

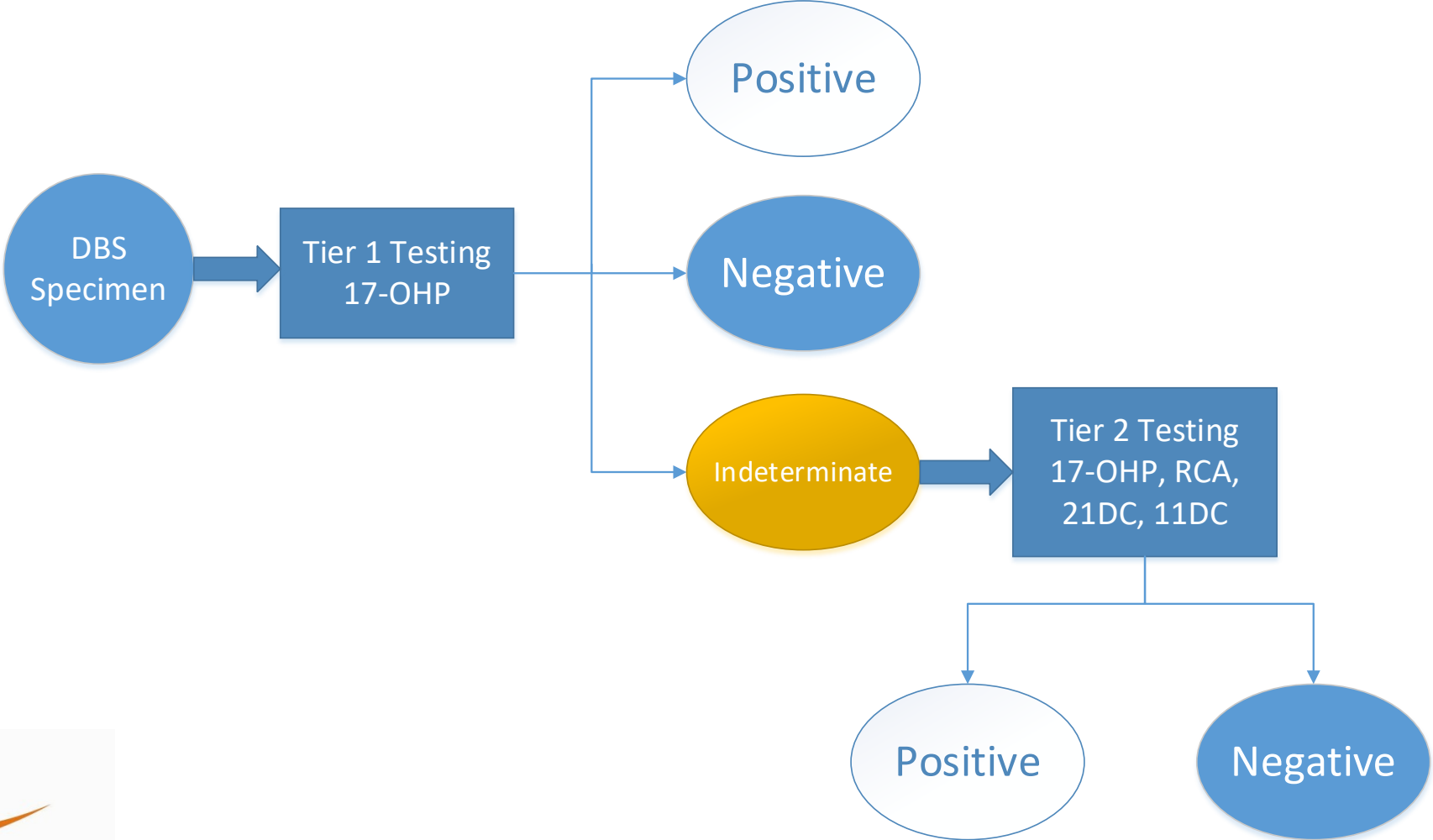
Baby Power: Improving Congenital Adrenal Hyperplasia Screening Performance with Neonatal Characteristics

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Current CAH screening workflow



CAH current cutoffs (17-OHP) and overall screening performance stratified by birth weight, 2018

Birth Weight	Indeterminate (nmol/L)	Positive (nmol/L)
<1000 g	80	300
1000-1499 g	80	200
1500-2499 g	55	80
≥2500 g	50	70

Birth Weight	Tier 1			Tier 2		Overall		
	Screen Positive	Indeterminate	True Positive	Screen Positive	True Positive	Screen Positive	True Positive	PPV
<1000 g	16	810	0	136	0	152	0	0.00%
1000-1499 g	14	447	0	110	0	124	0	0.00%
1500-2499 g	388	1134	1	21	0	409	1	0.24%
≥2500 g	305	1090	23	0	0	305	23	7.54%
Total	723	3481	24	267	0	990	24	2.42%

Our endeavor

- Identify cost-effective changes in CAH Tier 1 screening algorithm to improve overall screening performance
- Our goal: assess risk factors and cutoffs →
 - lower the number of false positives called out
 - increase overall PPV
- Step 1. Retrospective population-based cohort analysis to identify neonatal factors associated with 17-OHP level using multiple regression.
- Step 2. Presumptive positive only cohort analysis to simulate positive predictive value (PPV) based on the results from Step 1.
 - Identify potential cutoffs with visualizing logistic regression predictive curve

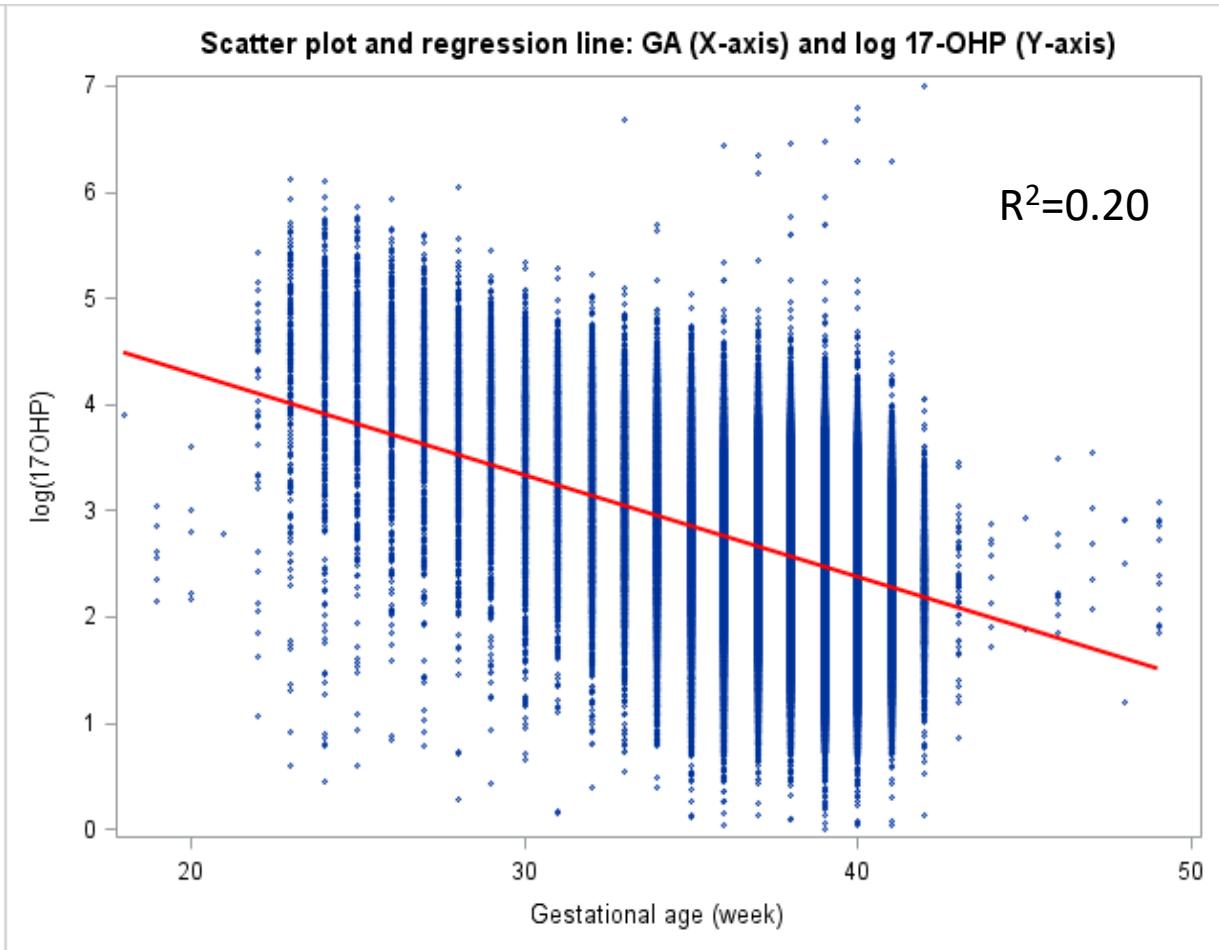
Step 1. Identify the neonatal factors for 17-OHP level

- Using 2017 California NBS data (N≈480,000), 3 random subsets of 50,000 and a 90 percentile subset (for verification purpose)
- Multiple regression model on 17-OHP (natural log transformed) and neonatal factors, including age at collection, sex, gestational age (GA), birth weight, nursery type
 - Interaction between factors also explored
- Results
 - **GA** is the strongest factor
 - followed by **nursery type**
 - **birth weight** is also a significant factor, but not as strong as GA

Correlation between 17-OHP and birth weight/GA



Birth Weight (grams)



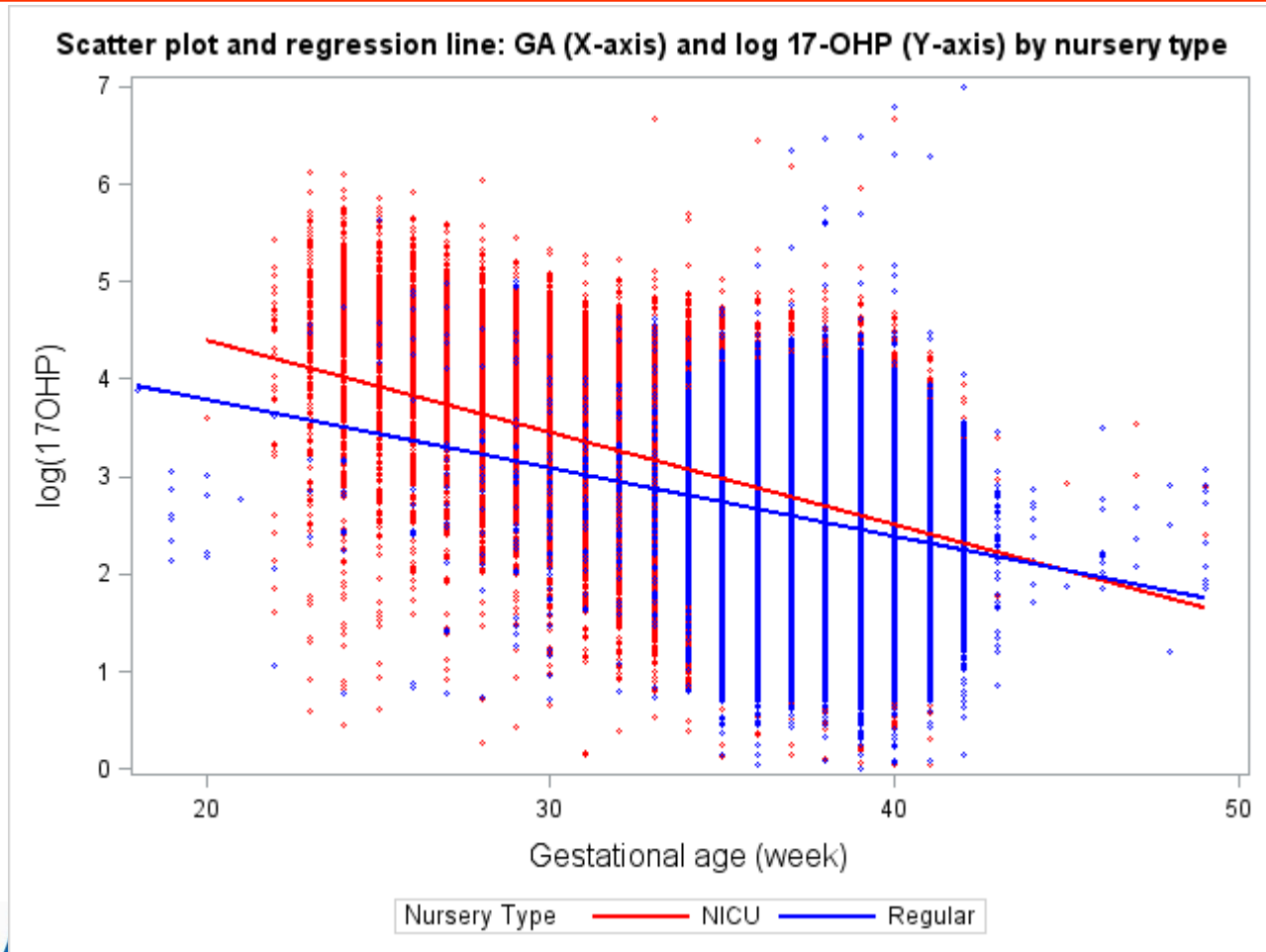
Gestational age (weeks)

NICU effect

A combination of prematurity and the presence of neonatal medical conditions potentially lead to higher 17-OHP levels in NICU settings.

	Presumptive Positive	Indeterminate	True Positive	PPV
NICU	891	2954	7	0.79%
Non-NICU	89	527	17	19.10%
Total	990	3481	24	2.42%

17-OHP value and gestational age, by nursery type



- In both NICU and regular nursery, the earlier the GA, the higher the 17-OHP level.
- 17-OHP level is higher in NICU newborns, especially among premature babies.
- **Nursery type difference diminishes among older gestational age newborns.**

17-OHP value and birth weight, by nursery type



- 17-OHP level is higher in NICU low birth weight newborns compared to regular nursery.
- Nursery type difference diminishes among normal birth weight newborns.
- **17-OHP level does not significantly correlate with birth weight among regular nursery newborns.**

Conclusion and Reflection for Step 1

- Among neonatal factors, gestational age (GA) has the strongest association with 17-OHP.
 - 17-OHP cutoff adjustment based on gestational age (GA) could lead to improved screening performance.
- Similar results are found using smaller verification subsets, including the 90 percentile sample.
- 17-OHP cutoff based on birth weight could be fine-tuned.
- Nursery type is a moderator for both GA and birth weight in relation to 17-OHP, and could be built into interpretation algorithm.

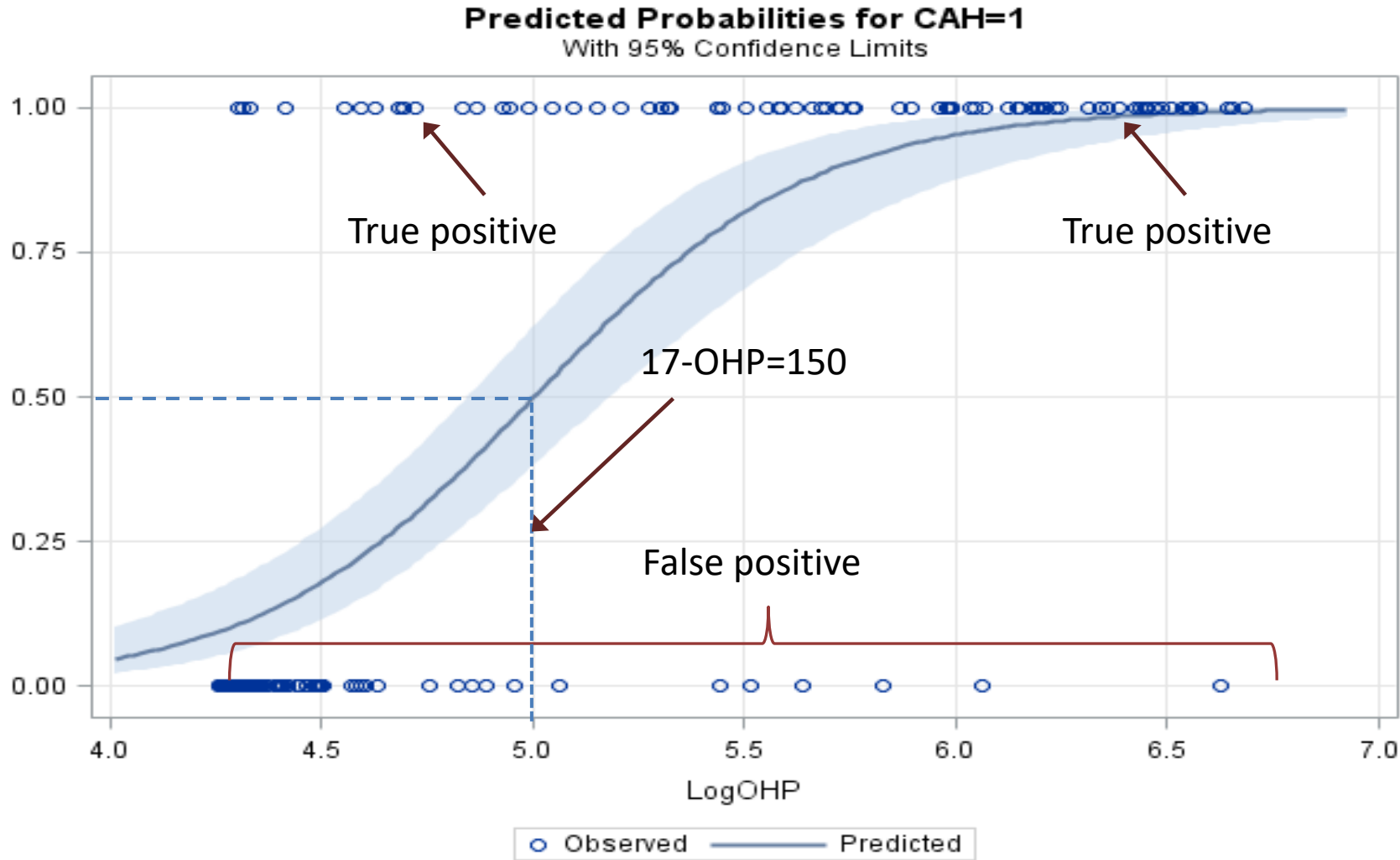
Step 2. Identify new 17-OHP cutoffs

- Using 2012-2015 and 2017 California CAH presumptive positive data (N≈4,000), confirmed true positive cases (classical) included.
 - Before 2012, gestational age (GA) data are not available
- Logistic regression predictive curve (CAH true positive = 1) sliced with nursery type and gestational age (GA) group
 - To help visualize and locate potential cutoff points
 - Two cutoffs, Tier 1 Positive and Tier 1 Indeterminate
- Using 2016 and 2018 NBS data to validate the performance of the new cutoffs.
 - Further fine-tuning if needed.

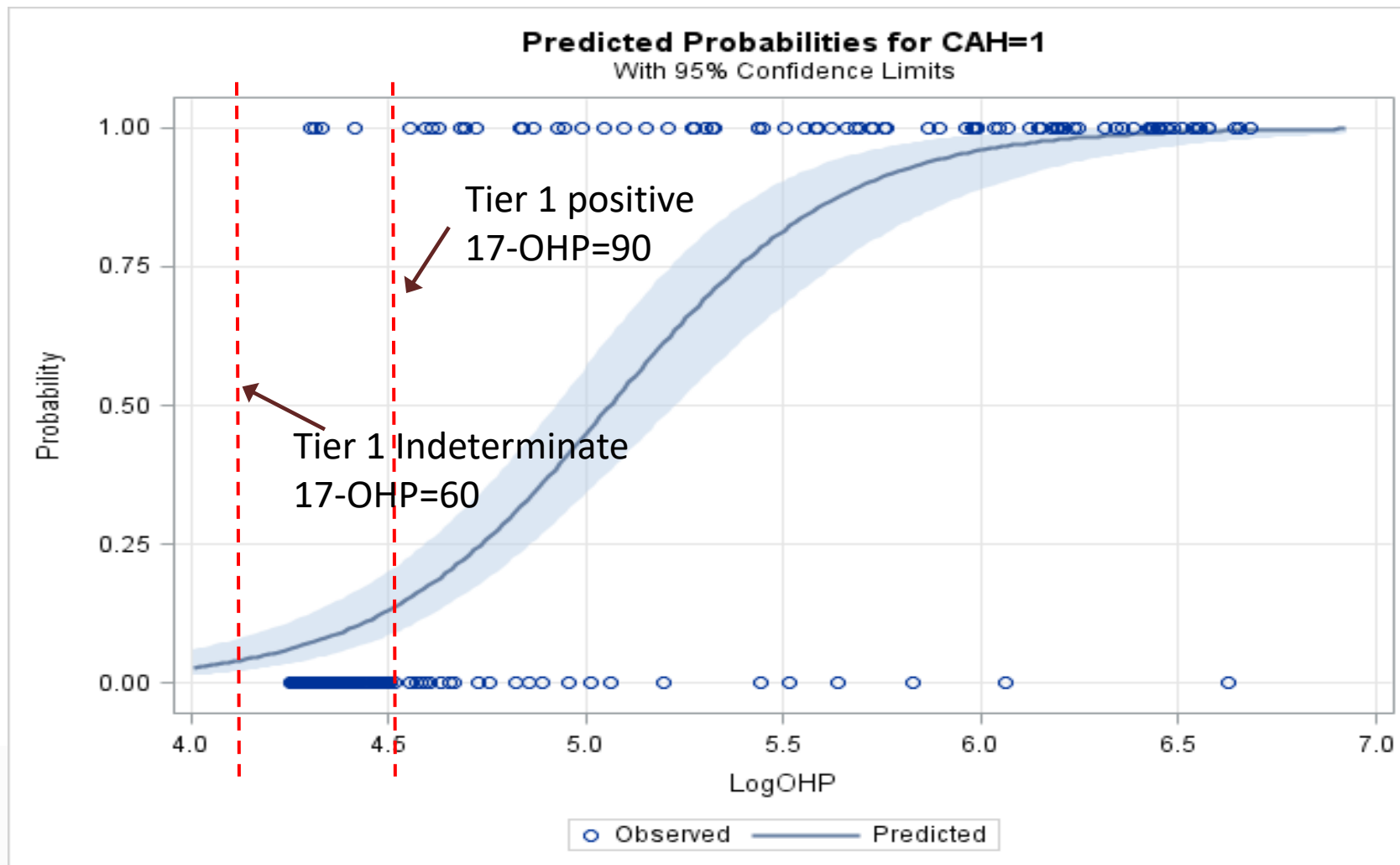
Predicting CAH true positive with 17-OHP for non-NICU presumptive positives

It's actually a PPV!

Probability



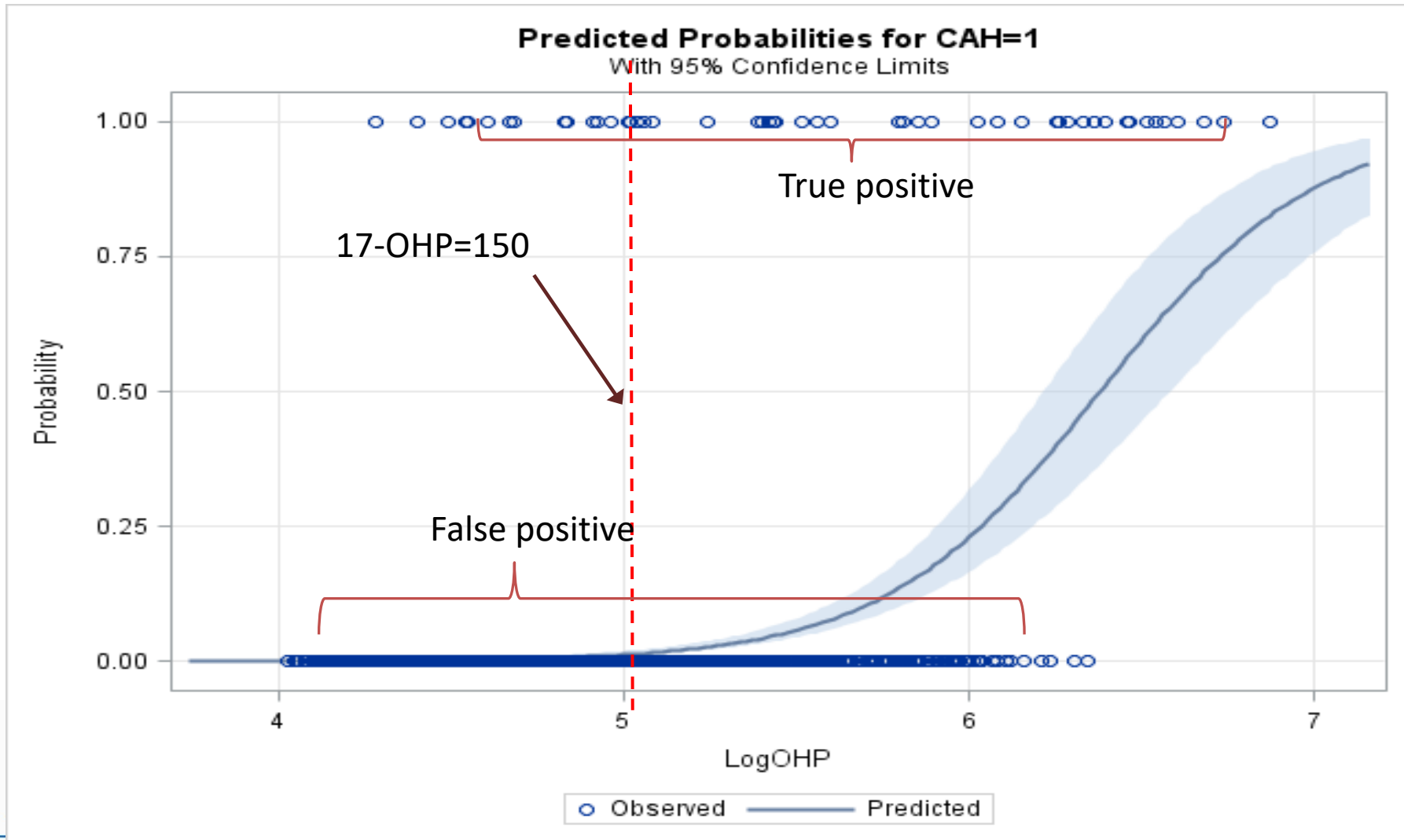
Predicting CAH true positive with 17-OHP for **non-NICU** presumptive positives, GA \geq 37 weeks



How to spot a cutoff point using retrospective data?

- A decent PPV (Y axis value) based on the predictive curve, at least an observable PPV (> 0)
- Try not to leave too many true positives to be called out in second tier
 - Second tier testing may have false negative
- Be conservative with indeterminate cutoff

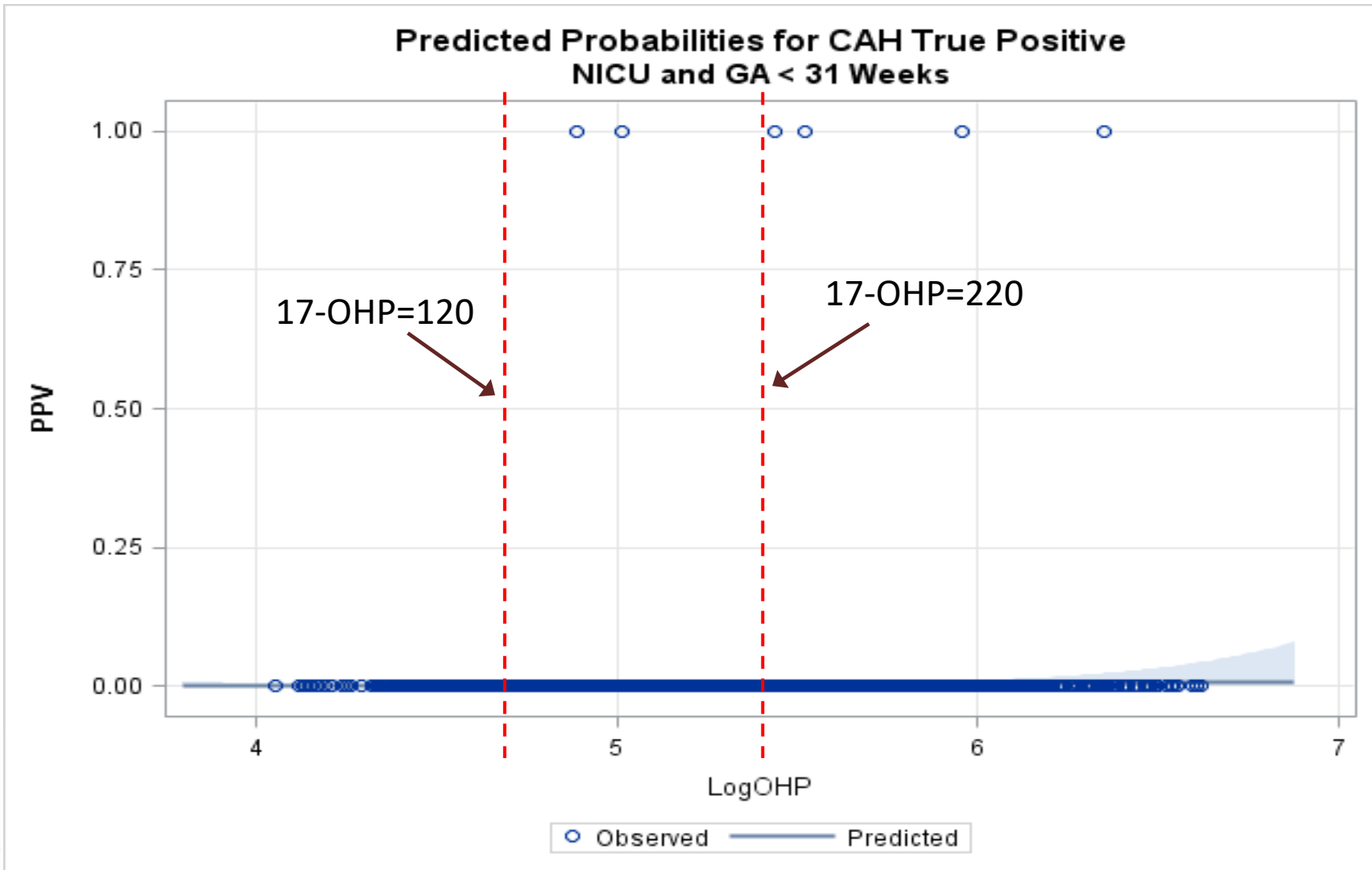
Predicting CAH true positive with 17-OHP among all NICU presumptive positives



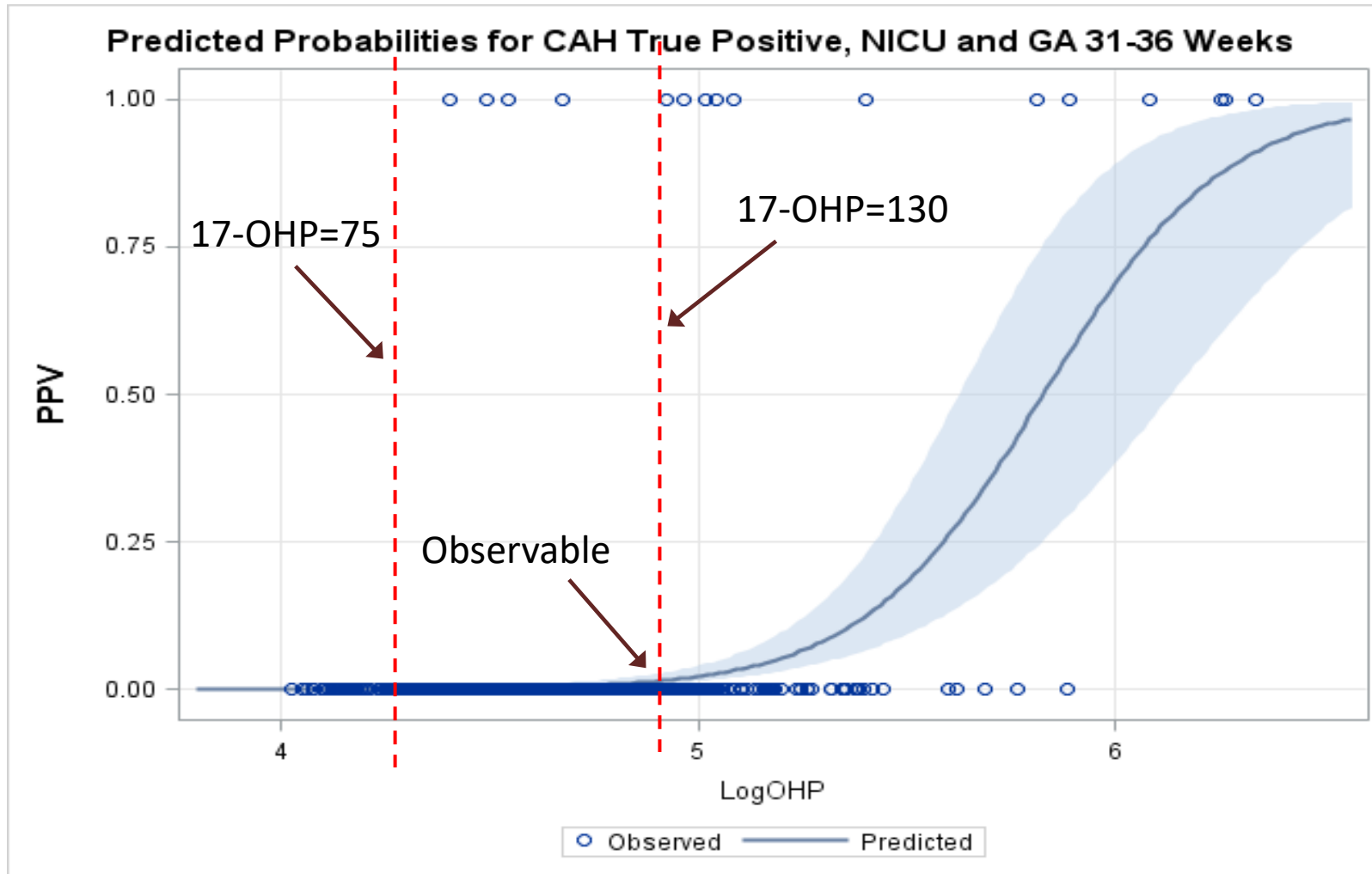
What does the previous slide tell us?

- Overall, CAH predictive model in NICU is not “perfect”
 - PPV is not observable until 17-OHP=150
 - Difficult to spot a good point for positive cutoff
 - Too many false positives
 - Too many true positives specimens would be called out by Tier 2 testing
- Sliced by gestational age (GA) may help
 - Recall the analysis from Step 1, GA effect is stronger in NICU

Predicting CAH true positive with 17-OHP among NICU presumptive positives, GA \leq 30 weeks



Predicting CAH true positive with 17-OHP among NICU presumptive positives, GA 31-36 weeks



Potential CAH Tier 1 interpretation algorithm based on nursery type and gestational age

	Gestational age	Indeterminate (nmol/L)	Positive (nmol/L)
NICU	<30 weeks	120	220
	31-36 weeks	70	200
	≥37 weeks	65	90
Non-NICU	<37 weeks	80	150
	≥37 weeks	55	90

Current birth weight-based cutoffs

Birth weight	Indeterminate	Positive
<1000 g	80	300
1000-1499 g	80	200
1500-2499 g	55	80
≥2500 g	50	70

The RESULTS: 1st Tier after suggested cutoff

- Using 2016 and 2018 NBS data (N ≈ 1 million screened) as testing datasets, the new cutoffs would yield:
 - 75% reduction in 1st tier presumptive positives (PP).
 - 60% reduction in indeterminate cases for 2nd tier testing.
 - 95% of true positive cases would be called out in the first tier.
 - No missing cases (0 false negative)
 - PPV could increase 400% after 2nd tier screen positives are counted.

	Current		Experiment	
Year	Indeterminate	1 st Tier PP	Indeterminate	1 st Tier PP
2016	3315	660	1260	168
2018	3481	723	1455	171

Conclusions and discussion

- Our existing framework of using birth weight-specific cutoffs is reasonable but needs improvement.
 - 17-OHP is a reliable biomarker for CAH screening except for premature newborns in NICU. (If practical, a re-draw would be desirable.)
- Modifying cutoffs by taking nursery type and gestational age into consideration can significantly reduce false positives and increase PPV.
 - Similar process can be used to find new cutoffs for different birth weight groups.