

Newborn Screening and Congenital Hypothyroidism

Updating Algorithms and Timeliness of Screening

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Disclosures

- Nothing to disclose

Background- Congenital Hypothyroidism

- Reported Incidence: 1:1,660 to 1:2,828 live births which translates to 18-40 cases per year
- Goal is to make diagnosis and start treatment quickly
 - National timelines suggest treatment should be started within 14-21 days
 - Some states test once and some test twice which is reflected in the timelines
 - Early onset of treatment is key to preventing mental retardation
 - Missed diagnosis can result in cretinism or severe mental retardation
- Historical standards were based upon testing done at 72 hours of age reflecting the duration of hospitalization after birth
 - Most babes are now discharged in 24-48 hours

Background to Current Analysis

- Endocrinologist developed a new TSH testing device and wanted to promote it's use in newborn screening
 - Stated goal was to improve the timeliness of screening by making test available with almost immediate result
- Undertook an analysis of TSH values in the pediatric population
 - Reviewed a large amount of lab data in children under the age of 2 years
 - Assumed that all high TSH values(> 20 mIU/L) in this age group were due to congenital hypothyroidism
 - No chart review was performed
- Concluded that the state newborn screening program is missing cases and children in the state are inadequately treated
 - Suggested diagnosis was delayed in 50% of cases

“Missed Cases and Delayed Diagnosis”

- Reviewed 5959 TSH values collected at Intermountain Healthcare facilities between 2006 and 2016 and identified patients under age 2 years with TSH \geq 20 mIU/L for chart review.
- 99 patients identified with TSH over 20.
 - 96 patients analyzed.
 - 72 were diagnosed with CH (75%),
 - 62 (86%) diagnosed and treated appropriately
 - 10 (14%) had a delay in diagnosis or treatment
 - 21 (21.9%) did not have CH (normal labs on repeat, intercurrent illness, medication, etc)
 - 3 (3.1%) unable to determine diagnosis.

Questions

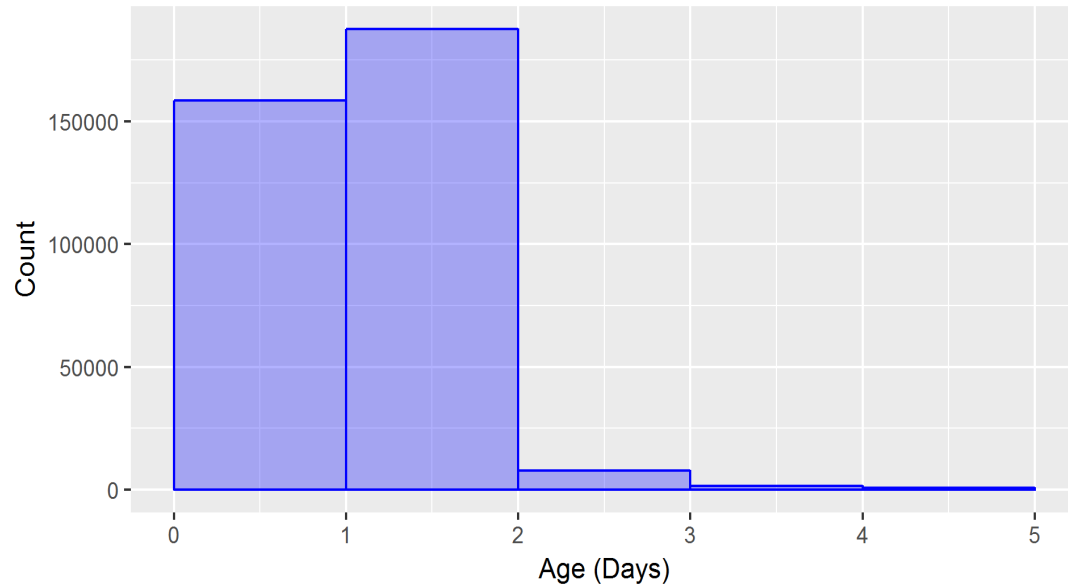
- Is the program missing cases or is the diagnosis delayed?
- What are our program statistics?
 - Are defined TSH values for both first screen and second screen correct?
 - Are screens being done in a timely manner, eg when expected
- Can we improve our processes?
 - Is there justification to doing 2 tests?
 - Is the follow up to an abnormal screen appropriate?

Data Analysis

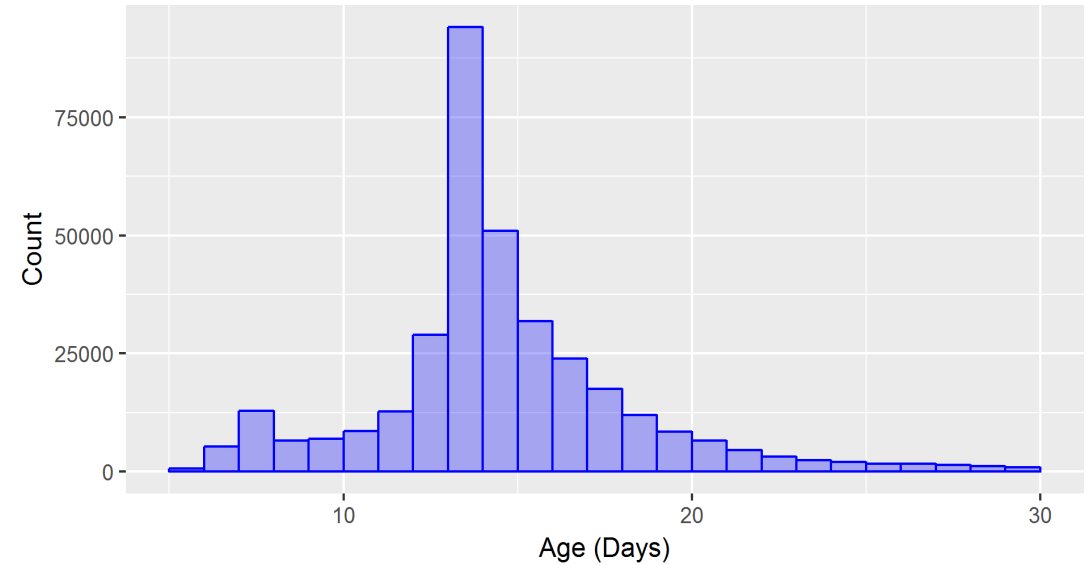
- NBS data for 359, 342 infants born between 2010 and 2016 was analyzed
 - 359,432 first screens analyzed
 - First screen recommended at 24-48 hours
 - Abnormal is defined as TSH > 40 mIU/L, critical is defined as > 230
 - 356,599 second screens analyzed
 - Second screen recommended at 7-21 days
 - Abnormal is defined as TSH > 40 mIU/L and critical as > 230
- Data reviewed on the babies identified on either screen as having hypothyroidism
 - 130 cases were identified during this time frame
 - 98 were identified on the first screen and 25 on the second
 - 18-19 cases per year identified average consistent with reported incidence
 - 7 cases did not have complete TSH data available
- This study compared TSH concentrations of the overall population to 130 CH cases and performed a retrospective cut-off analysis to assess the impact of lowering TSH cut-offs³

Characteristics of Newborn Screen Collection

Age of 2010 - 2016 TSH First Card



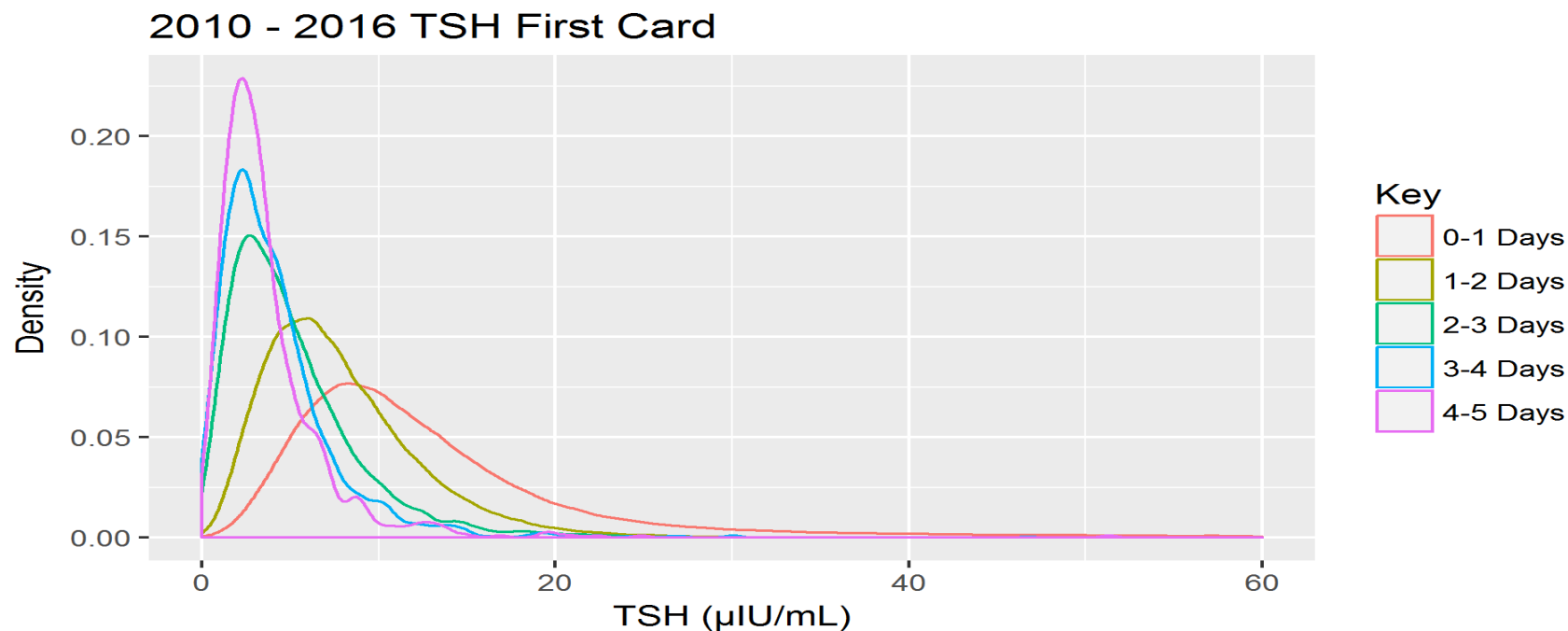
Age of 2010 - 2016 TSH Second Card



First screen is fairly timely

Second screen much more variable

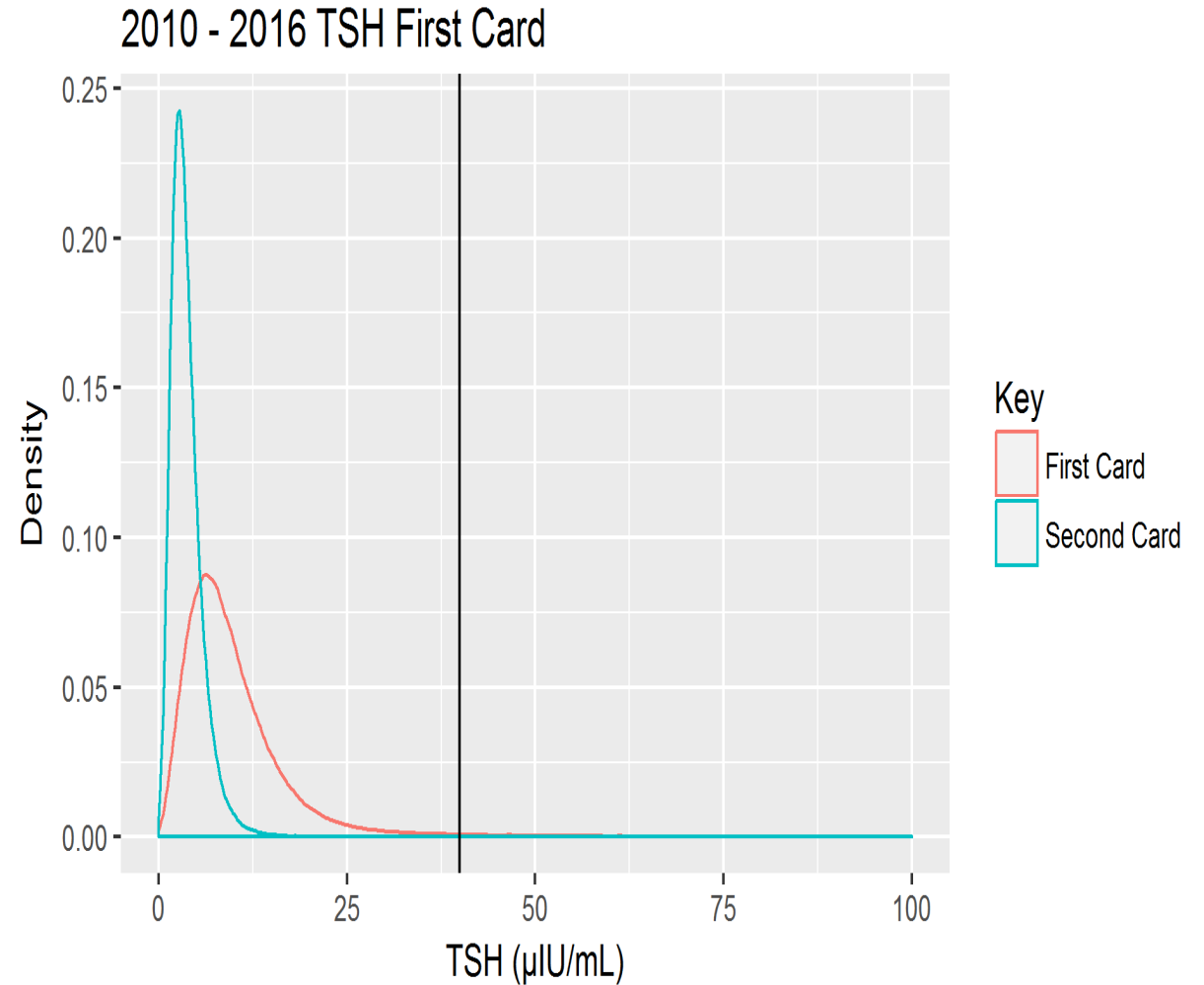
TSH Values on Screen #1 by Day



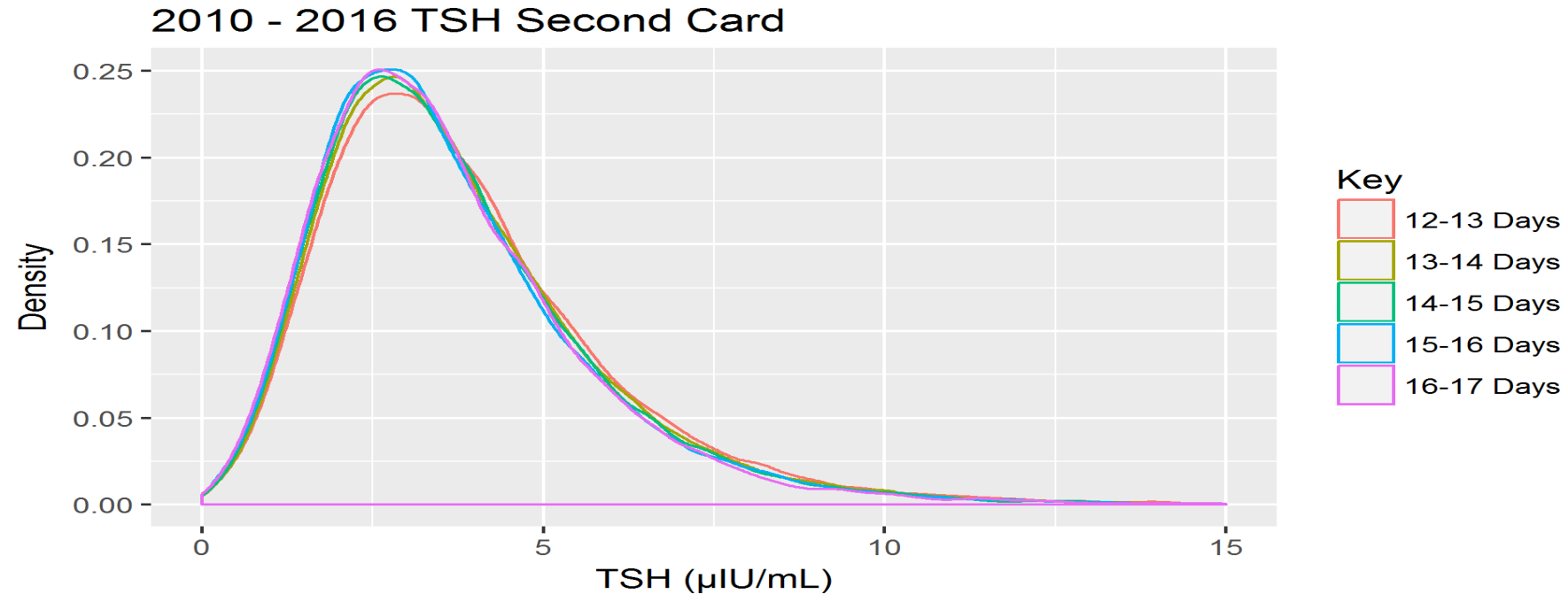
Inclusion Criteria	Mean ($\mu\text{IU/mL}$)	Standard Deviation	Sample Size
FIRST, TSH, 0-1 Days	14.30	29.44	158581
FIRST, TSH, 1-2 Days	8.01	8.79	187615
FIRST, TSH, 2-3 Days	5.27	8.61	7817
FIRST, TSH, 3-4 Days	4.23	4.97	1473
FIRST, TSH, 4-5 Days	4.45	20.58	752

TSH Results by Screening Test

Inclusion Criteria	Mean ($\mu\text{IU/mL}$)	Standard Deviation	Sample Size
FIRST, TSH	10.67	20.91	359432
FIRST, T4C	11.12	4.03	7099
SECOND, TSH	3.85	17.81	356599
SECOND, T4C	11.06	3.45	2662



TSH Values on Screen #2 by Day



Inclusion Criteria	Mean ($\mu\text{IU/mL}$)	Standard Deviation	Sample Size
SECOND, TSH, 12-13 Days	3.94	4.82	28890
SECOND, TSH, 13-14 Days	3.95	33.06	94087
SECOND, TSH, 14-15 Days	3.78	5.34	50957
SECOND, TSH, 15-16 Days	3.73	4.90	31850
SECOND, TSH, 16-17 Days	3.66	2.62	23923

Summary

- TSH results vary by collection date
- TSH results do not look the same for both first and second sample
 - Clinician would not be surprised by this given the normal physiology of newborn thyroid
 - But we have been using the same reference for both samples
- Collection dates more consistent for first sample and TSH values vary quite a bit by day of collection
- Collection dates more variable for second sample but TSH values do not vary much by day of collection

- Should we be using the same cutoff for both screens?

Congenital Hypothyroid Infants

- 130 infants diagnosed with congenital hypothyroidism
 - 123 / 130 patients had complete data
- 98/123 were diagnosed on the first screen
 - 20% of the patients were diagnosed on the second screen
- 6504 false positive cases during the screening period were identified

Confirmed Congenital Hypothyroidism

Population	Measurement	Screen #1	Screen #2	[p]
Total	Sample Size	359432	356599	
	Mean [μ IU/mL]	10.67	3.85	< 0.0001
Confirmed CH	Sample Size	130	130	
	Mean [μ IU/mL]	315.29	191.25	<0.0001
	[p]	<0.0001	<0.0001	

Characteristics of Hypothyroid Infants

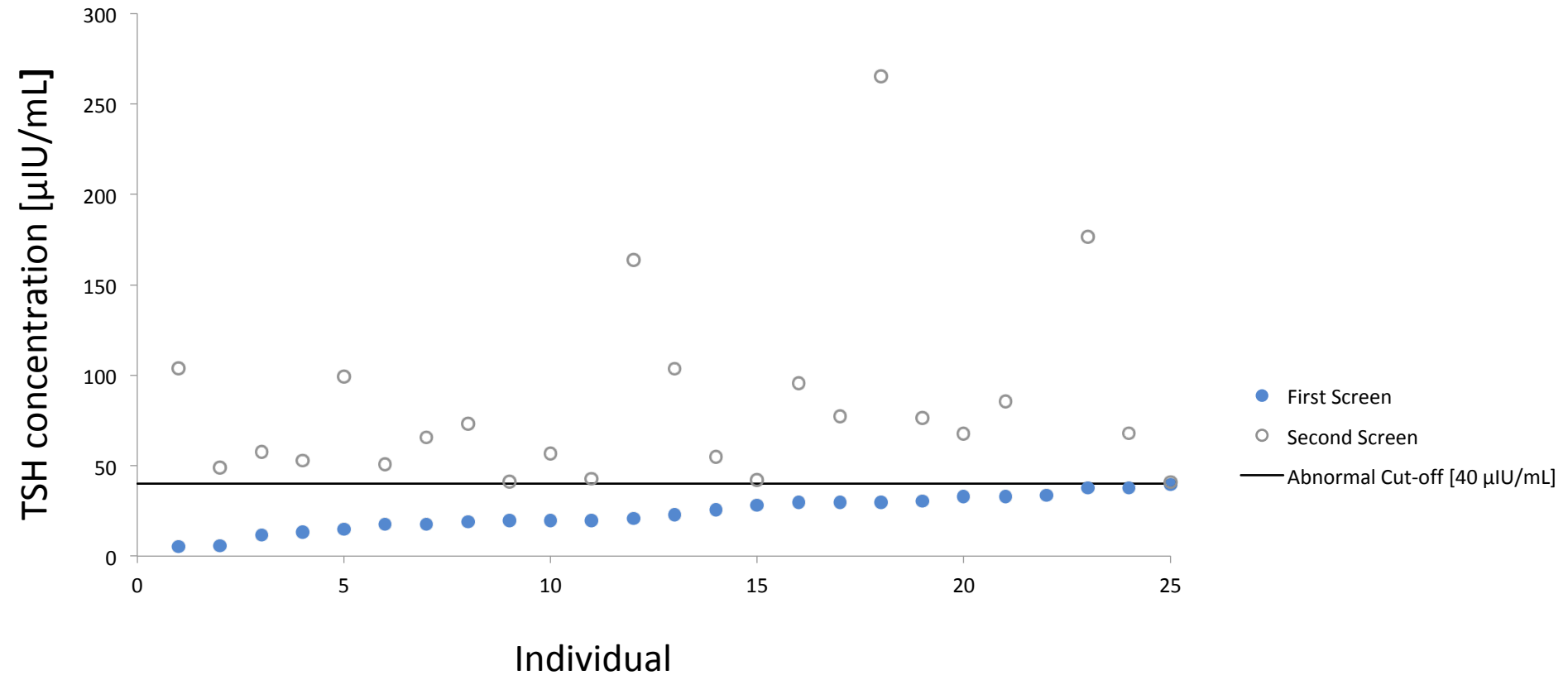
Population	Measurement	Screen #1	Screen #2	[p]
Abn Screen #1 Abn Screen #2	Sample Size	105		
	Mean [μ IU/mL]	386.02	211.51	<0.0001
Normal Screen #1 Abn Screen #2	Sample Size	25		
	Mean [μ IU/mL]	23.86	107.60	<0.0001
	[p]	<0.0001	0.0273	

Summary

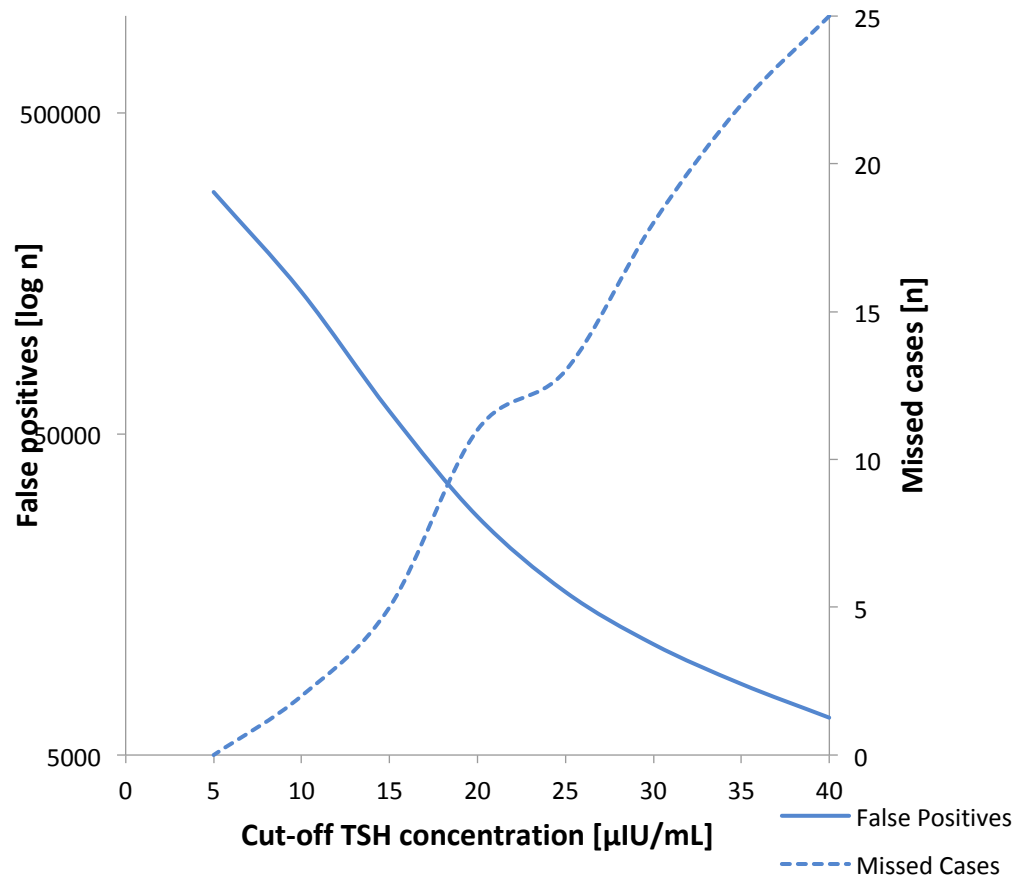
- Majority of infants are diagnosed on first screen (80%)
- However, a significant number have a normal first screen and are diagnosed on the second screen

- What do these infants look like on testing?
- Can we change the cutoff so as to make the diagnosis for all infants on the first screen and save everyone from having to do the second screen?

Infants diagnosed on Second Screen



Effect of lowering Cut-Off for Abnormal



Cut-Off	Abn Samples	Increase	Missed Cases
40	6634		
30	11170	4536	
20	27722	21088	11
10	138241	131607	
5	282979	276345	0

Possible Cut-off for Abnormal

	Current Cut-Off	3 SD	97th Percentile	98th Percentile	99th Percentile
FIRST, TSH ($\mu\text{IU}/\text{mL}$)	40	73	31	38	53
SECOND, TSH ($\mu\text{IU}/\text{mL}$)	40	57	9	10	11

Summary

- Can't identify a lower number for first screen that will capture all those picked up on second screen without significant increase in false positives
- Substantially increasing the number of false positives will increase financial and emotional costs

New Screening Algorithm: Tier 1

First Newborn Screen, Day 1-2 of life

- Normal = $<40 \mu\text{IU/mL}$
 - *Elevated = $>40 \mu\text{IU/mL}$ and $<100 \mu\text{IU/mL}$ (*if preemie/sick marked true)
- Abnormal = $>40 \mu\text{IU/mL}$ and $<230 \mu\text{IU/mL}$
 - Abnormal defined as $> 2\text{SD}$ above population mean for state data
- Critical = $>230 \mu\text{IU/mL}$
 - Consider lowering the critical value after reviewing the data

Second Newborn Screen, Day 7-14 of life

- Normal = $<20 \mu\text{IU/mL}$
- Abnormal = $>20 \mu\text{IU/mL}$ and $<230 \mu\text{IU/mL}$
 - Abnormal is defined as $>3 \text{SD}$ above the mean for Utah data

Abnormal Screen and Then What?

- Previously did confirmatory testing with a T4 at Newborn screening lab
 - Delays the report out and the clinicians want confirmatory testing right away no matter what the state screen says
- New paradigm: skip the screening program repeat and report it out
 - Saves the program money and does not have any impact upon the clinicians or family

Preterm Low Birthweight infants

Data

- TSH values from infants born <27 weeks gestation
- 2013-2017
- 1489 results from 636 infants
 - Mean BW 791 grams mean GA 24 weeks, 57% male
 - Samples obtained day 1, 9, 40 days of life
- Preliminary review of the data demonstrated differences from normal newborns
 - Mean TSH was lower in preterm infants than normal (7.2+/-7.4 vs 10.7 +/- 3.9 μ IU/mL)
 - 10% of infants had undetectable TSH on first NBS and remained low in 1%.
 - 51% had a rising TSH or at least one value > 10 μ IU/mL
 - None of these patients were diagnosed officially with congenital hypothyroidism nor did they require long term follow up with endocrinology

Conclusions

- Preterm infants do not follow the “normal” pathway
- New paradigms need to be considered for preterm or low birth weight infants

Summary

- Clinical perspective is important in understanding abnormal labs
 - Chart review significantly changed the data interpretation of abnormal TSH in children less than 2 years of age and association with congenital hypothyroidism
 - Understanding the clinical context allows better analysis of data and may lead to population specific normals, eg the preterm infant
- When attempting to adjust normal ranges, engagement of clinicians can help to support changes and help them work into the practitioners work flow which may improve compliance
 - Collecting samples between 10 and 14 days will yield same results, fit in with normal WCC visits, and prevent delays in sample collection
 - Understanding the impact of “false positives” on families