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Robust cost efficacy of a novel, validated screening test at 12–20 Weeks gestation for the prediction of preterm birth (PTB) at or before 32 Weeks in singletons

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ABSTRACT

Objective: Preterm birth (PTB) at or before 32 weeks complicates up to 2 % of United States (US) births and accounts for 80 % of perinatal expenditures in the first year of life. Existing screening tests for PTB performed from 12 weeks to 19 weeks 5 days have receiver operated area under the curve (AUC) indices of <80 % and at most <70 %. We evaluated FutureBIRTH™, a unique maternal screening test comprised of plasma cell-free RNA for the prediction of PTB ≦ 32 weeks due to spontaneous labor (sPTB) with or without preterm premature rupture of the membranes (PPROM) or early-onset pre-eclampsia before 34 weeks (EOP). FutureBIRTH™ is supported by multiple validation studies derived from 12 weeks to 19 weeks 5 days gestation achieving AUCs of 84.2 % for sPTB and 94.1 % for EOP.

Methods: Using the US rates for EOP (0.5 %) and sPTB ≦ 32 weeks (1.8 %) and adjusting the US pregnancy/neonatal medical costs to US dollars (2017 value), we calculated the cost per 100,000 singletons with or without universal FutureBIRTH™ testing before 19 weeks and 6 days using three detection rates and assuming screen-positive women would be treated with and respond to aspirin (assumed 80 % efficacy for EOP) and vaginal progesterone (assumed 38 % efficacy for sPTB). We also assessed test performance at disease incidence rates below that of the US (down to 0.46 %). For considering screening costs, we assumed test costs of $750, and treatment costs of $1000 for patients over 20 weeks gestational age.

Results: The identification and treatment of 'at-risk' pregnancies by FutureBIRTH™ with existing therapies would reduce direct healthcare costs by up to $95 million per 100,000 births. The projected savings were robust and achievable at each FutureBIRTH™ price despite the conservative costs, efficacy, and detection rate assumptions. The incidence of PTB ≦ 32 weeks would decline by 40 %–50 % with a test cost of $750 and an 80 % detection rate.

Conclusion: The accurate risk assessment provided by universal FutureBIRTH™ screening coupled with existing preventative treatments could lead to a 40 %–50 % decrease in PTB ≦ 32 weeks due to sPTB and EOP among 'at-risk' pregnancies, covering the cost of screening and treatment while still saving $450-$950 per pregnancy.

1. Introduction

Over 15 million preterm births (PTB) worldwide annually result in greater than 1 million deaths[1] and lifelong sequelae for many survivors.[2] Very premature (28–32 weeks) and extremely premature (<28 weeks) newborns have the highest long-term complication rates and constitute the highest cost category in terms of healthcare.[3–5]

FutureBIRTH™ is a novel maternal blood test comprised of 5 plasma

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cell-free (PCF) RNAs (*PSME2*, *NAMPT*, *APOA1*, *APOA4*, and *Hsa-Let-7g)* measured between 11 weeks to 19 weeks 5 days weeks for the identification of women with high probability for PTB ≦32 weeks due to spontaneous labor (sPTB) with or without preterm premature rupture of the membranes (PPROM) or early-onset preeclampsia (EOP), which were shown to have the highest prognostic accuracy of any test reported to date.[6–8] The PCF RNAs appear to originate from the placenta and *in silica* studies support biologic plausibility further leading to the hypothesis that PTB associated with labor ± PPROM and EOP are related disorders.[6] The identification of these PCF RNA markers by 11 weeks in the majority of women who experience PTB ≦32 weeks strongly suggests that the occurrence of either sPTB, PPROM, or EOP is 'set' before 11 weeks of gestation. This conclusion is supported by trial data indicating that the efficacy of aspirin to prevent EOP declines with placental maturation and should be initiated by 16 weeks for maximal efficacy.[9]

Predictors of PTB include historical, biological, and mechanical markers.[10–12] Studies of these markers are often modest in sample size, and metrics such as sensitivity, specificity, and negative/positive predictive values are affected by disease prevalence. As a result, the receiver operated area under the curve (AUC), which is less affected by disease prevalence, is considered to be one of the most useful parameters with which to evaluate model efficacy, as it provides an aggregate measure of performance across all possible classification thresholds.[13] An AUC between 90 % and 100 % is considered to be excellent, 80 %–90 % is good, 70 %–80 % is fair, 60 %–70 % is poor, and 50 %–60 % is a failure.[14] Prior FutureBIRTH™ studies have applied the resulting AUCs to calculate the detections rates for three fixed FPRs ranging from 10 to 30 %[7] recognizing that an acceptable false-positive rate will vary with the therapy risk, cost, and efficacy.

Before the development and validation of FutureBIRTH™, AUCs in the good to excellent range were elusive regarding PTB screening. For example, cervical fetal fibronectin (fFN) performed at 16–22 weeks yields AUCs of 51 %–54 % for sPTB≦32 weeks, and transvaginal sonographic cervical length (CL) at similar gestations yields AUCs of 51 %–58 % for sPTB≦32 weeks.[15] These AUCs are similar to those achieved by clinical history alone.[10] The ratio of insulin-like growth factor binding protein 4/sex hormone-binding globulin (IBP4/SHBG) is marketed for the prediction of PTB ≦32 weeks. In this case, a maternal blood sample is obtained at 19.1–20.9 weeks, and the test subject to several large validation studies.[16,17] In the largest and most recent clinical study, 847 women were selected from a biobank of 5011 pregnancies.[18] The BMI-corrected AUC was 76 % for the prediction of PTB <32 weeks. In contrast, the AUC for FutureBIRTH™ was 84.1 % for sPTB≦32 weeks and only FutureBIRTH™ also screened for EOP (AUC of 94.5 %).[6–8] FutureBIRTH™ perform equally well in nullipara and multipara.

The objective of this study was to examine the potential cost impact of applying FutureBIRTH™ or another test of similar prognostic accuracy to a representative US population of 100,000 singleton pregnancies assuming universal screening with test-identified at-risk patients using only currently available therapies with demonstrated[5] or suggested efficacy.[19,20]

Table 1
Basis for calculations.

Maternal and Child Costs[23] Adjusted for Medical Inflation (2017 USD $) *Delivery and Year 1*	
Normal Full Term	$ 26,788
≦ 32w and or < 1500 g	$184,000
Other Preterm	$ 98,008
US Rates[21]	
Rate of EOP < 34 w	0.5 %
Rate of sPTB ≦ 32w	1.8 %
Treatment costs per pregnancy	
Assumes 20 weeks of treatment at a self-pay rate	
sPTB positive screen	$27.97
EOP positive screen	$ 6.80

2. Methods

The United States (US) incidence rates for EOP (<34 weeks) and sPTB≦32 weeks were identified as 0.5 % and 1.8 %, respectively[21,22] (Table 1). The medical costs for mother and child[23] were derived from a comprehensive database including term pregnancy, delivery ≦32 weeks, a birth weight below 1500 g (the average weight of a 32-week newborn in the US), and all other PTBs. The costs were then adjusted for medical inflation to the value of the US dollar in 2017 (Table 1). We next tested the cost efficacy of screening with and without universal FutureBIRTH™ screening using a patient cost of either $750 or $1000 and a clinically relevant range of detection rates derived from prior FutureBIRTH™ validation studies (100 %, 80 %, and 60 %) (Table 2).[7] Lastly, to enhance the robustness of our cost-efficacy estimates, we repeated the analysis reducing the incident rates for sPTB≦32 weeks and EOP by 60 %, 40 %, and 20 % of the US rate, such that the tested incident rates were 1.38 %, 0.92 %, and 0.46 %, respectively. As a result, the findings of this study should apply to any country in the world. The costs of preterm infants delivered >32 weeks were allocated to the other preterm category.

The efficacy rate currently used to calculate the impact of the preventative treatments for women at risk for PTB≦32 weeks was a conservative estimate derived from a current meta-analysis, if available, or the guiding randomized controlled trial. In doing so, we had to make several assumptions as follows. For EOP, the related trials[24] were confined to women who had an abnormal first trimester screening test comprised of maternal characteristics, clinical and medical past histories, a uterine artery Doppler resistance, and two biochemical markers (pregnancy-associated plasma protein A [PAPP-A] and serum placental growth factor [PlGF]).[9] The reported detection rates ranged from 80 % to 95 % and the AUC percentage was typically in the low 90s. The detection rate of FutureBIRTH™ for EOP in a prospective cohort was 100 % with a 20 % fixed false positive rate.[7] In this study, we assumed that the population identified by these two screening tests had to greatly overlap based on their mutually high detection rates. Next, the efficacy of aspirin to prevent EOP is compliance-dependent with the highest prevention rates associated with >90 % compliance and an absent maternal history of chronic hypertension. For the purposes of this study, we assumed at-risk women for EOP began taking aspirin before 16 weeks, but that it would prevent only 80 % of EOP cases.

Progestogen supplementation for the prevention of sPTB≦32 weeks has been proposed for decades. Despite considerable effort, its efficacy remains to be confirmed. We agree with Norman[25] that the conflicting views on efficacy may ultimately be resolved by a Patient-Centered Outcomes Research Initiative (PCORI)-funded individual patient data meta-analysis. Until then, we utilized the analysis of Romero et al.[26] who compiled individual patient data from 5 prospective randomized trials employing vaginal progesterone and concluded that vaginal progesterone reduced the sPTB≦32 weeks rate by 38 % (Romero et al. Figure, 3[26]). The selection criteria employed by these trials varied but typically included a prior PTB and/or a short sonographic cervical length; i.e., the women were at high risk for PTB. In our prior cohort study, FutureBIRTH™ had a detection rate for sPTB≦32 weeks of 79 % with a 30 % fixed FPR.[7] In the same study,[7] a cervical length determination performed 3–4 weeks after the FutureBIRTH™ test panel increased the

Table 2
Summary of FutureBIRTH™ prospective performance.

	AUC	*P*	Detection Rate (%)		
			10 % FPR	20 % FPR	30 % FPR
sPTB ≦ 32 weeks (plus prior PTB history)	84.2	<0.001	62	76	79
EOP < 34 weeks (plus prior PreE history, MAP)	94.1	<0.001	83	100	100
All PTB ≦ 32 weeks		<0.001	69	78	89

FPR = fixed false-positive rate.

overall detection rate for sPTB≦32 weeks to 87 %. For this study, we assumed that vaginal progesterone reduced the rate of FutureBIRTH™-identified at-risk women who were compliant to be 38 %.

Total treatment costs for the duration of pregnancy (20 weeks, 16–36 weeks gestation) were calculated by an end-user cost obtained from a national US marketer- 100 mg micronized progesterone qd pv- $27.97 (SingleCare™ on 8/24/20, US zip code 66208) and low dose aspirin 81 mg qhs -$6.80 (SingleCare™ on 8/24/20, US zip code 66208).

3. Results

At a cost of $750 per patient, universal screening before 20 weeks of gestation for the prediction of PTB≦32 weeks using the FutureBIRTH™ test panel with an 80 % detection rate would be cost-effective and produce a PTB≦32 weeks incidence of just 0.46 %, or one-fifth of the current US incidence rate (Table 3a). Even with a lower detection rate of 60 %, universal screening with FutureBIRTH™ would be a cost-effective measure in a population with an incidence rate of 1.38 % for PTB≦32 weeks (Table 3a). Under these conditions, universal screening with FutureBIRTH™ with an 80 % detection rate, a rate demonstrated in a prior prospective study, would save $61,291,268 in direct medical costs per 100,000 births, or $2.3 billion per year with the estimated 3.8 million annual births in the US.[7] Even at a cost of $1000 per test, universal screening via FutureBIRTH™ for PTB≦32 weeks would remain a cost-effective screen in a population with an incidence of 1.38 % and a 100 % detection rate, or an incidence of 2.3 % if the detection rate was 80 % (Table 3b).

4. Discussion

Preterm birth is responsible for about 80 % of all healthcare costs in the first year of life. Using recent estimates of therapeutic efficacy for existing treatments to prevent early PTB (in this instance, low dose aspirin and vaginal progesterone) employing detection rates that have been achieved with FutureBIRTH™, the current study of the impact of universal screening of pregnant women reaching 11–19 weeks shows a potential cost reduction for the US healthcare system of $61 million per 100,000 pregnancies net of screening and treatment costs, assuming a detection rate of 80 % for both sPTB≦32 weeks and EOP. Nationwide, universal screening of the 3.8 million pregnancies in the US annually at $750 per patient with detection rates between 60 and 80 % would avoid between $1.0–2.3 billion in direct healthcare costs annually.

Although our analysis was based on US data, we have expanded our analysis to look at the impact of screening should the population in question have a lower incidence of PTB≦32 weeks. Universal screening remained cost-effective even when the population screened had an incidence rate of 0.46 %, one-fifth of that of the US, with an 80 % detection rate. While the cost of healthcare delivery may well be different, the likelihood of local applicability is high.

Our findings were similar to those published by Caughey et al.[27] with several important differences. Most notably, the test that they envisioned did not exist at the time, but it does now. FutureBIRTH™ fulfills their test criteria while the estimated cost of the test was lower than Caughey et al. suggested. Furthermore, our assumed efficacy for progesterone (38 %) was less than half of what Caughey et al. assumed it would be. In addition, FutureBIRTH™ is the only test performed before 20 weeks that accurately and independently predicts the future development of both sPTB and EOP.

Our estimates are likely an underestimate of the societal cost savings accrued by universal screening as they include only conservative estimates of direct medical costs for the delivery and the first year of life. Hall and Greenberg[28] found that preterm infants have poorer educational and labor force outcomes, and Hirschberger et al.[29] reported that among children born ≦32 weeks, 25 % had cognitive impairment at the age 10 years, 11 % had cerebral palsy, 7 % were diagnosed with autism

Table 3a
Cost Efficacy of Universal Screening with FutureBIRTH™ @ $750 per test by Population Incidence and Detection Rate.

100% Detection Rate							
				PTB≦ 32w Incidence Rate 2.30%	PTB≦ 32w Incidence Rate 1.38%	PTB≦ 32w Incidence Rate 0.92%	PTB≦ 32w Incidence Rate 0.46%
	Detected/ 100,000	Prevented		Savings			
EOP < 34w	500	80%	400	-$62,884,809	-$49,126,078	-$42,246,713	-$35,367,348
sPTB ≦ 32w	1,800	38%	684	-$107,533,023	-$84,005,594	-$72,241,879	-$60,478,164
Cost of Testing				$75,000,000	$75,000,000	$75,000,000	$75,000,000
Cost of Therapy				$50,345	$32,248	$21,498	$10,749
Net cost of screening				-$95,367,487	-$58,099,424	-$39,467,094	-$20,834,763
80% Detection Rate							
				PTB≦ 32w Incidence Rate 2.30%	PTB≦ 32w Incidence Rate 1.38%	PTB≦ 32w Incidence Rate 0.92%	PTB≦ 32w Incidence Rate 0.46%
	Detected/ 100,000	Prevented		Savings			
EOP < 34w	400	80%	320	-$50,307,847	-$39,300,862	-$33,797,370	-$28,293,878
sPTB ≦ 32w	1,440	38%	547	-$86,026,418	-$67,204,475	-$57,793,503	-$48,382,532
Cost of Testing				$75,000,000	$75,000,000	$75,000,000	$75,000,000
Cost of Therapy				$42,997	$25,798	$17,199	$8,600
Net cost of screening				-$61,291,268	-$31,479,539	-$16,573,674	$-1,667,810
60% Detection Rate							
				PTB≦ 32w Incidence Rate 2.30%	PTB≦ 32w Incidence Rate 1.38%	PTB≦ 32w Incidence Rate 0.92%	PTB≦ 32w Incidence Rate 0.46%
	Detected/ 100,000	Prevented		Savings			
EOP < 34w	300	80%	240	-$37,730,885	-$29,475,647	-$25,348,028	-$21,220,409
sPTB ≦ 32w	1,080	38%	410	-$64,519,814	-$50,403,356	-$43,345,127	-$36,286,899
Cost of Testing				$75,000,000	$75,000,000	$75,000,000	$75,000,000
Cost of Therapy				$32,248	$19,349	$12,899	$6,450
Net cost of screening				-$27,218,451	-$4,859,654	$6,319, 744	$17,499,142

Table 3b
Cost Efficacy of Universal Screening with FutureBIRTH™ @ $1000 per test by Population Incidence and Detection Rate.

100% Detection Rate							
				PTB≦ 32w Incidence Rate 2.30%	PTB≦ 32w Incidence Rate 1.38%	PTB≦ 32w Incidence Rate 0.92%	PTB≦ 32w Incidence Rate 0.46%
	Detected/ 100,000	Prevented		Savings			
EOP < 34w	500	80%	400	-$62,884,809	-$49,126,078	-$42,246,713	-$35,367,348
sPTB ≦ 32w	1,800	38%	684	-$107,533,023	-$84,005,594	-$72,241,879	-$60,478,164
Cost of Testing				$100,000,000	$100,000,000	$100,000,000	$100,000,000
Cost of Therapy				$50,345	$32,248	$21,498	$10,749
Net cost of screening				-$70,367,487	-$33,099,424	-$14,467,094	$4,165,237
80% Detection Rate							
				PTB≦ 32w Incidence Rate 2.30%	PTB≦ 32w Incidence Rate 1.38%	PTB≦ 32w Incidence Rate 0.92%	PTB≦ 32w Incidence Rate 0.46%
	Detected/ 100,000	Prevented		Savings			
EOP < 34w	400	80%	320	-$50,307,847	-$39,300,862	-$33,797,370	-$28,293,878
sPTB ≦ 32w	1,440	38%	547	-$86,026,418	-$67,204,475	-$57,793,503	-$48,382,532
Cost of Testing				$100,000,000	$100,000,000	$100,000,000	$100,000,000
Cost of Therapy				$42,997	$25,798	$17,199	$8,600
Net cost of screening				-$61,291,268	-$31,462,340	$8,426,326	$23,332,190
60% Detection Rate							
				PTB≦ 32w Incidence Rate 2.30%	PTB≦ 32w Incidence Rate 1.38%	PTB≦ 32w Incidence Rate 0.92%	PTB≦ 32w Incidence Rate 0.46%
	Detected/ 100,000	Prevented		Savings			
EOP < 34w	300	80%	240	-$37,730,885	-$29,475,647	-$25,348,028	-$21,220,409
sPTB ≦ 32w	1,080	38%	410	-$64,519,814	-$50,403,356	-$43,345,127	-$36,286,899
Cost of Testing				$100,000,000	$100,000,000	$100,000,000	$100,000,000
Cost of Therapy				$32,248	$19,349	$12,899	$6,450
Net cost of screening				-$27,218,451	$20,140,346	$31,319,744	$42,499,142

spectrum disorder, and 7 % were diagnosed with epilepsy. Stevens et al.[30] found that of children born within 28–32 weeks of gestation to women with EOP, 2.7 % died, 41.3 % experienced respiratory distress, 20.3 % had sepsis, 5.9 % an interventricular hemorrhage (IVH), and 3.9 % had retinopathy of prematurity. Further, 3 % of the mothers experienced acute renal failure, 3 % seizures, 5.2 % thrombocytopenia, and 0.2 % died. They estimated that the average cost of EOP≦32 weeks for delivery plus 18 months thereafter totaled $311,701 per mother and child. By avoiding 40–50 % of births ≦32 weeks, the direct and indirect cost savings would be massive.

In 2018, US Medicaid[31] insured 43 % of all births while commercial carriers covered 49.1 %. Medicaid paid for a greater share of births in rural areas, among women under 19 years, and women with lower levels of educational attainment-all of which are considered risk factors for PTB. Medicaid also paid for a greater share of Black, Hispanic, American Indian, and Alaska Native women's births. Two-thirds of women covered by Medicaid have had a prior birth and 6 % a prior PTB. In addition, more than half of the women with Medicaid-covered births were either overweight or obese and almost 15 % smoked tobacco prior to pregnancy. One percent of women covered by Medicaid had pre-pregnancy diabetes and 2 % had pre-pregnancy hypertension, both of which are risk factors for PTB and EOP. The share of women with potential complicating health conditions was similar across rural and urban areas for those covered by Medicaid except for tobacco use, which was more prevalent in rural areas. Eleven percent of infants born to Medicaid-covered mothers and 9 % of those born to privately insured and uninsured women delivered <37w. The Medicaid rate of preterm births (<37 weeks) was highest in Mississippi (14.4%) and lowest in Vermont (8.7%). It is unlikely Medicaid costs are lower than those modeled in the current study, and would therefore also support universal screening as outlined in this study as cost-effective.

It has been argued the risk of aspirin is so low, that all women should take low-dose aspirin (variously defined as 60 mg–150 mg qd) throughout pregnancy. Excluding the risk of severe allergy, there are at least three potential flaws to this position. The first is patient compliance. Prevention of EOP is compliance-dependent with the optimal compliance rate >90 %.[9] While there are no studies of pregnant women outside of clinical trial conditions, there have been several studies of patients prescribed secondary therapy for a prior myocardial infarction. Risk factors associated with poor adherence (defined as in those studies as <50 % of prescribed tablets) include common pregnancy risk factors such as cigarette smoking, obesity, and a lack of exercise.[32] Compliance with an aspirin regimen in patients with a prior myocardial infarction was particularly low- 65 % (53 %–77 %).[33] It seems unlikely that the compliance of young, self-described healthy women who lack the motivational fear of suffering another myocardial infarction will be higher. The second flaw is the potential for unexpected outcomes secondary to aspirin. Petersen et al.[34] noted more than a doubling of bilateral spastic cerebral palsy in children exposed to aspirin across gestation.

The final potential flaw is that low-dose aspirin does not appear to lower PTB rates from PPROM or spontaneous labor when given to all nulliparas,[35] but rather reduces only those PTBs associated with hypertension.[36] If true, universal aspirin would not address more than two-thirds of the births ≤32 weeks. Taken together, while the simplicity and availability of universal aspirin treatment are appealing, it will not solve the problem of extreme PTB and may make the outcomes worse. Targeted therapy would minimize unnecessary exposure and provide a compliance incentive.

The impact of supplemental progestogens for the prevention of sPTB remains controversial. And while several professional organizations consider vaginal progesterone a standard of care for certain indications,[19] there is no consensus on its effectiveness[25,37]. We have utilized the most up-to-date and comprehensive meta-analysis to illustrate the potential impact of vaginal progesterone as a potential 38 % reduction in PTB≦32 weeks, but realize whether the current treatment is

progesterone, cervical cerclage, or pessary, new targeted treatments for sPTB are desperately needed. The prospect of being able to objectively identify a high-risk pool of subjects in early pregnancy should benefit future therapeutic trials. Also, since the financial costs of PTB≦32 weeks represent the majority of all health care costs in the first year of life, even a small decrease in the PTB≦32 weeks rate could be cost-effective. Further, vaginal progesterone is no longer the only option. After the completion of this study, Carlson et al. published the results of a randomized clinical trial demonstrating a DHA supplement of 1000 mg per day given to at risk women decreased PTB≦32 by 50 %.[38]

In conclusion, universal screening of pregnant women with a singleton before 20 weeks with either FutureBIRTH™ or some yet to be discovered panel combined with current preventative therapy has the potential to reduce PTB≦32 weeks by 40 %–50 %, freeing up families and societies from the burden of extreme PTB.

Disclosure of interests

Robert Lee PhD: No related conflicts of interest.

Carl P. Weiner MD MBA: Founder of Rosetta Signaling Laboratory which controls the intellectual property related to plasma nucleic acid extraction and the RNA markers described including EU Patent No. 2646554, US patent No. 10,954,564 and European and US trademarks on the name FutureBIRTH™ (Serial No. 87/110459).

Contribution to authorship

Robert Lee PhD: Directed and performed the analyses, contributed to and edited the manuscript.

Carl P. Weiner MD MBA: Originated the study and wrote the manuscript.

Details of ethics approval

Exempt.

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