2 weeks
SBP	0.67 (0.62; 0.71)
DBP	0.70 (0.65; 0.74)
AST	0.66 (0.61; 0.71)
ALT	0.61 (0.56; 0.66)
Creatinine	0.65 (0.60; 0.70)
Platelets	0.57 (0.52; 0.62)
sFlt-1:PlGF	0.92 (0.89; 0.94)

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Table 2. Demographic and Clinical Characteristics of the Primary Study Population (Validation Cohort).*

Characteristic	All (N=556)	No Severe Features (n=370)	Severe Features (n=186)
Baseline and enrollment			
Age — yr	31.7±5.8	32.3±5.6	30.5±6.1
Race			
Asian	33 (5.9)	21 (5.7)	12 (6.5)
Black/African American	169 (30.4)	120 (32.4)	49 (26.3)
White/Caucasian	296 (53.2)	199 (53.8)	97 (52.2)
Ethnicity			
Hispanic	90 (16.2)	56 (15.1)	34 (18.3)
Parity			
Nulliparous	157 (28.2)	83 (22.4)	74 (39.8)
First-trimester BMI	35.2±11.4	35.7±12.0	34.2±10.0
Current smoker	47 (8.5)	32 (8.7)	15 (8.1)
Outpatient ASA in pregnancy	253 (45.5)	181 (48.9)	72 (38.7)
Gestational age at enrollment — wk	30.4±3.1	30.6±3.1	30.1±3.1
Highest systolic blood pressure at enrollment — mm Hg	158.5±19.9	154.7±19.8	166.0±18.0
Highest diastolic blood pressure at enrollment — mm Hg	94.8±13.0	92.1±13.5	100.1±10.3
Creatinine at enrollment — mg/dl	0.6±0.2	0.6±0.2	0.7±0.2
AST at enrollment — U/l	20.9±16.3	20.0±18.6	22.6±10.6
ALT at enrollment — U/l	20.5±38.6	21.5±47.5	18.6±11.2
Platelets at enrollment — $\times 10^3/\mu l$	252.9±71.6	256.7±70.6	245.7±73.3
Highest urine protein: creatinine at enrollment	1.0±2.1	0.7±1.8	1.5±2.5
Study period and delivery†			
Highest systolic blood pressure — mm Hg	158.0±20.3	150.8±18.5	172.1±15.6
Highest diastolic blood pressure — mm Hg	94.9±13.8	90.1±11.9	104.4±12.2
Creatinine — mg/dl	0.7±0.2	0.6±0.2	0.7±0.3
AST — U/l	34.3±52.2	23.4±24.4	49.5±73.0
ALT — U/l	34.1±64.7	28.1±67.4	42.5±59.8
Platelets — $\times 10^3/\mu l$	234.1±72.1	244.3±68.9	218.8±74.4
Gestational age at delivery — wk	33.8±3.3	35.0±2.7	31.4±3.1
Neonatal weight at birth — g	2193.3±887.5	2508.3±781.5	1568.5±743.9

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NEJM Evidence

Circulating Angiogenic Factor Levels in Hypertensive Disorders of Pregnancy

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Table 2. Demographic and Clinical Characteristics of the Primary Study Population (Validation Cohort).*

Characteristic	All (N=556)	No Severe Features (n=370)	Severe Features (n=186)
Baseline and enrollment			
Age — yr	31.7±5.8	32.3±5.6	30.5±6.1
Race			
Asian	33 (5.9)	21 (5.7)	12 (6.5)
Black/African American	169 (30.4)	120 (32.4)	49 (26.3)
White/Caucasian	296 (53.2)	199 (53.8)	97 (52.2)
Ethnicity			
Hispanic	90 (16.2)	56 (15.1)	34 (18.3)
Parity			
Nulliparous	157 (28.2)	83 (22.4)	74 (39.8)
First-trimester BMI	35.2±11.4	35.7±12.0	34.2±10.0
Current smoker	47 (8.5)	32 (8.7)	15 (8.1)
Outpatient ASA in pregnancy	253 (45.5)	181 (48.9)	72 (38.7)
Gestational age at enrollment — wk	30.4±3.1	30.6±3.1	30.1±3.1
Highest systolic blood pressure at enrollment — mm Hg	158.5±19.9	154.7±19.8	166.0±18.0
Highest diastolic blood pressure at enrollment — mm Hg	94.8±13.0	92.1±13.5	100.1±10.3
Creatinine at enrollment — mg/dl	0.6±0.2	0.6±0.2	0.7±0.2
AST at enrollment — U/l	20.9±16.3	20.0±18.6	22.6±10.6
Study period and delivery†			
Highest systolic blood pressure — mm Hg	158.0±20.3	150.8±18.5	172.1±15.6
Highest diastolic blood pressure — mm Hg	94.9±13.8	90.1±11.9	104.4±12.2
Creatinine — mg/dl	0.7±0.2	0.6±0.2	0.7±0.3
AST — U/l	34.3±52.2	23.4±24.4	49.5±73.0
ALT — U/l	34.1±64.7	28.1±67.4	42.5±59.8
Platelets — $\times 10^3/\mu l$	234.1±72.1	244.3±68.9	218.8±74.4
Neonatal weight at birth — g	2193.3±887.5	2508.3±781.5	1568.5±743.9

Mechanisms of APOs

- Unknown for almost all APOs
- Syndromes or phenotypes of a single mechanism

Early pathways, biomarkers, and four distinct molecular subclasses of preeclampsia: The intersection of clinical, pathological, and high-dimensional biology studies

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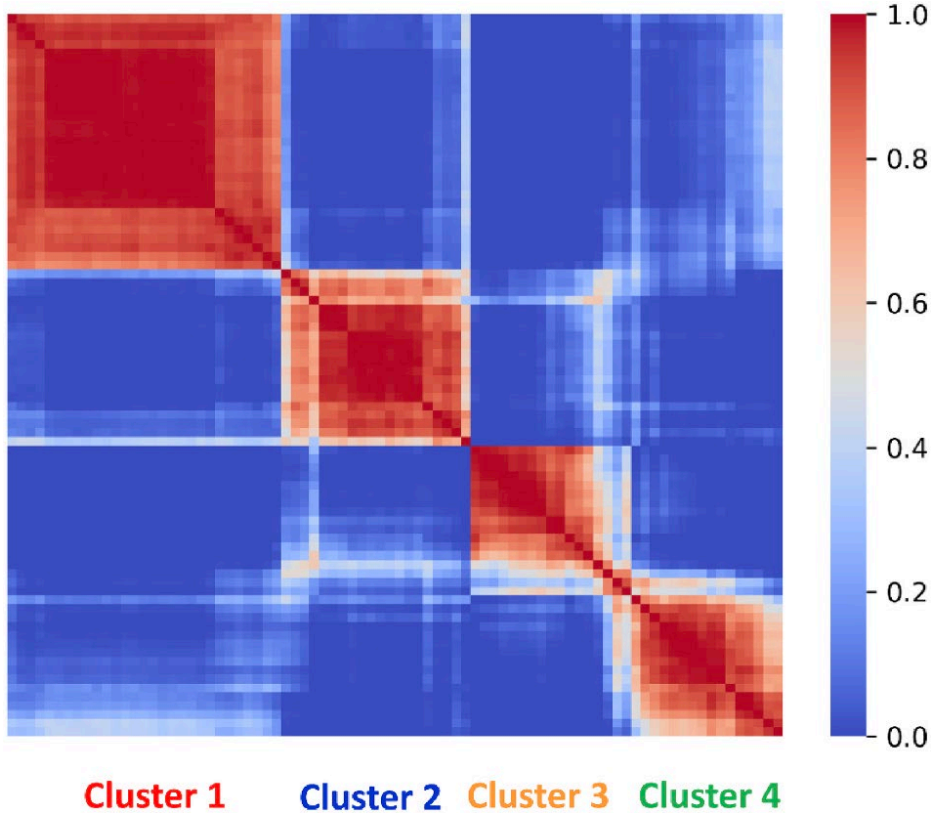

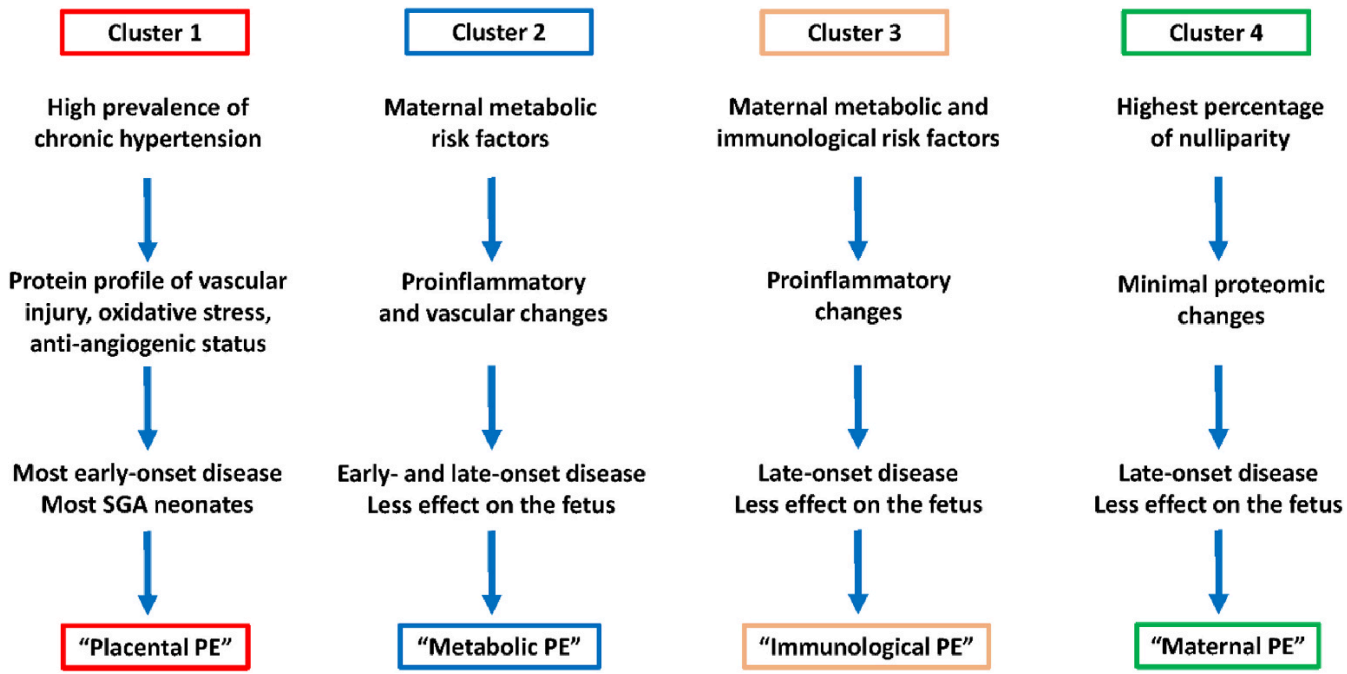

Placenta 125 (2022) 10–19

Placental Evaluation Using Novel Ultrasound Tools in Association with Adverse Pregnancy Outcome: Prospective Longitudinal Study

Alfred Abuhamad MD[1], Elena Sinkovskaya MD PhD[1], Angela Toepp PhD[1], Madeline Rice PhD[2], Todd Erpelding PhD[3], Ann Przybylska RN[1], Aimee Heeze RDMS[1], Maria Wilson-Jimenez RN[4]; Ester Godbold RDMS[4], George Saade, MD[4]

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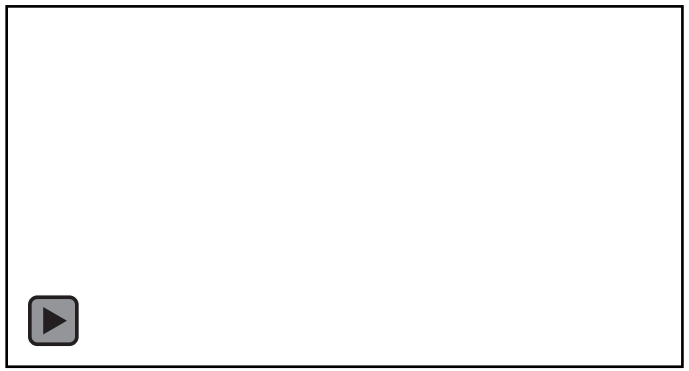
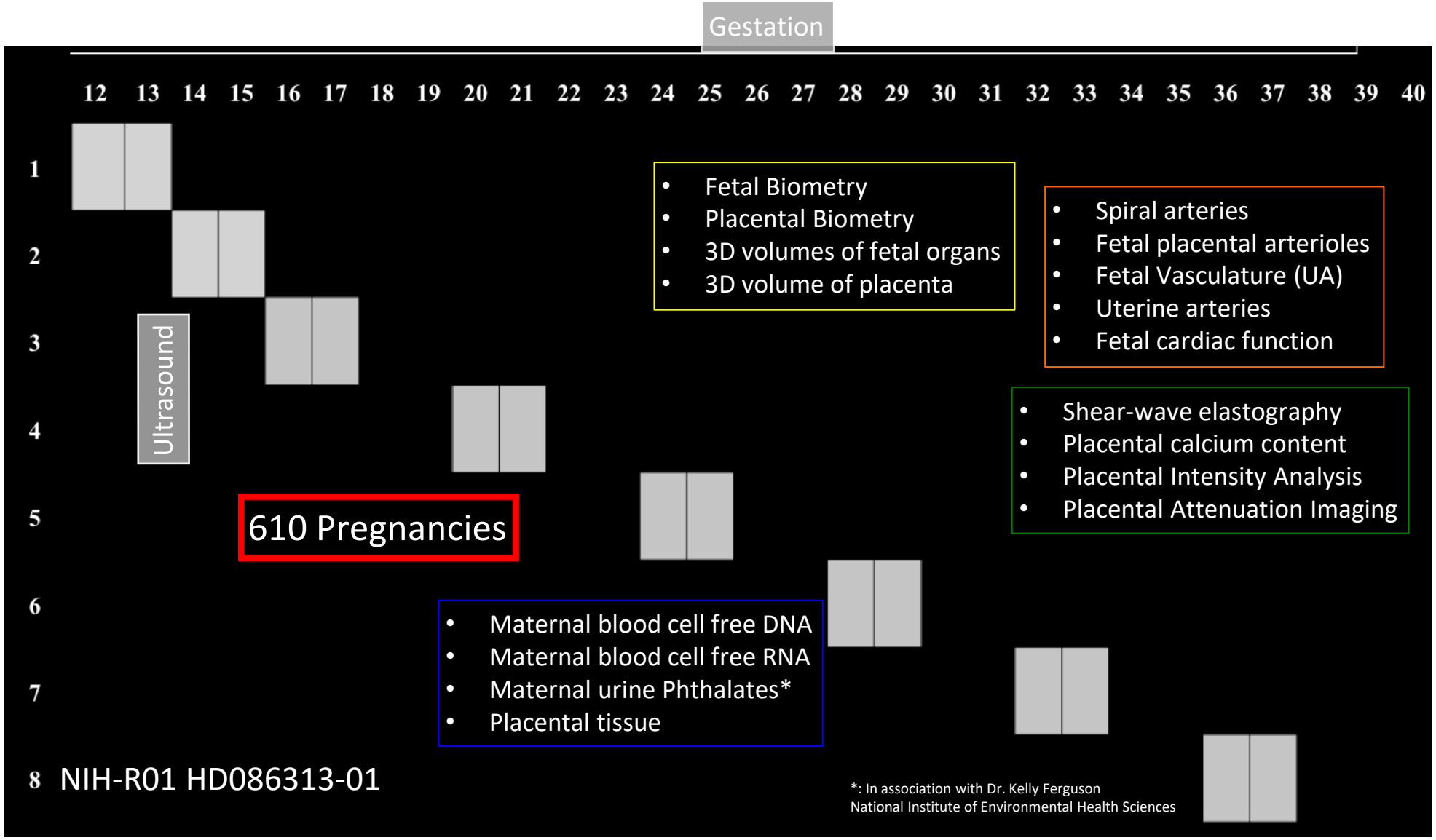
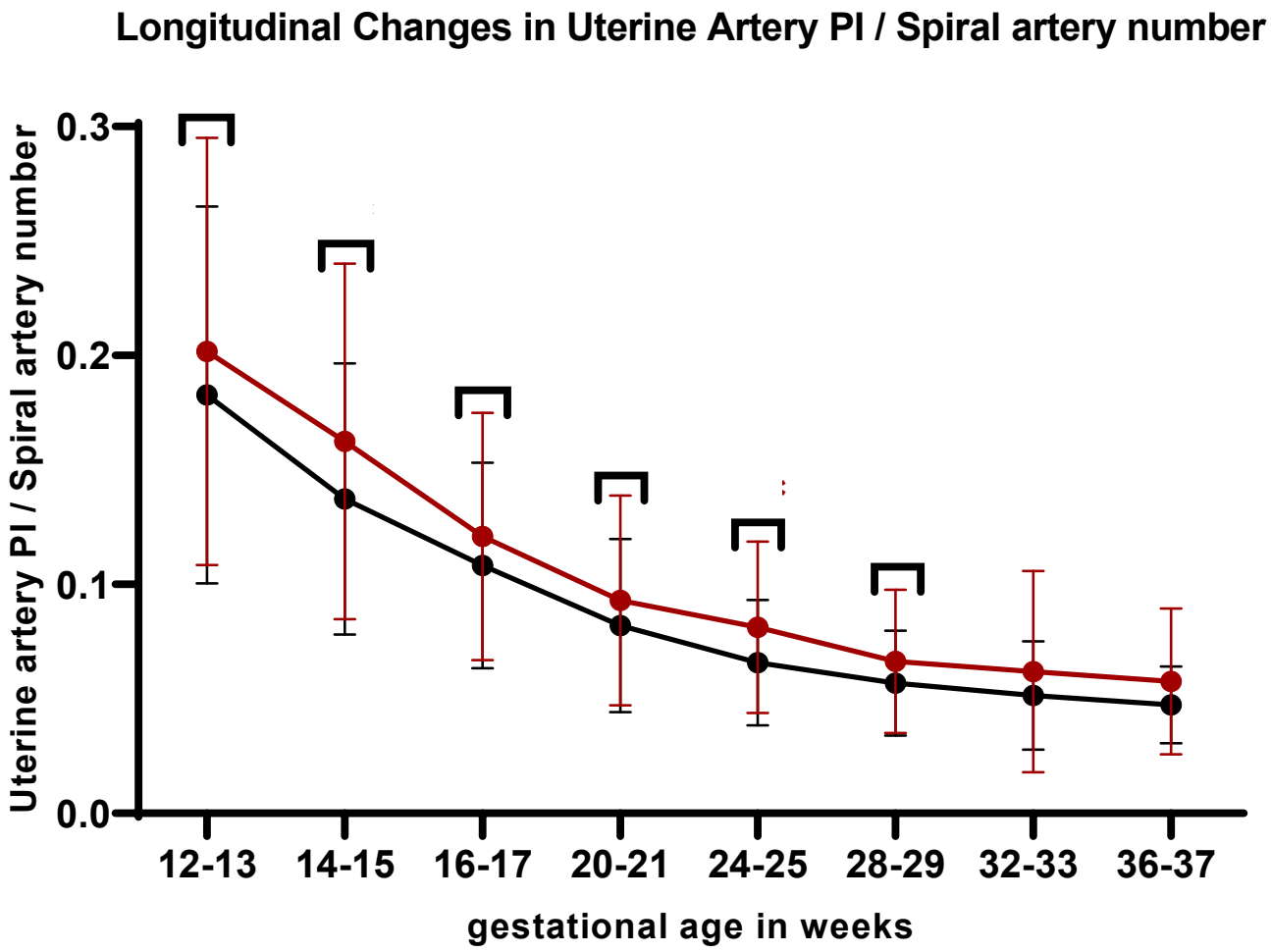


NIH-R01 HD086313-01

Study Design



Early Utero-Placental Vasculature



Horgan et al. In Press

Take Home Message

Pitfalls

- Noisy outcomes
- Two-step process (clinical utility)
- Dynamic gestation
- Comparator
- Mechanisms

Challenges

- Develop objective outcomes
- Insist on clinical utility
- Accurate dating and GA window
- Insist on clinical comparator
- Advocate for preclinical research

Take Home Message

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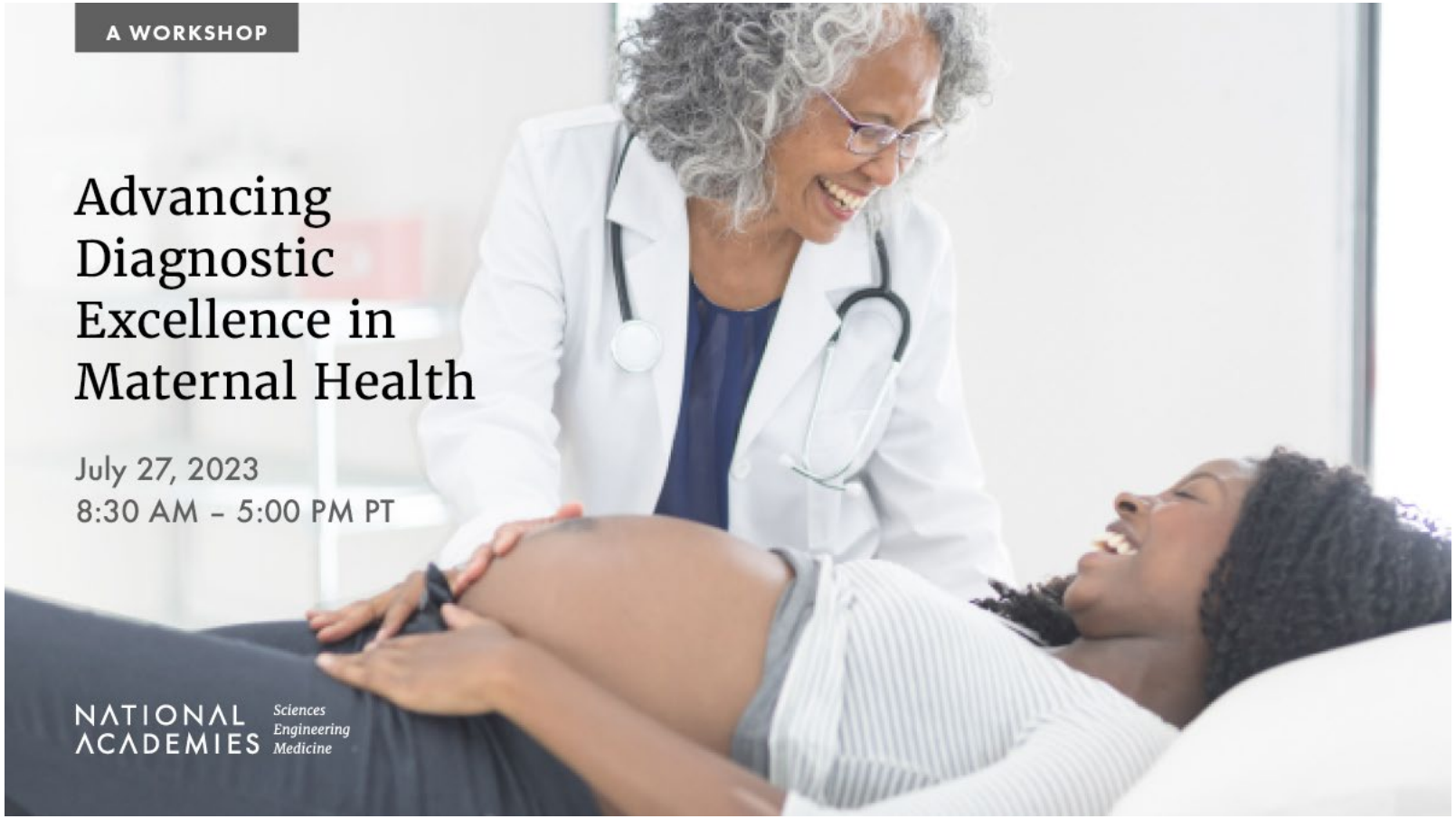
Thank You


A WORKSHOP
Advancing Diagnostic Excellence in Maternal Health
July 27, 2023
8:30 AM – 5:00 PM PT
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