Predicting Preterm Birth in Ho Chi Minh City

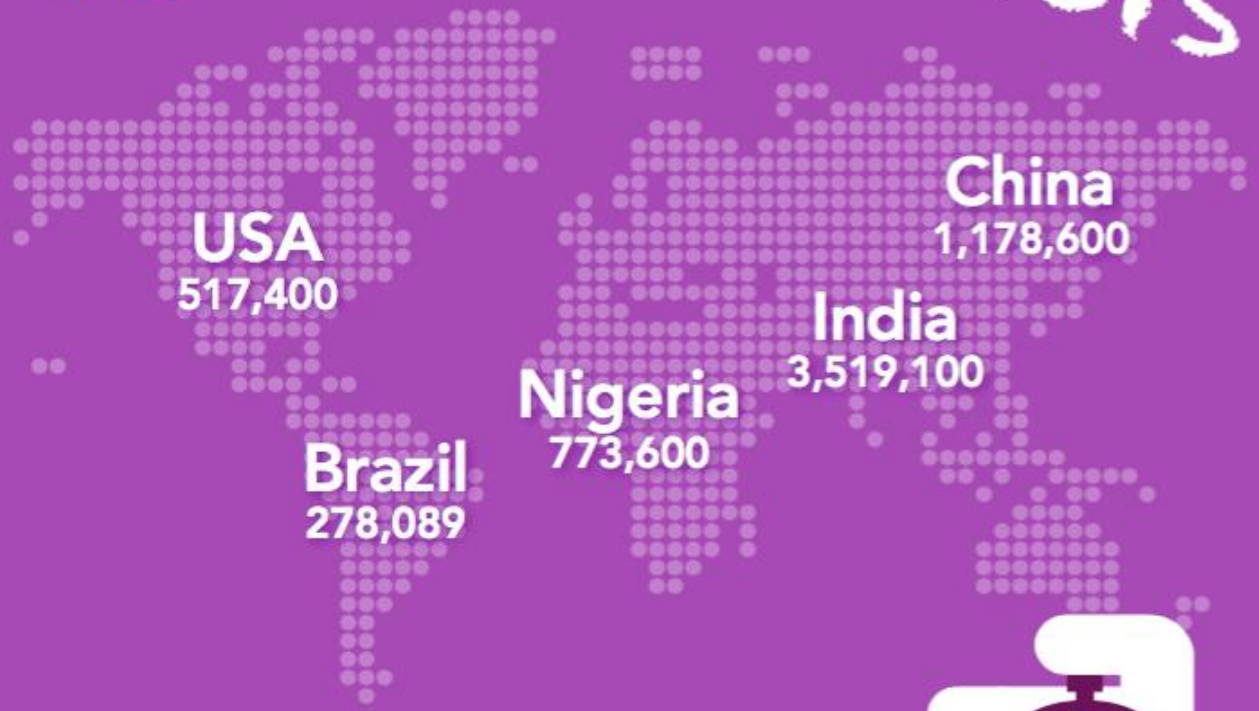
Validation of a biomarker profile to identify women at high risk of preterm birth

Dr. Jane Hirst on behalf of the investigator group

PREMATURE BIRTH

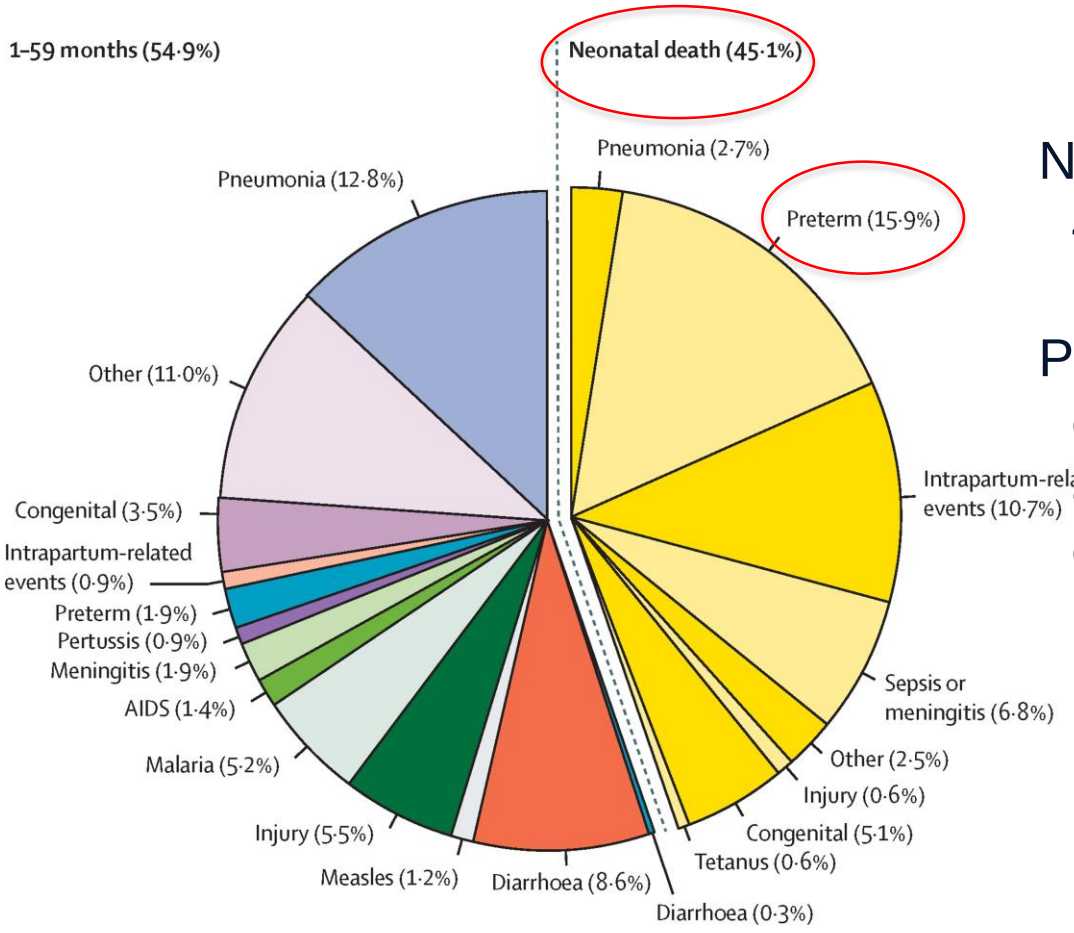
15 million babies are born too soon every year.

CRISIS



Premature birth kills **1 baby** every **30 seconds.**

The Global Impact of Prematurity

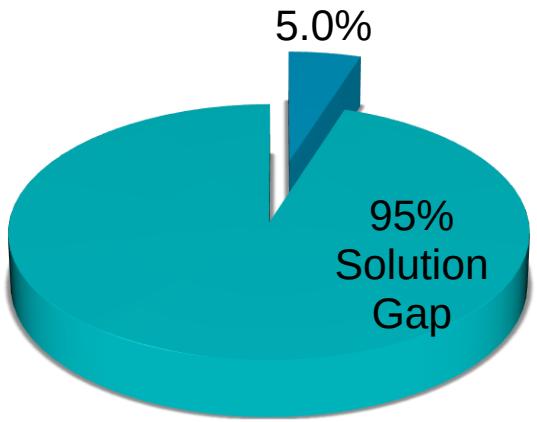


- Neonatal deaths account for 45% of under 5 childhood mortality
- Preterm birth is the leading cause of neonatal deaths/yr and the leading cause of < 5 childhood mortality

Liu et al. Global, regional, and national causes of under-5 mortality in 2000-2015: an updated systematic analysis with implications for the Sustainable Development Goals. Lancet 2016; 388:3027

The Solution Gap

Impact of currently available prevention interventions



- Reduction from 9.6% to 9.1% if all known interventions applied
  - Smoking cessation
  - Single embryo transfer
  - Cerclage
  - Progesterone
  - Reduction in elective deliveries
    - Chang HH, et al. Lancet 2013;381

If all solutions were implemented worldwide, there would still be more than 10 million PTB.

Challenges in Reducing Preterm Birth

Many causes of preterm birth

- **Etiology is is multifactorial and differs by gestational age and ethnicity**

"Preterm birth is a syndrome defined by time and clearly is not a distinct clinical phenotype."

Goldenberg RL, et al. Am J Obstet Gynecol. 2012;206:119

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The survival gap

Where you are born makes a big difference in your chances of surviving premature birth.

High-income countries: **10% die***

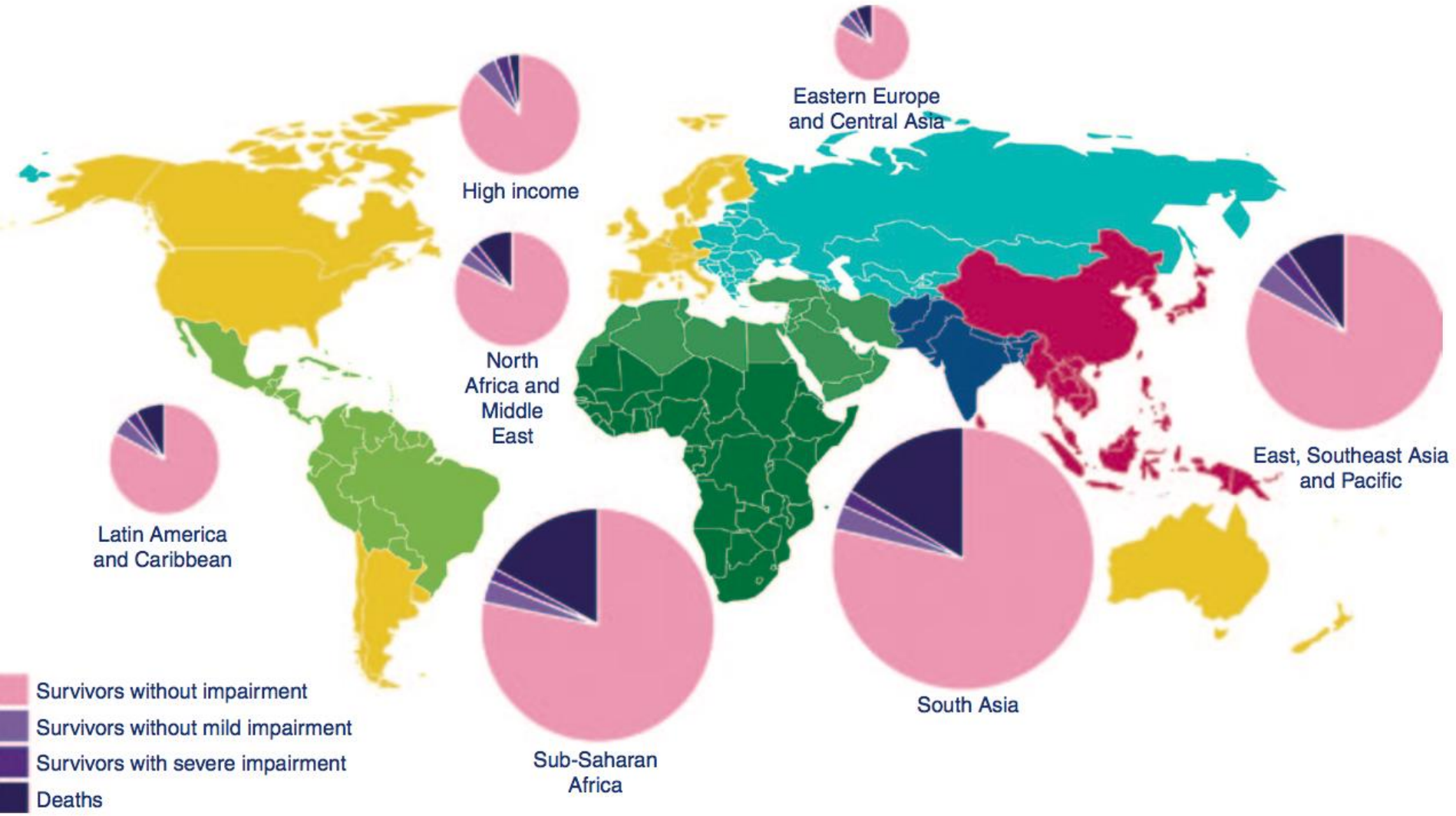
Low-income countries: **90% die***

Sources

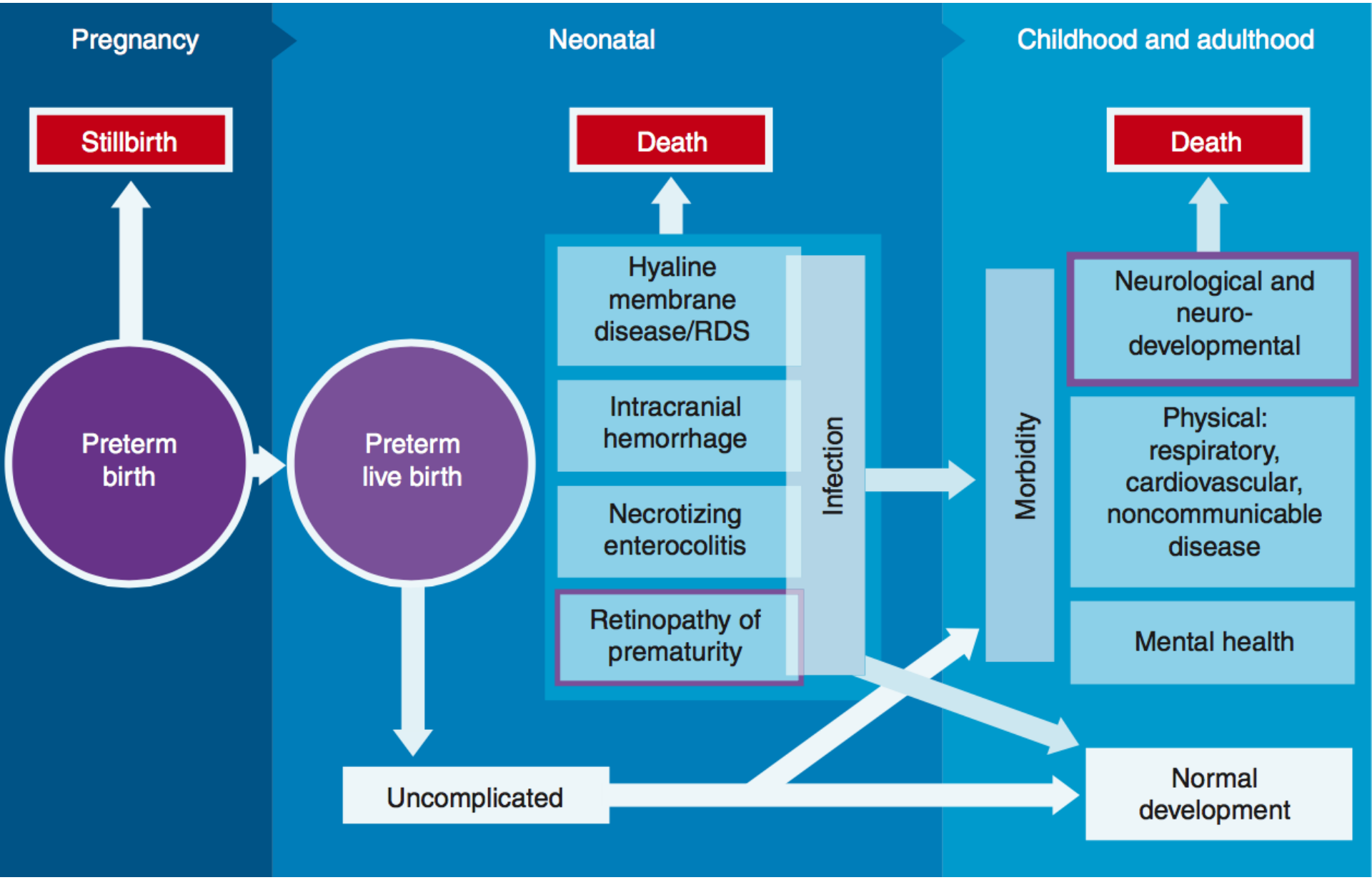
Born Too Soon: The Global Action Report on Preterm Birth. Eds. Howson CP, Kinney MV, Lawn JE. March of Dimes, PMNCH, Save the Children, World Health Organization. New York 2012.

Global, regional, and national causes of child mortality: an updated systematic analysis for 2010 with time trends since 2000. Liu L, Johnson HL, Cousens S, Perin J, et al. Lancet 2012; 379: 2151-61.

*Of extremely preterm babies (<28 weeks gestation)



Source: Blencowe et al, Ped Res 2013



Source: Blencowe et al, Ped Res 2013

Background

- Preterm birth is defined as birth before 37 weeks gestation
- It can be spontaneous or provider induced
- Over half of spontaneous preterm births are not predicted by clinical risk factors or cervical length measurement.
- Accurate recognition of women at high risk of preterm birth would enable preventative therapies to be targeted and the women more closely monitored.

Challenge: Which women will deliver preterm?

Image source: pinterest.com

Prediction research

1. **Discovery** of predictors and formulation of risk model/prediction rule

2. **Internal validation**: Does it predict the outcome in the population it was developed in?

3. **External validation**: Does it predict the outcome in other populations?

4. Does it change **clinician behaviour**?

5. Does it improve **clinical outcomes**?

Biomarkers to predict preterm birth

- Systematic review in 2010 found no one biomarker was particularly good at predicting preterm birth [1]

- Since then, Sera Prognostics identified two proteins that are altered in women that go on to delivery preterm:
  - Sex hormone binding globulin (SHBG) ↓
  - Insulin-like binding factor 4 (IBF4) ↑

- In a study of 5000 American women, the ratio of these proteins demonstrated fair predictive ability to identify women that would deliver under 35 weeks (AUC = 0.75-0.97)[2]

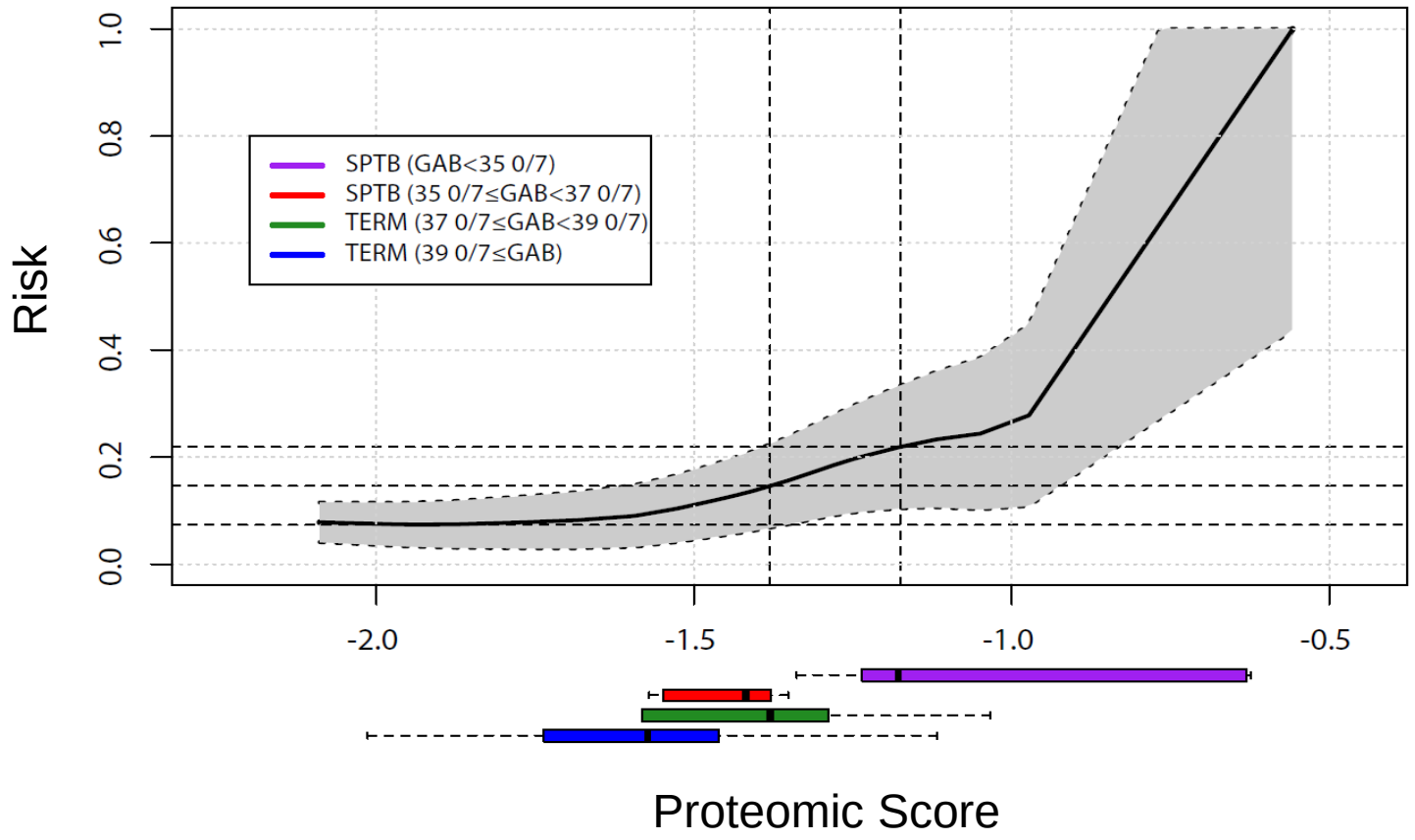
1. Conde-Agueldo 2010
2. Saade et al , AJOG 2016

Sera's Spontaneous Preterm Birth Test

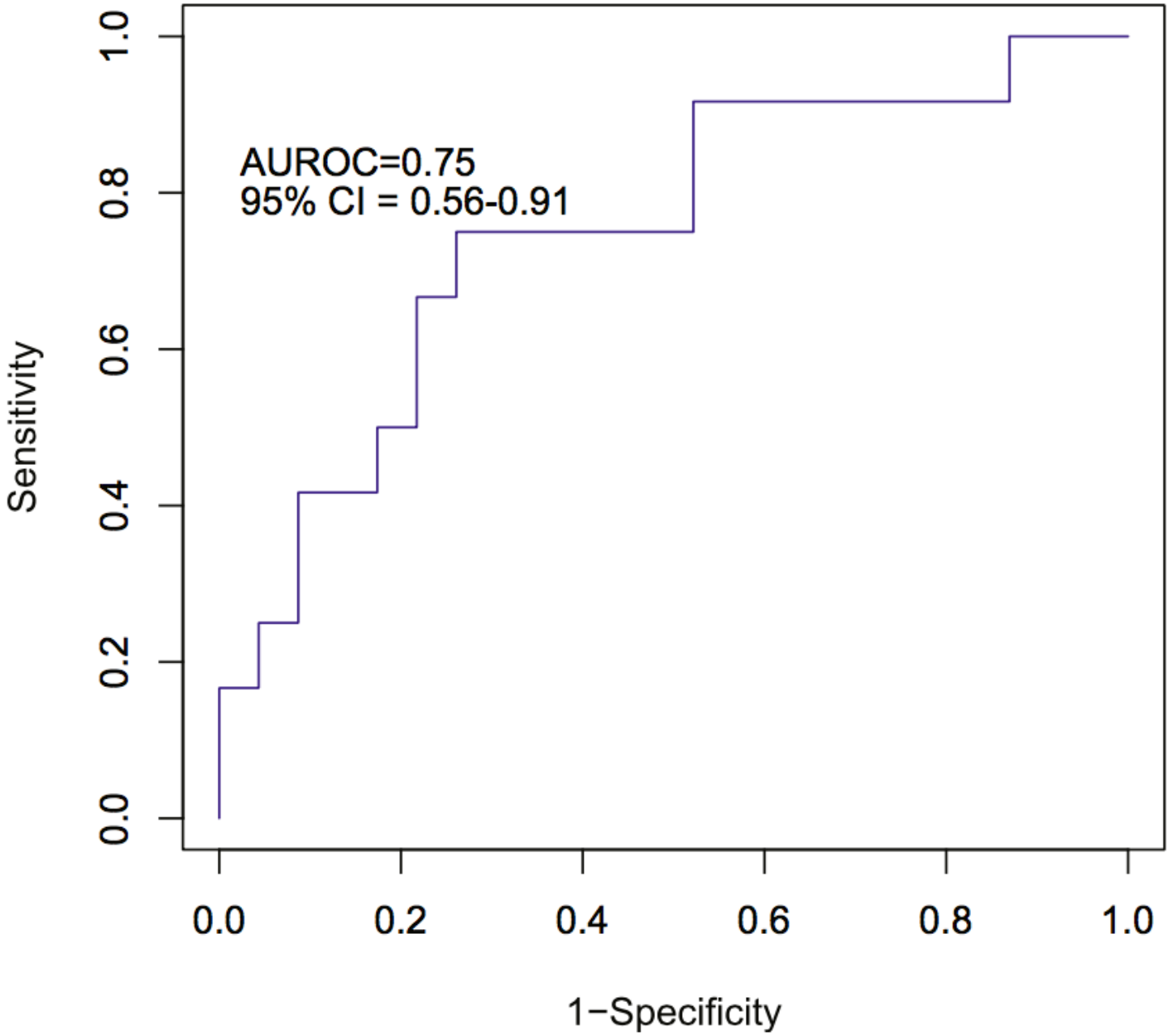
PreTRM™
TEST FOR RISK MANAGEMENT

Powerful test that combines multiple serum biomarkers predictive of preterm birth (PTB)
Accurate, early, individualized prediction of PTB risk to help physicians in clinical decision-making
Singleton pregnant women (asymptomatic)
Blood sample collected as part of routine obstetrical work-up and blood draws
Non-invasive diagnostic, rapid turnaround time

Validation Risk Curve



- As the Proteomic Score (x-axis) increases the risk of spontaneous preterm birth (y-axis) increases.



ROC curve of SHBG/IGF4 ratio to predict birth < 37 weeks, AJOG Saade 2016

PreTRM®
TEST FOR RISK MANAGEMENT

Predict Early

CLICK TO CHAT

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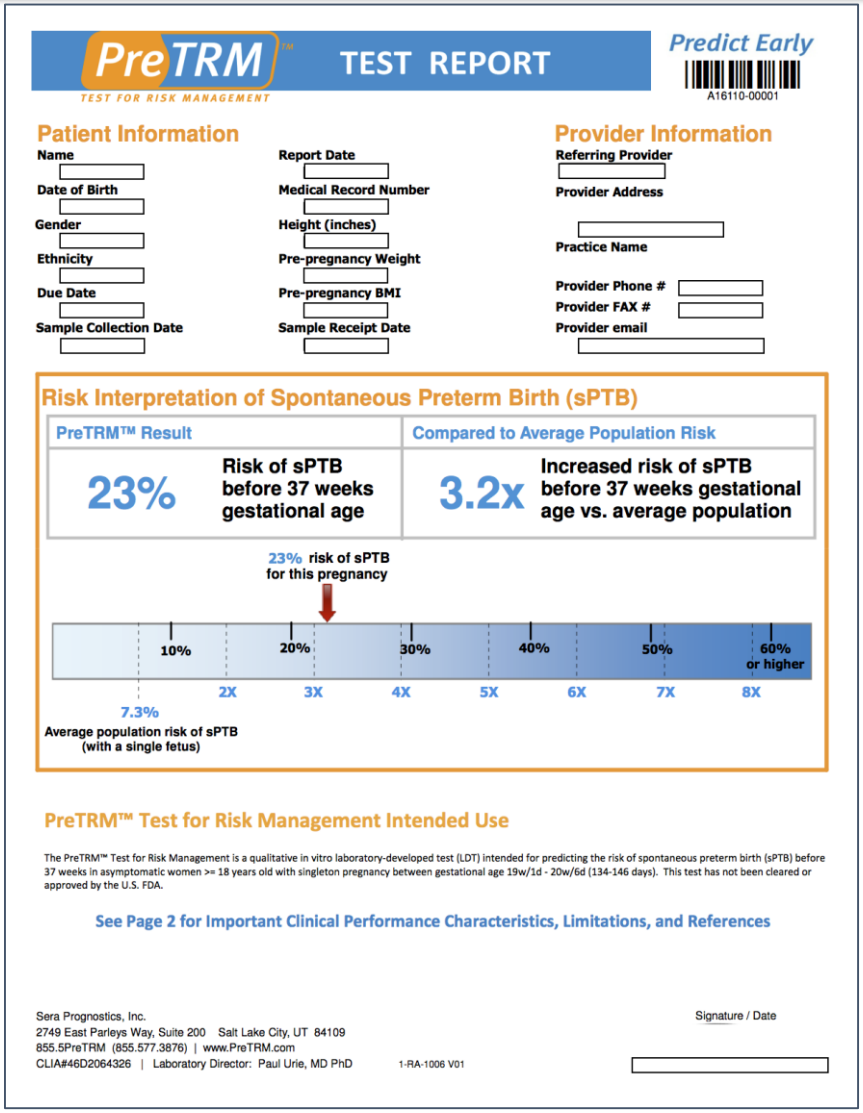
About PreTRM®—a Simple Blood Test

POWERFUL. EARLY. INDIVIDUAL.

Predicting early enables proactive interventions to help better inform decisions made in managing the patient's pregnancy.

The PreTRM® Test Report

- Accurate proteomic biochemical prediction specific to each woman early in her particular pregnancy
- Reports a woman's individualized risk of delivering prematurely as a percentage
- Also reports her relative risk compared to the average risk in the intended use population
- Physician and patient can decide how to address her particular risk more proactively



PreTRM™ TEST REPORT
TEST FOR RISK MANAGEMENT
Predict Early
A16110-00001

Patient Information

Name
Date of Birth
Gender
Ethnicity
Due Date
Sample Collection Date
Report Date
Medical Record Number
Height (inches)
Pre-pregnancy Weight
Pre-pregnancy BMI
Sample Receipt Date

Provider Information

Referring Provider
Provider Address
Practice Name
Provider Phone #
Provider FAX #
Provider email

Risk Interpretation of Spontaneous Preterm Birth (sPTB)

PreTRM™ Result		Compared to Average Population Risk	
23%	Risk of sPTB before 37 weeks gestational age	3.2x	Increased risk of sPTB before 37 weeks gestational age vs. average population

PreTRM™ Test for Risk Management Intended Use

The PreTRM™ Test for Risk Management is a qualitative in vitro laboratory-developed test (LDT) intended for predicting the risk of spontaneous preterm birth (sPTB) before 37 weeks in asymptomatic women >= 18 years old with singleton pregnancy between gestational age 19w/1d - 20w/6d (134-146 days). This test has not been cleared or approved by the U.S. FDA.

See Page 2 for Important Clinical Performance Characteristics, Limitations, and References

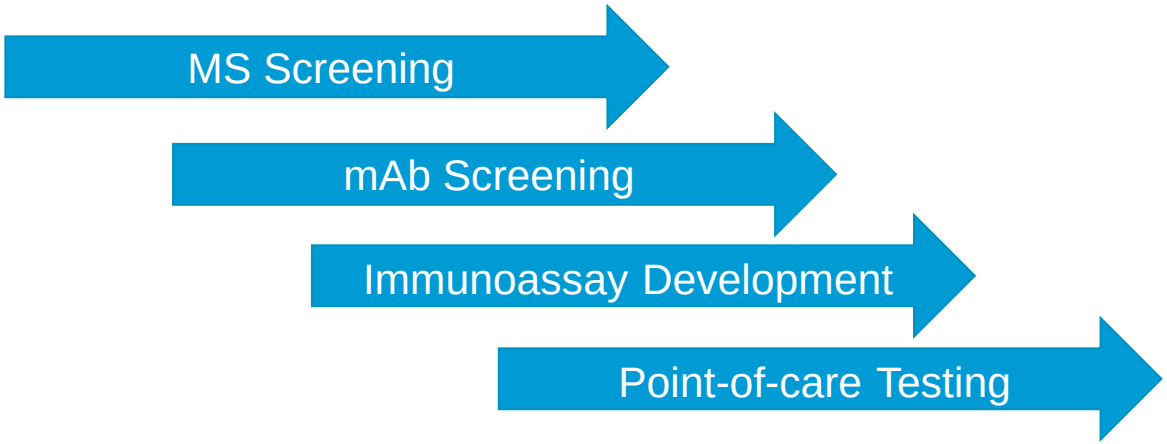
Sera Prognostics, Inc.
2749 East Parleys Way, Suite 200 Salt Lake City, UT 84109
855.5PreTRM (855.577.3876) | www.PreTRM.com
CLIA#46D2064326 | Laboratory Director: Paul Urie, MD PhD

1-RA-1006 V01

Signature / Date

SERA PROGNOSTICS™

Viet Nam Test Development



- Test development initiates with LC-MS analysis of serum samples.
- LC-MS is highly multiplexed allowing for 100's of proteins to be analyzed in a single run.
- Protein biomarkers of interest are then prioritized for monoclonal antibody (mAb) screening
- The identification of mAbs and their validation on a robust platform enables eventual development of a point-of-care test

Study Question

Can the ratio of two proteomic markers,

- Sex hormone binding globulin (SHBG).
- Insulin like growth factor receptor 4(IGF4) (known as the Sera biomarker profile),

measured between 19-21+6 weeks **accurately identify women at risk of spontaneous preterm birth in a Vietnamese population?**

Study design

- Prospective observational cohort study of 4800 women
- 2 years (between 09/2016 – 08/2018)
- Hospital based convenience sample of women who have antenatal care **and** plan to deliver at Tu Du
- Followed through to delivery and discharge from hospital

➔ *Women may not be typical of other women delivering in the hospital or the local population.*

Inclusion Criteria

- ≥ 18 years old
- Singleton fetus
- Between 19+0 and 21+6 weeks gestation at the time of recruitment
- Estimated due date confirmed by ultrasound performed before <13+6 weeks' gestation
- Able to give written, informed consent
- Willing to provide a 7ml blood sample
- Planning to deliver at Tu Du hospital

Exclusion Criteria

- Signs and/or symptoms of threatened miscarriage at the time of recruitment
- Evidence of major fetal abnormality
- Maternal progesterone use during pregnancy*
- Maternal heparin use in pregnancy
- Maternal blood transfusion during the current pregnancy prior to blood sample collection

Further exclusions after sample collection will apply:

- Evidence of significant hemolysis of sample
- Maternal jaundice

*After steering group meeting in 2017, these women were eligible

Participant Flow

All pregnant women presenting between 19-21^{+6} weeks gestation will be given the Patient Information Statement and Informed Consent Form (ICF) and screened for Study eligibility using the ELG form.
If eligible:

- Maternal baseline form (MBF).
- Blood collected

↓

Automated reminder SMS sent at 32 weeks asking the woman to confirm (yes/ no) to the two questions:

- Is she still pregnant?
- Is she planning to deliver at Tu Du

Phone call for follow up if no response, or not planning to deliver at Tu Du.

↓

At delivery:

- Pregnancy and delivery form completed (DEV)
- Blood collected for 500 women of the Dengue in Pregnancy study.

Safety

- No direct risk to the patient or her fetus.
- If have:

  - Any concerns raised by the women with regards to their pregnancy,

  - New symptoms

  - Other clinical information not previously disclosed

  ➔ will be referred to the clinical team in the hospital.

  ➔ SAEs will be reported to the study steering committee for assessment of potential risk to the sponsor.

Ethics considerations

Informed Consent

- All women will receive the patient information statement.
- Will be given time to ask questions or discuss with their family or health provider**.**
- Will be free to withdraw their consent at any time without any influence on their clinical care.

Confidentiality

- Maintained
- Adhere to the principles of GCP in research

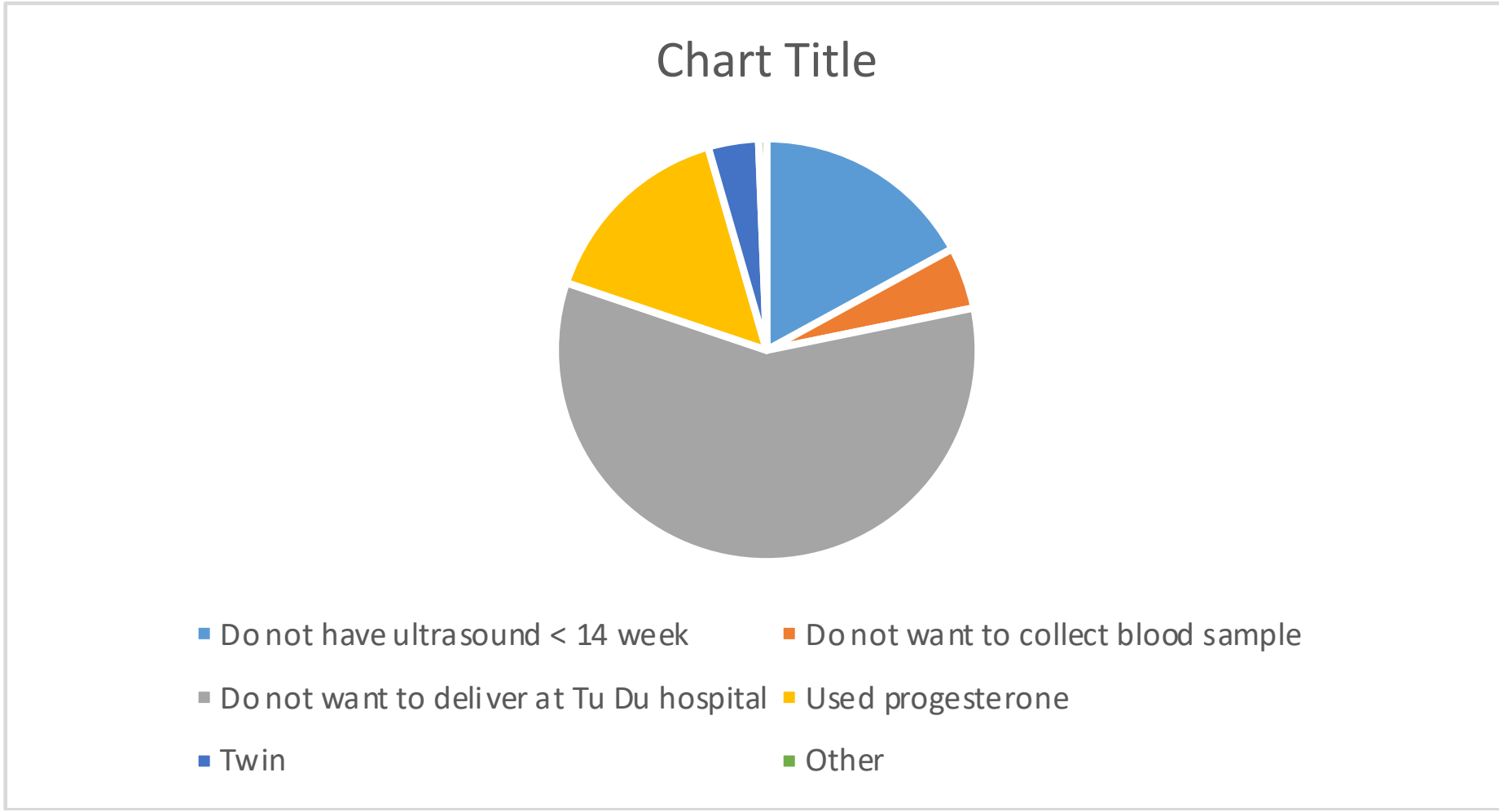
Benefits and Risks

- Risks: very low risk, just discomfort associated with the blood test,
- No direct benefit for women in taking part.

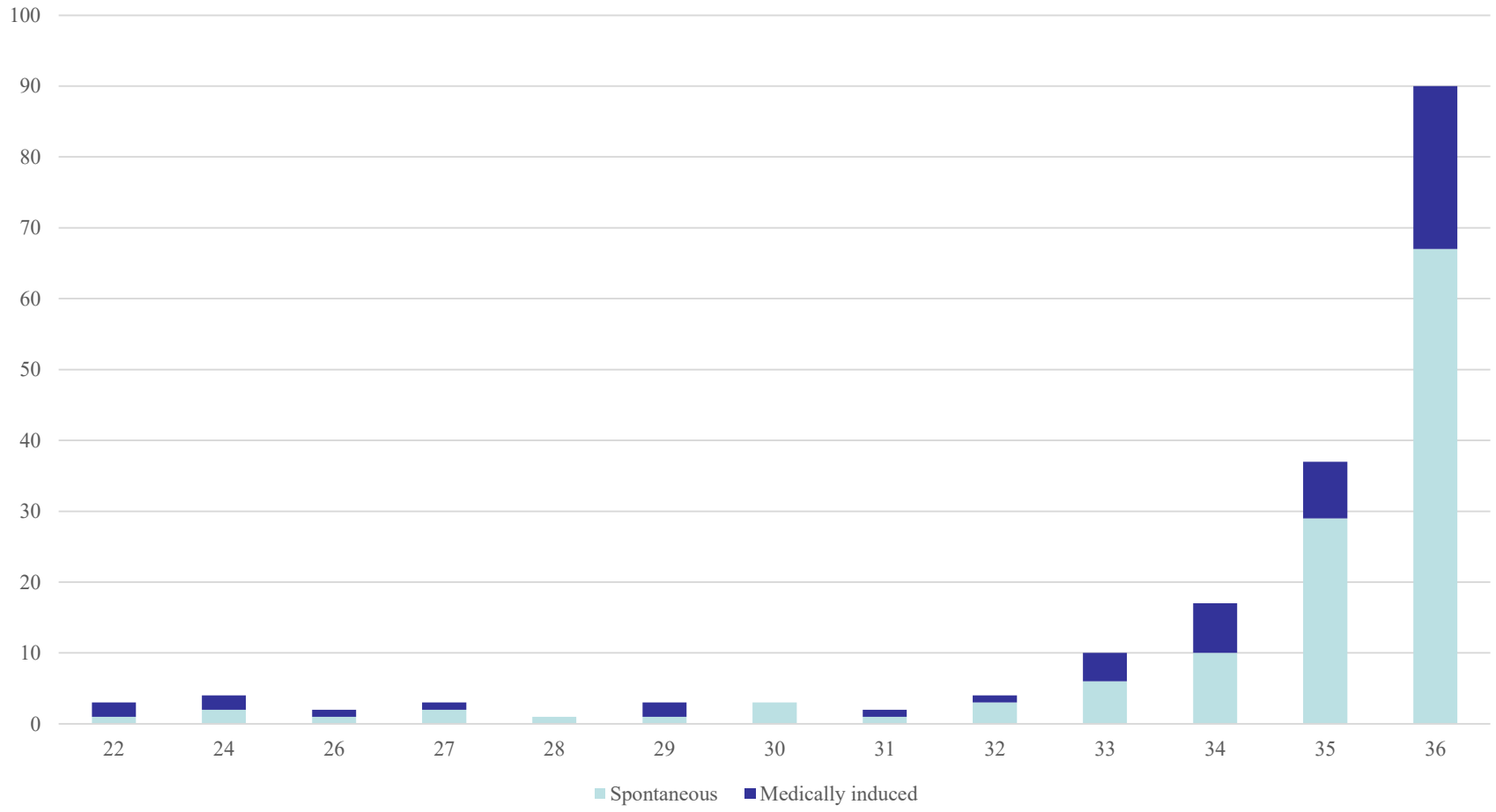
Progress to date

		Number	Percentage
Screened		10301	
Enrolled		4807	
Total preterm birth		211	
Tu Du	Spontaneous	90	
	Medical	46	
	Other	1	
External hospital	Spontaneous	38	
	Medical	8	

Reasons for non participation



Preterm births



Next steps

All women will have delivered by August 2018

Analysis by Sera complete early 2019

? Clinical validation

Opportunities for secondary data analysis and serum testing

Oxford University Clinical Research Unit