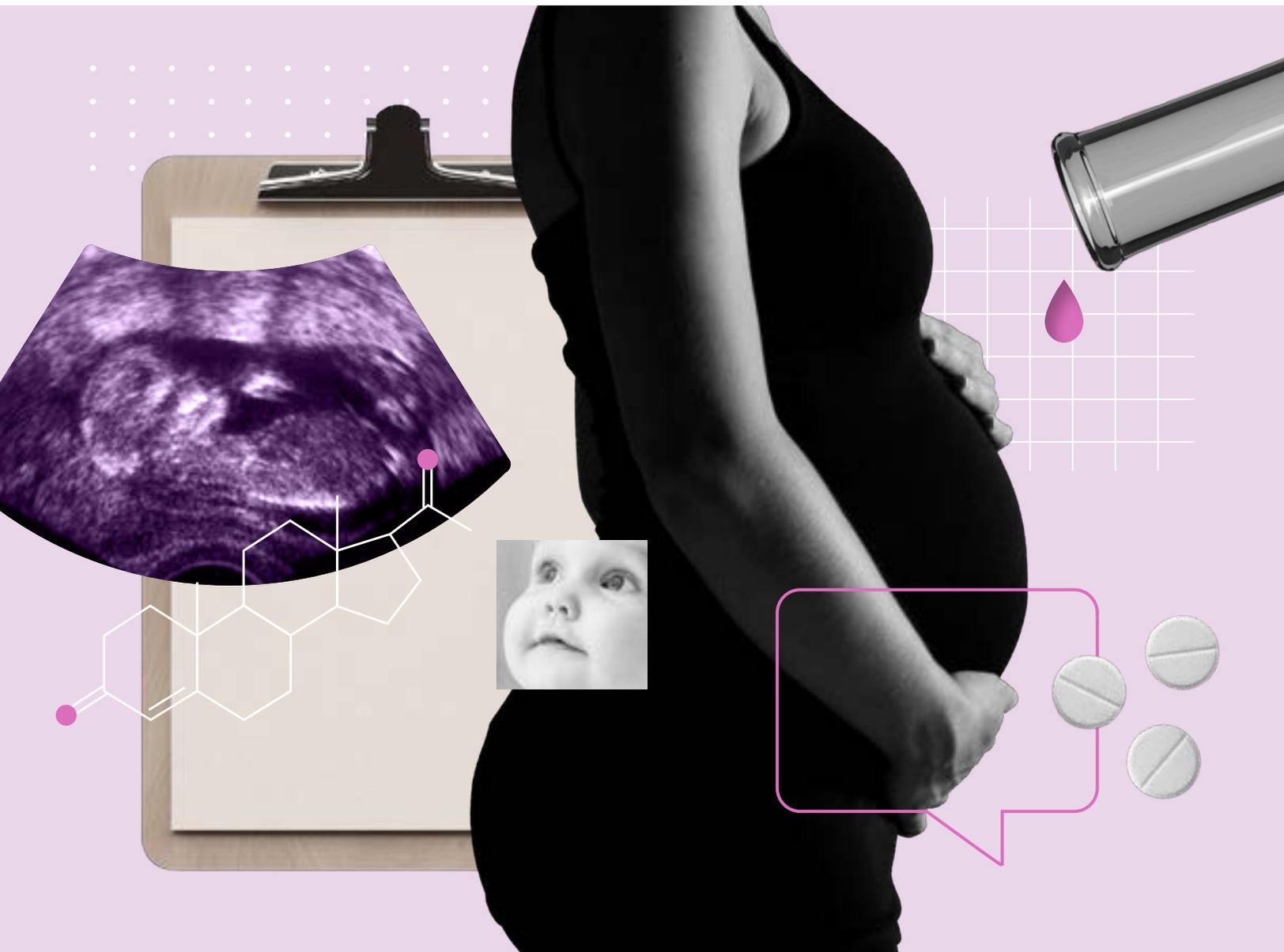


PRIME STUDY

*A New Evidence-Based Approach
to Early Identification & Care
for Patients at Higher Risk of
Spontaneous Preterm Birth*

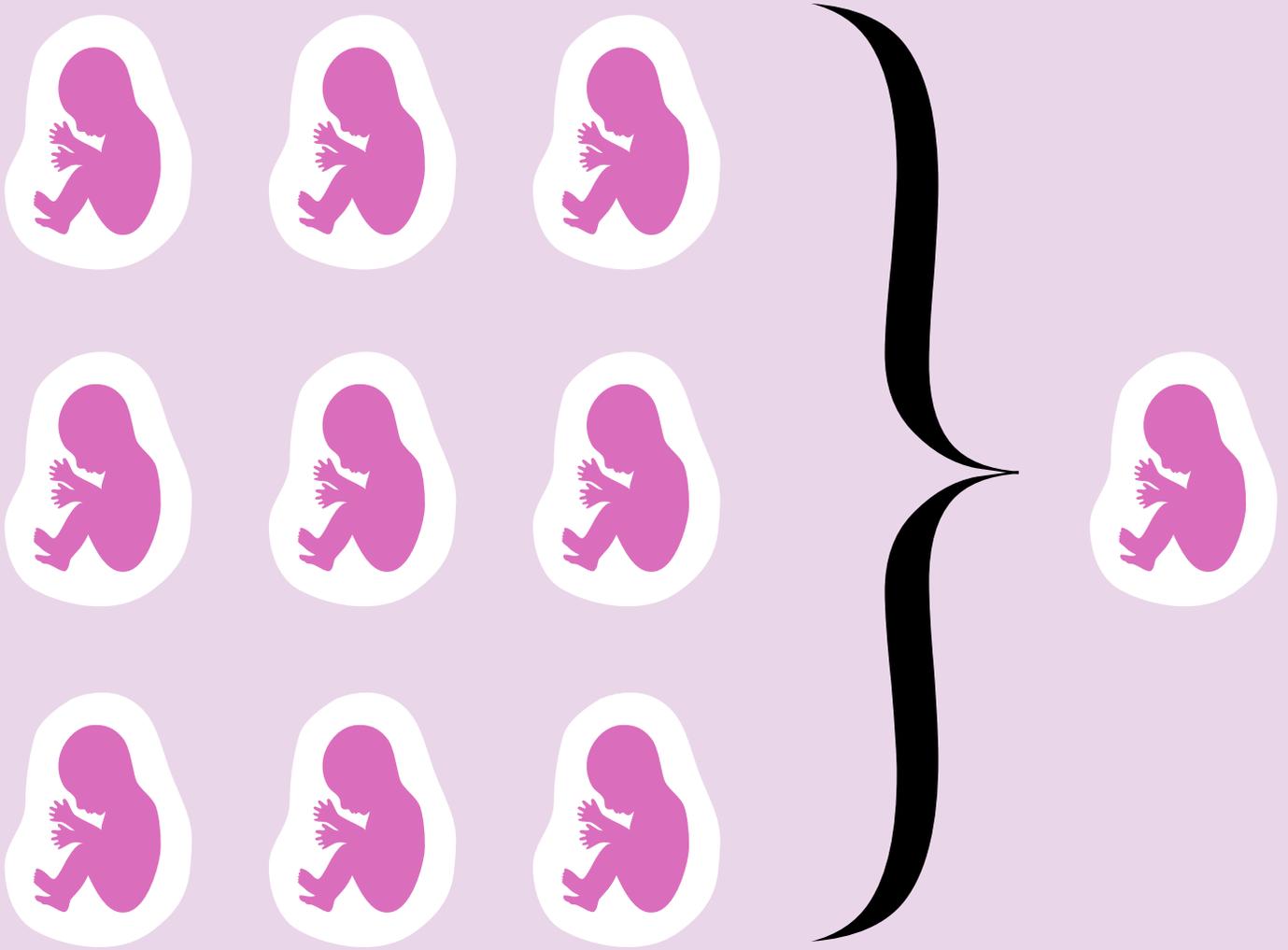


1 in 10 BABIES BORN IN THE U.S. ARE PREMATURE

Preterm Birth is One of the Most Devastating and Costly Adverse Pregnancy Outcomes

Preterm birth—deliveries earlier than 37 weeks of gestation—is a common endpoint of numerous problems that can occur during pregnancy.

Approximately 1 in every 10 babies in the United States is premature.¹ This rate has remained constant for decades, contributing substantially to neonatal morbidity and mortality.² The most recent estimate³ places the nation's annual economic burden of preterm birth at \$25.2 billion, underscoring its substantial impact on mothers and families, employers, payers, and healthcare resources. Reducing the preterm birth rate requires attention to a long-standing, twofold challenge: the lack of proven risk assessment methods and care practices for at-risk pregnancies.



Approximately 1 in every 10 babies
in the United States is premature¹

Preventing Preterm Birth Starts with an Accurate Risk Assessment

The most-recognized clinical predictors of preterm birth risk are a history of preterm delivery, a multiple-gestation pregnancy, or a shortened cervix. But these issues are not seen in most mothers of premature babies.⁴ And one of these predictors, prior preterm delivery, is not available for women who are first-time mothers.

UP TO

50%

of U.S. women delivering prematurely have no known risk factors.⁵



Improving Preterm Birth Outcomes Requires Extending Gestation in At-Risk Pregnancies

Because preterm birth complications are most severe in the earliest-born babies, prolonging gestation is a critical step in addressing prematurity. Established interventions⁴ to extend gestation among those with risk factors for preterm delivery include vaginal progesterone and cervical cerclage for shortened cervix. Low-dose aspirin also shows promise in preterm birth prevention⁶ but has not become standard of care for preterm birth alone as it has for preeclampsia.⁷

Focused care management, a routine intervention in oncology, has been evaluated as a preventive intervention for preterm birth. Care management programs commonly include increased outreach, education, care coordination, and specialist support. How care management is delivered and experienced by patients can vary widely. Individual programs have shown promise in clinical studies, but due to the variability in maternity care management programming, its overall efficacy is not well established.⁸

The PreTRM[®] Test and Targeted Interventions Usher in a New Era of Personalized Prenatal Care



Current practice guidelines emphasize tailoring prenatal care based on the patient's individual risk.⁹

One tailored screen-and-treatment strategy has produced improved neonatal outcomes among pregnancies determined to be at higher risk by a validated biomarker test called called PreTRM.

The test measures two proteins, called insulin-like growth factor-binding protein 4 (IGFBP4) and sex hormone-binding globulin (SHBG). The protein ratio in a mid-second-trimester maternal blood sample, combined with clinical variables into an algorithm, stratifies preterm birth risk in women who have otherwise been identified as having a clinically low-risk pregnancy.¹⁰⁻¹³

The PreTRM Test, followed by the targeted interventions of vaginal progesterone, low-dose aspirin and patient-centered care management, has been shown to prolong gestation amongst the earliest deliveries (32- and 35-week deliveries), reduce the severity of preterm birth-associated neonatal complications, lower NICU admissions, and shorten neonatal hospital stays.^{14, 15}

These findings suggest that better preterm birth outcomes can be realized by combining a validated risk assessment method, the PreTRM Test, with strategies to prolong gestation.



THE PRIME STUDY¹⁵

Targeted Interventions

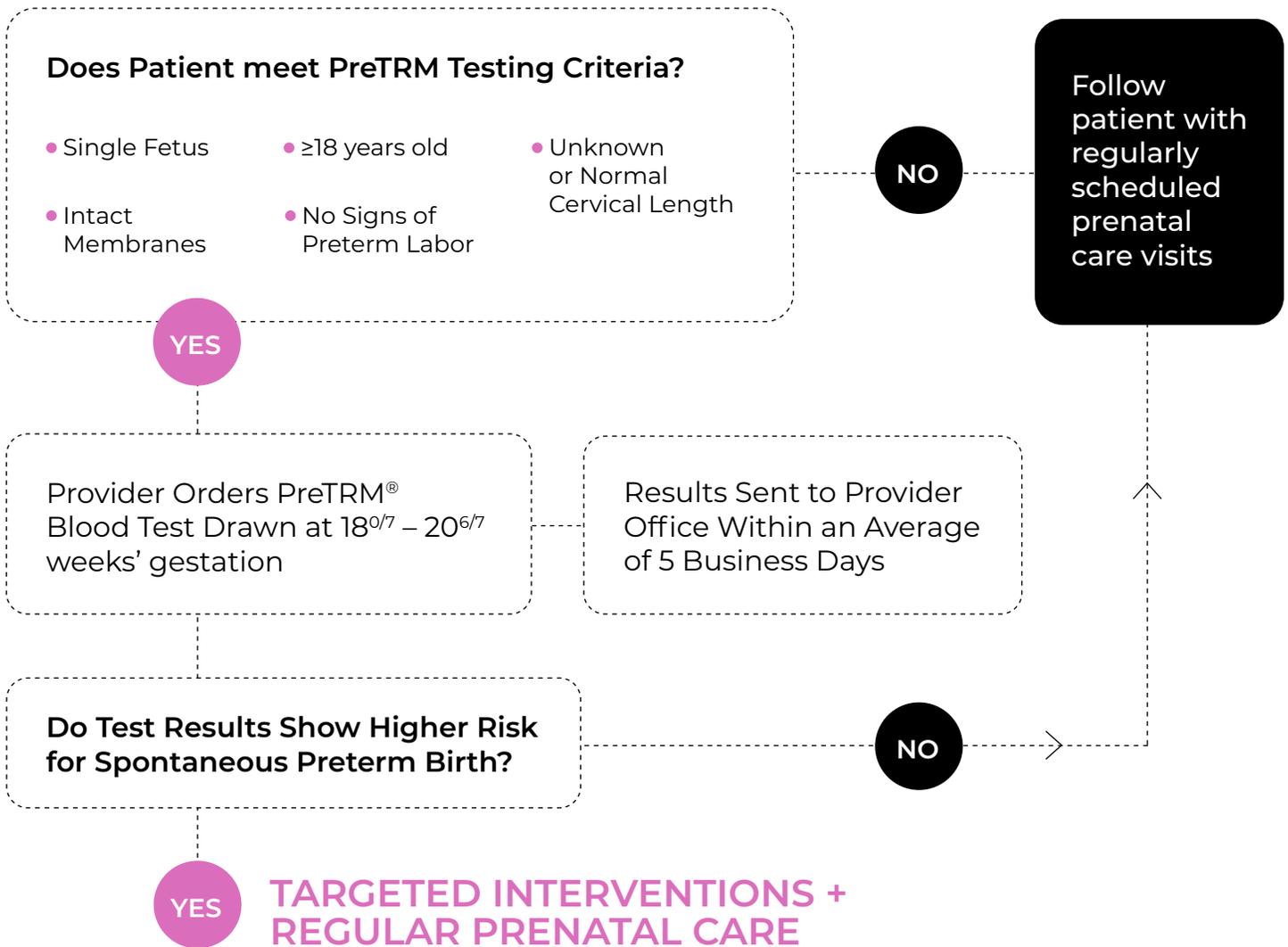
- Maternal blood was drawn for the PreTRM[®] Test at 18^{0/7} – 20^{6/7} weeks' gestation, and results were returned by a CLIA certified, CAP accredited lab in an average of 5 business days after receipt of sample.

Targeted interventions were started for those participants reported to be at higher risk by 24^{0/7} weeks' gestation.

- **Low-Dose Aspirin (81 Mg)**
Taken orally on a daily basis until 36^{6/7} weeks' gestation.
- **Vaginal Progesterone (200 Mg)**
Administered daily as a 200 mg micronized progesterone suppository until 36^{6/7} weeks' gestation.
- **Care Management**
Weekly phone calls were made by a trained registered nurse to discuss opportunities to help reduce the likelihood of preterm delivery. Telephonic nurse outreach focused on early signs and symptoms of preterm labor, encouraged timely reporting, compliance with care recommendations, and referral to evaluation and coordination resources when appropriate.

CLINICAL PATHWAY

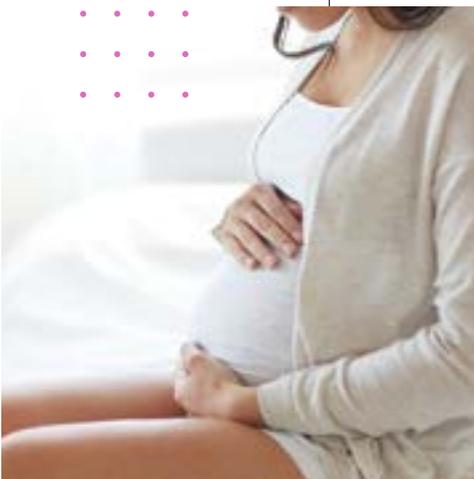
A Biomarker Test & Targeted Interventions Improve Neonatal Outcomes in Those Identified at Increased Risk



Those identified as higher risk in screen-guided care arm were also offered two additional transvaginal cervical length assessments at 21^{0/7} through 23^{6/7} weeks and 26^{0/7} through 28^{6/7} weeks.

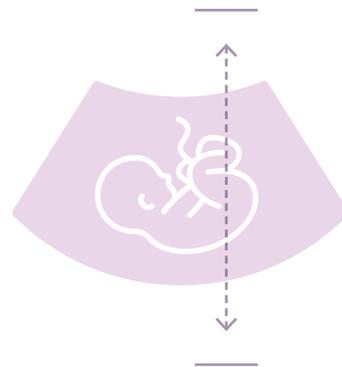
WHY HAVE 'TARGETED INTERVENTIONS' SEEN SUCCESS IN IMPROVING PREMATURITY- RELATED OUTCOMES?

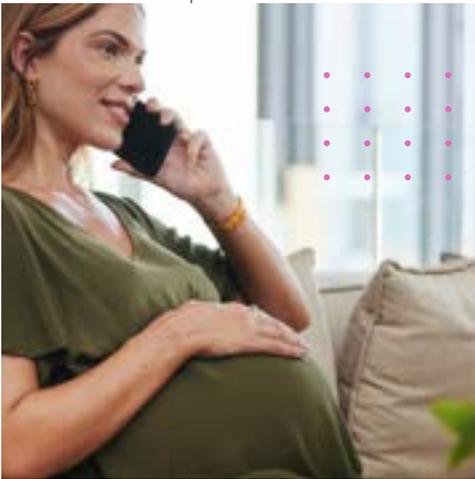
The multiple causes of preterm birth have historically made it unlikely that any single intervention would be effective at addressing all population-level preterm birth risks. The combination of treatments here addresses the placental protein changes seen by PreTRM and support a varied population.



SHOULD CERVICAL LENGTH SCREENING CONTINUE OR BE ADDED TO THE MANAGEMENT PLAN?

Cervical length screening was part of the original protocol in the PRIME study. If that is part of your clinical routine, it is reasonable to continue. Additionally, the group of patients at risk for preterm delivery—those whose PreTRM Test shows elevated values—are also the women who may be most likely to benefit by the addition of cervical length screening. Women whose test results show elevated risk and who are now on progesterone based on current guidelines may benefit from cerclage if their cervical length then shortens to less than 25 mm.¹⁶



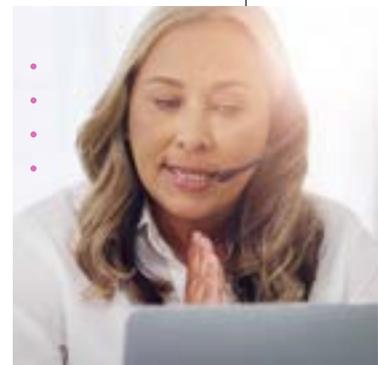


WHAT IS THE VALUE OF CARE MANAGEMENT?

Weekly calls with expecting mothers and their care team can help support better education and understanding of behaviors shown to be associated with preterm delivery. Examples include smoking and substance use. Regular communication also supports symptom recognition and care need identification. This personalized strategy supports timely identification of preterm birth symptoms. This can help ensure appropriate care is established to address both clinical and non-clinical factors driving to reduce future risk of preterm delivery.

HOW IS CARE MANAGEMENT PUT INTO PRACTICE?

Care management providers can work within an obstetric medical group, a health plan, or contracted by supporting partners to provide services. Typically, these are certified clinicians who have special training and experience in obstetrics. There are visuals, including at the end of this paper, that provide the list of questions care managers used in the PRIME trial. Care management programs can utilize multiple tools and platforms such as digital health apps, to offer convenient ways for the care team and mothers to connect throughout the pregnancy.





HOW DO I BEGIN?

Create a trusted relationship and plan with the patient that builds awareness of the signs and symptoms of premature labor and what to do if they recognize any changes. Instill higher sensitivity for any unusual changes or symptoms. Give direction for whom to contact immediately. Support education for the patient on when an immediate call to her care team is better than watch-and-wait approach.



WHAT DO CARE MANAGERS REVIEW WITH THE EXPECTANT MOTHER?

Care managers can support members and the care team. The PRIME study protocol is included at the end of this document. This focused support for preterm birth signs, symptom awareness, and education helped improve outcomes for both mom and baby.

IN SUMMARY

Few inroads have been made toward reducing the likelihood of premature delivery or mitigating related complications.

Options such as antenatal corticosteroids have been the mainstay of improving outcomes related to prematurity-associated respiratory immaturity. Other standard-of-care options are vaginal progesterone for short cervix and cervical cerclage for selected patients at risk of cervical incompetence.

The American College of Obstetricians and Gynecologists⁹ emphasizes the importance of reducing disparities and preventing adverse outcomes through recognizing risks early and adjusting care as needed.

It is also recommended that providers engage in shared decision making. With PreTRM, you can identify pregnant patients who may benefit from additional high touch interventions to lessen the impacts of preterm birth upon them and their children. The PreTRM Test offers an opportunity to address preterm birth preventive care beyond medications alone—when it’s most needed. This approach supports more personalized healthcare and aims to improve pregnancy outcomes through proactive and collaborative actions.



HIGHER RISK



NOT HIGHER RISK



NOT HIGHER RISK

Dr. Barbi Phelps-Sandall Shares a Patient Pregnancy Story

At a 6-week postpartum appointment, I walked into the exam room and my patient greeted me with a big smile and said...



**I'M SO GRATEFUL FOR
THE PRETRM TEST!"**

Because after she took it, the results showed an extremely high risk for preterm labor. We worked together during the next 4 months and the outcome was a vaginal delivery, at term, with a healthy baby.



My patient then told me...

I CAME HOME FROM THE HOSPITAL WITH A HEALTHY BABY I CAN HOLD. MY FRIEND CAN ONLY TOUCH HER BABY IN AN INCUBATOR.”

My patient just returned from a visit with a friend who was also pregnant—with a due date close to her own. The friend had a preterm delivery. She did not have the PreTRM test available to her and now both mom and baby were in the NICU.

I’M SO GLAD WE DID THE PRETRM TEST.”



REFERENCES

1. Martin JA, BE H, MJK O. Births in the United States, 2023. NCHS Data Brief, no 507. Hyattsville, MD: National Center for Health Statistics, 2024.
2. Xu J, Murphy SL, Kochanek KD, Arias E. Mortality in the United States, 2021. NCHS Data Brief 2022(456):1-8. (In eng).
3. Waitzman NJ, Jalali A, Grosse SD. Preterm birth lifetime costs in the United States in 2016: An update. *Semin Perinatol* 2021;45(3):151390. DOI: 10.1016/j.semperi.2021.151390.
4. American College of Obstetricians and Gynecologists' Committee on Practice Bulletins—Obstetrics. Prediction and Prevention of Spontaneous Preterm Birth: ACOG Practice Bulletin, Number 234. *Obstet Gynecol* 2021;138(2):e65-e90. DOI: 10.1097/AOG.0000000000004479.
5. Institute of Medicine Committee on Understanding Premature Birth, and Assuring Healthy Outcomes. The National Academies Collection: Reports funded by National Institutes of Health. In: Behrman RE, Butler AS, eds. *Preterm Birth: Causes, Consequences, and Prevention*. Washington (DC): National Academies Press (US); 2007.
6. Hoffman MK, Goudar SS, Kodkany BS, et al. Low-dose aspirin for the prevention of preterm delivery in nulliparous women with a singleton pregnancy (ASPIRIN): a randomised, double-blind, placebo-controlled trial. *Lancet* 2020;395(10220):285-293. DOI: 10.1016/S0140-6736(19)32973-3.
7. Henderson JT, Whitlock EP, O'Connor E, Senger CA, Thompson JH, Rowland MG. Low-dose aspirin for prevention of morbidity and mortality from preeclampsia: a systematic evidence review for the U.S. Preventive Services Task Force. *Ann Intern Med* 2014;160(10):695-703. (In eng). DOI: 10.7326/M13-2844.
8. Garite TJ, Manuck TA. Should case management be considered a component of obstetrical interventions for pregnancies at risk of preterm birth? *Am J Obstet Gynecol* 2023;228(4):430-437. (In eng). DOI: 10.1016/j.ajog.2022.09.022.
9. American College of Obstetricians and Gynecologists' Committee on Practice Bulletins—Obstetrics. Tailored Prenatal Care Delivery for Pregnant Individuals: ACOG Clinical Consensus No. 8. (<https://www.acog.org/clinical/clinical-guidance/clinical-consensus/articles/2025/04/tailored-prenatal-care-delivery-for-pregnant-individuals>).
10. Saade GR, Boggess KA, Sullivan SA, et al. Development and validation of a spontaneous preterm delivery predictor in asymptomatic women. *Am J Obstet Gynecol* 2016;214(5):633 e1-633 e24. (In eng). DOI: 10.1016/j.ajog.2016.02.001.
11. Markenson GR, Saade GR, Laurent LC, et al. Performance of a proteomic preterm delivery predictor in a large independent prospective cohort. *Am J Obstet Gynecol MFM* 2020;2(3):100140. (In eng). DOI: 10.1016/j.ajogmf.2020.100140.
12. Burchard J, Polpitiya AD, Fox AC, et al. Clinical Validation of a Proteomic Biomarker Threshold for Increased Risk of Spontaneous Preterm Birth and Associated Clinical Outcomes: A Replication Study. *J Clin Med* 2021;10(21):5088. DOI: 10.3390/jcm10215088.
13. Bradford C, Severinsen R, Pugmire T, et al. Analytical validation of protein biomarkers for risk of spontaneous preterm birth. *Clinical Mass Spectrometry* 2017;3:25-38. DOI: 10.1016/j.clinms.2017.06.002.
14. Hoffman MK, Kitto C, Zhang Z, et al. Neonatal Outcomes after Maternal Biomarker-Guided Preterm Birth Intervention: The AVERT PRETERM Trial. *Diagnostics* 2024;14(14):1462.
15. Iriye BK, O'Brien JM, Ennen CS, et al. Neonatal impact of maternal biomarker screening for risk of preterm birth with targeted interventions (PRIME): A multicenter, randomized, controlled trial. *Pregnancy* 2026;2(1):e70202. DOI: <https://doi.org/10.1002/pmf2.70202>.
16. Hoffman MK. Prediction and Prevention of Spontaneous Preterm Birth: ACOG Practice Bulletin, Number 234. *Obstet Gynecol*. 2021 Dec 1;138(6):945-946. doi: 10.1097/AOG.0000000000004612. PMID: 34794160; PMCID: PMC8607754.

CARE MANAGEMENT DIRECTIVES

Use the Following Outline as a Guide in Your Practice

Call Length

After the first phone interview, calls typically take 5-7 minutes to complete but up to 20 minutes if the expectant mother raises concerns during the questionnaire.

Discussion Topics

Establish rapport with patient during first contact. Some suggestions for topics include:

- + What is the sex of the fetus? (if mom knows)
- + Are mom/partner taking parenting classes?
- + Does she plan on parental leave from work after delivery?
- + What types of books is she reading?
- + Are mom/partner planning a nursery/babymoon/baby shower?

Any additional non-clinical topics around pregnancy that engage mom are encouraged. More examples can be provided if needed.

Scheduling Calls

Offer schedule flexibility. Have evening and/or weekend availability versus limiting calls to core business hours. Accommodate holidays to avoid missing weekly contact.

Develop a Plan

Create a plan that builds awareness of the signs and symptoms of premature labor and what to do if they recognize any changes

- + Instill higher sensitivity for any unusual changes or symptoms
- + Give direction for who to contact immediately
- + Reinforce it's better to call right away than to wait or contact a close friend/family member

Continuity of Care

Provide continuity of care – one nurse assigned to each patient with occasional backup coverage as needed for nurse unavailability.

CARE MANAGEMENT

Weekly Nurse Support Call & Compliance Questionnaire*

Patient _____

Phone _____

Weekly call performed? Yes Date: _____ Time: _____
 No Date of last call attempt: _____

The highest level of risk assessed for any question will also be the overall risk for the subject

Have you had a hospital visit since last contact due to symptoms of preterm labor/birth?

Yes No

Have you had a confirmed diagnosis of COVID-19 via an FDA-authorized diagnostic test since our last contact?

Yes No

Have you had any other illnesses since our last contact?

Yes No

Have you had any signs and symptoms of Preeclampsia since last contact?

Yes No

If "Yes," which of these symptoms did you have?

Headache
 Swelling
 Blurred vision or spots in front of eyes
 Upper right quadrant pain/epigastric pain
 None of the above

Have you had any accidents, falls or traumas since our last contact?

Yes No

If "Yes," please explain:

Have you complied with daily dosing of Progesterone since last contact?

Yes No N/A

If "No," how many doses did you miss since our last contact?

Have you complied with daily dosing of Aspirin since last contact?

Yes No N/A

If "No," how many doses did you miss since our last contact?

Have you smoked, vaped, or used nicotine since our last contact?

Yes No

(Whether new or continued use, please indicate "Yes" if the subject has used nicotine, smoked, or vaped since last contact)

How would you describe the movement of your baby?

Normal (Does Not Alter Risk) Increased (Does Not Alter Risk) Decreased (Recommend Kick Counts, High Risk) Absent (Recommend Kick Counts, High Risk)

Have you had a fever (>100° F) since our last contact?

Yes (High Risk) No (Low Risk)

Have you had any episodes of contractions since our last contact?

Yes No

If "Yes," how often are you having an episode of contractions?

One per day
(Low Risk)

2-3 times per day
(Moderate Risk)

3 times per day
(Moderate Risk)

During the episode, how many contractions do you have per hour?

<1 per hour
(Low Risk)

1-2 per hour
(Low Risk)

3-5 per hour
(Moderate Risk)

6 or more per hour
(High Risk)

During the episode, how intense are the contractions?

Very mild—slight tightening
(1-2/10) (Low Risk)

Mild—more intense tightening but not painful
(3-4/10) (Low Risk)

Moderate—light cramping, like a period
(5-6/10) (Moderate Risk)

Strong—cramping unable to talk during contractions due to discomfort
(7-8/10) (High Risk)

Severe pain
(9-10/10) (High Risk)

Do the contractions stop when you rest or drink fluids?

Yes
(Low Risk)

No
(Moderate Risk)

Have you experienced any vaginal bleeding since our last contact?

Yes No

If "Yes," How long have you had vaginal bleeding?

(Does not alter risk)

<24 hours

<1-2 days

<3-4 days

>4 days

Did bleeding begin within 24 hours of intercourse?

Yes
(Low Risk)

No
(Moderate Risk)

How would you describe the color of the bleeding?

Pink tinged
(Low Risk)

Dark brown
(Moderate Risk)

Bright red
(High Risk)

How would you describe the amount of bleeding?

Spotting; 1-2 drops on underwear or streaks in mucous. Does not require a pad.
(Low Risk)

Moderate—like a light period. Requires 1-2 pads per day.
(Moderate Risk)

Heavy—Greater than or equal to a heavy period. Requires >2 pads per day.
(High Risk)

Have you experienced a change in your vaginal discharge since our last contact?

Yes No

If "Yes," How long have you had vaginal discharge?

(Does not alter risk)

<24 hours

<1-2 days

<3-4 days

>4 days

How would you describe your discharge?

Mucous
(Moderate Risk)

Bloody
(High Risk)

Other
(Moderate Risk)

Have you experienced any leaking of watery, clear fluid since our last contact?

Yes No

If "Yes," How long have you been leaking watery, clear fluid?

(Does not alter risk)

<24 hours <1-2 days <3-4 days >4 days

How much fluid are you leaking?

A few drops. Does not require a pad.
(Low risk)

Moderate amount—intermittent with underwear wet. Requires 1 pad per day.
(Moderate risk)

Large amount—continuous trickle or gush. Requires >1 pad per day.
(High risk)

Have you felt pressure in your pelvis or vagina since our last contact?

Yes No

If "Yes," how long have you felt pressure?

(Does not alter risk)

<24 hours <1-2 days <3-4 days >4 days

How would you describe the pressure that you feel?

Very mild
(low risk)

Mild
(low risk)

Moderate
(moderate risk)

Strong
(high risk)

Severe
(high risk)

Have you experienced any other symptoms, not already addressed, that are concerning to you?

Yes No

If "Yes," please specify:

Did you visit the OB Triage or Emergency Department at the hospital this past week for pregnancy-related problems??

Yes No

If "Yes," please provide the indication:

Preterm Birth Assessment

Low Risk

No change in care recommended at this time

Moderate Risk

These symptoms should be reported to your primary obstetrics provider at your next visit. If you have any concerns before your next visit, call your primary obstetrics provider.

High Risk

These symptoms indicate a high risk for preterm birth. You should call your primary obstetrics provider immediately or go directly to the hospital where you plan to deliver for immediate evaluation.



CUSTOMER SUPPORT

CALL: (801) 990-6600

FAX: (801) 990-6601

EMAIL: support@preterm.com

*This form is based on the one used in the PRIME study and is provided as an illustrative example of what can be used for care coordination for a patient identified by the PreTRM® test having higher risk of preterm birth. The sharing of this example form does not constitute the practice of medicine or medical advice by Sera Prognostics, Inc. This form may not be appropriate to be used as-is for all patients, and each provider must either (a) independently adopt the form after carefully evaluating it for use with the provider's patients; or (b) adapt this form to the provider's own patients and processes. Sera Prognostics, Inc. disclaims any liability for the use of this form.



TOGETHER, WE CAN DO BETTER

Educate Providers.
Empower Moms. Help Babies.
Advance Science. Elevate Care.
Reach Maternity Deserts.
Inform Payers. Evoke Change.