

Data-driven Approach to Revising Screening Cutoffs for Congenital Adrenal Hyperplasia (CAH)



Background

- * Michigan began screening for CAH in 1993
- * 184 CAH cases have been identified in Michigan since screening began (1:18,000 babies screened)
- * In 2020, for CAH screening:
 - * Positive predictive value: 9.8%
 - * False positive rate: 0.1%
 - * **97.9%** of positive CAH screens were among NICU babies



Current CAH Algorithm

Table 1. 17-hydroxyprogesterone (17-OHP) Reference Ranges

Result Determination	Normal birth weight (≥ 2500 grams) and age at collection >12 hours	Normal birth weight (≥ 2500 grams) and age at collection ≤ 12 hours	Low birth weight
Negative	< 55	< 90	< 100
Borderline Positive	55-89	90-149	100-149
Strong positive	≥ 90	≥ 150	≥ 150

Current CAH Algorithm

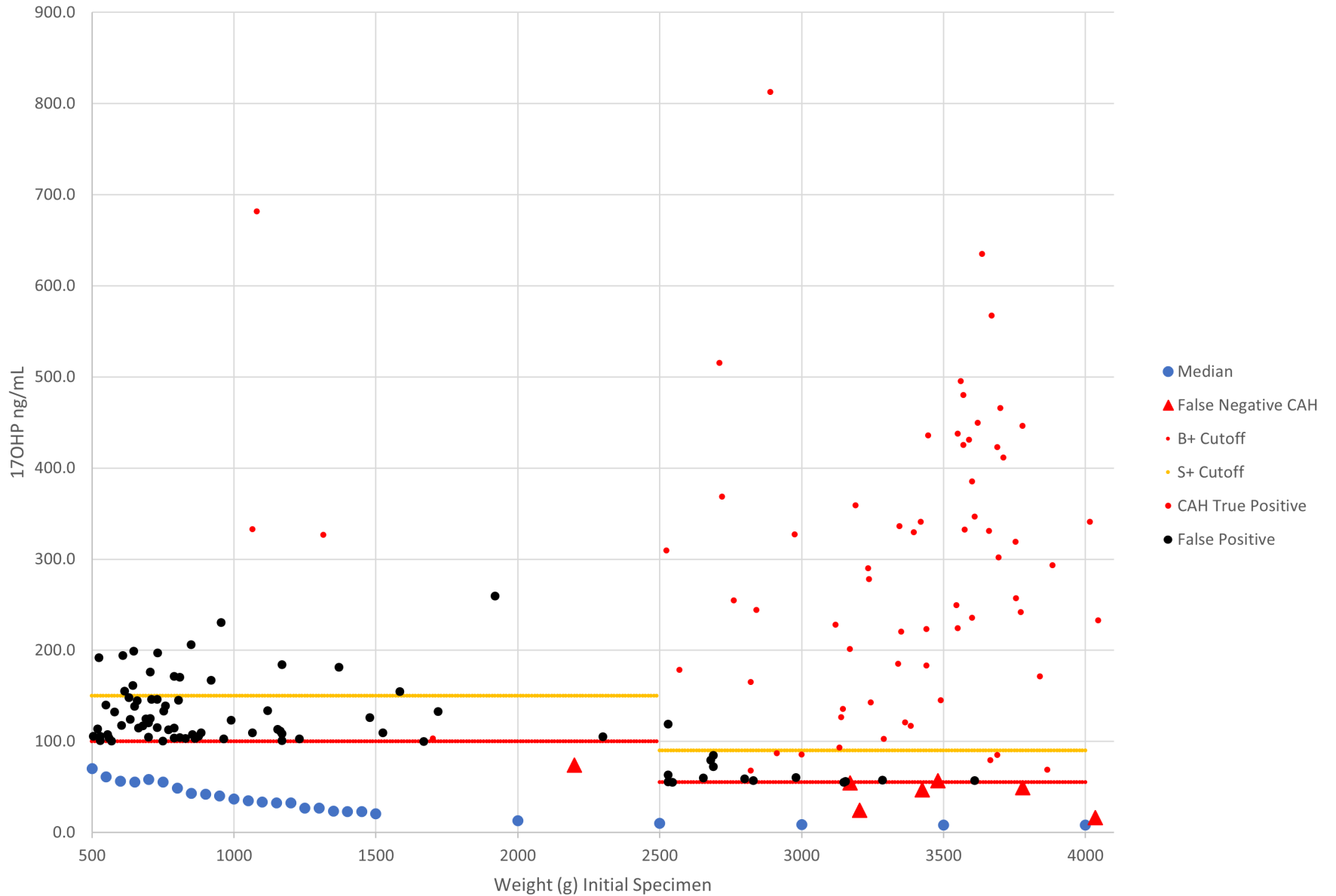
- * Repeat screen requested for borderline positives
- * Serum 17-OHP requested for strong positives
- * All borderline and strong positive screens are sent to Mayo Medical Laboratories for supplemental 2nd tier analysis

False Negatives for CAH

Table 2. Newborn Screening False Negative CAH cases, 2010-2020

17OHP	Birth weight (grams)	Age at collection (hours)
16	4035	24
21	3205	30
47	3425	25
49	3779	24
55	3170	26
57	3480	30
74	2200	30

17-OHP vs. Weight



Cut-off Analysis

- * Goal

- * Evaluate the CAH screening algorithm to determine if changes are needed to improve performance metrics, particularly increasing sensitivity

- * Methods

- * CAH screening data, including 17-OHP value, age at time of collection, birth weight, screening determination, and final diagnostic outcome, for Michigan births from 2010-2020 were analyzed
- * Analysis focused on increasing the number of reference ranges based on birth weight, so the initial proposed algorithm included 19 categories based on 200-gram intervals
- * Subsequent screening algorithms were refined based on screening performance metrics, including sensitivity, false positive rate, and positive predictive value

Results

Table 3. Proposed 17-OHP concentration cut-offs

#	Weight category	Lowest confirmed case [17-OHP]	Proposed algorithm	
			B+	S+
1	less than 500, any collection time	-	300	500
2	500-999, any collection time	-	200	275
3	1000-1499, any collection time	326.6	125	175
4	1500-1999, > 12 h	103.1	90	110
5	2000-2499, > 12 h	73.9	65	110
6	2500-2999, > 12 h	67.8	55	110
7	3000+ > 12 h	47.4	40	70
8	≤ 12 h, ≥ 1500	102.9	100	150

Results

Table 4. Positive Screens, by Weight Category, 2019

#	Weight category	Screens in each category	Positive Screens, Current Algorithm (S+)	Positive Screens, Proposed Algorithm (S+)	Cases 2010-2020
1	less than 500, any collection time	63	9 (3)	0 (0)	0
2	500-999, any collection time	857	62 (10)	5 (0)	0
3	1000-1499, any collection time	1274	11 (1)	4 (0)	3
4	1500-1999, > 12 h	2975	2 (0)	5 (1)	1
5	2000-2499, > 12 h	7780	0 (0)	8 (0)	1
6	2500-2999, > 12 h	21648	13 (0)	13 (0)	9
7	3000+ > 12 h	78879	12 (2)	42 (3)	52
8	≤ 12 h, ≥ 1500	835	1 (1)	1 (1)	8
	<i>Total</i>	114311	110 (17)	78 (5)	74

Results

Table 5. Number of CAH positives by Method, 2010-2020

Birth Year	Total Screens	Current algorithm total positives	Proposed algorithm total positives
2010	118,099	172	193
2011	118,091	152	161
2012	118,352	139	153
2013	118,943	171	191
2014	119,612	154	199
2015	118,080	139	157
2016	118,121	150	150
2017	117,018	119	115
2018	115,357	119	117
2019	114,311	110	78
2020	84,007	84	89

Results

Table 6. Positive Status of Confirmed CAH Cases, 2010-2020

Birth Year	Confirmed Cases	Positive on Current Algorithm		Positive on Proposed Algorithm	
	N	N	%	N	%
2010	5	5	100.0	5	100.0
2011	8	8	100.0	8	100.0
2012	9	8	88.9	9	100.0
2013	5	5	100.0	5	100.0
2014	11	11	100.0	11	100.0
2015	7	5	71.4	7	100.0
2016	3	3	100.0	3	100.0
2017	10	9	90.0	10	100.0
2018	7	5	71.4	5	71.4
2019	4	4	100.0	4	100.0
2020	5	4	80.0	5	100.0
<i>Total</i>	<i>74</i>	<i>67</i>	<i>90.5</i>	<i>72</i>	<i>97.3</i>

Summary

- * Cut-off changes were needed to improve the screening performance metrics for CAH
- * Additional reference ranges based on birth weight increase the sensitivity for CAH screening, particularly for normal birth weight infants

Next Steps - Laboratory

- * Worked with software vendor to update the laboratory information management system (LIMS) with proposed cutoffs

Weight category	New algorithm	
	B+	S+
less than 1000, any collection time	200	220
1000-1499, any collection time	125	175
1500-1999, > 12 h	90	110
2000-2499, > 12 h	65	110
2500-2999, > 12 h	55	110
3000+ > 12 h	40	70
≤ 12 h, ≥ 1500	100	150

Next Steps – Follow-up

- * Educational activities:
 - * Included an article in the American Academy of Pediatrics weekly email update
 - * Mailed a letter to primary care providers to alert of the cutoff changes
 - * Included an article in the quarterly NBS newsletter

Congenital Adrenal Hyperplasia Cutoff Changes: Coming Summer 2021

For congenital adrenal hyperplasia (CAH) screening, Michigan's NBS Program uses 17-hydroxyprogesterone (17-OHP) cutoffs based on age at time of collection and birth weight for congenital hyperplasia (CAH) screening. Currently, three reference ranges are used: one for normal birth weight (≥ 2500 grams) and age at collection >12 hours; one for normal birth weight and age ≤ 12 hours; and one for low birth weight (< 2500 grams). Following a false negative CAH case involving a mildly low birth weight infant, staff from the NBS Program evaluated the CAH screening algorithm to determine if changes were needed to improve performance metrics, particularly increasing sensitivity.

CAH screening data, including 17-OHP value, age at time of collection, birth weight, screening determination, and final diagnostic outcome, for Michigan births from 2010-2020 was analyzed. The results of the analyses were reviewed with Michigan's Pediatric Endocrine Advisory Council for input and guidance.

The screening algorithm that best balanced identifying newborns with CAH while minimizing false positives includes seven reference ranges based on time of collection and birth weight. This new screening algorithm will be implemented in summer 2021. The revised screening algorithm is anticipated to result in a similar number of positive screens per year compared to the current screening algorithm but shifts the majority of positive newborns from infants < 1500 grams to infants > 2500 grams. Due to this shift, NICUs will likely see a decrease in false positive screens for CAH among low birth weight newborns. The NBS Program will inform primary care providers of the algorithm change as well.

Take Home Messages

- * NBS Program routinely review screening performance metrics to determine if analyte cut-off adjustments would improve the outcomes for newborns
 - * Focus on balancing false positives and false negatives
- * Accurate information recorded on the NBS card is critical to ensure the best review possible
- * Major screening changes will be communicated via quarterly newsletter and/or email from NBS Program

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Michigan Pediatric Endocrine Advisory Committee (PEAC)