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Are Two Screens Necessary for Amino Acid, Fatty Acid Oxidation and Organic Acid Conditions Screening?

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Goals of Texas NBS Program



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Two screening tests for each baby born in Texas

- 24 – 48 hours of age
- 1 – 2 weeks of age

Infants testing positive receive prompt and appropriate confirmatory testing.

Diagnosed infants are maintained on appropriate medical therapy.

Texas Newborn Screening Workload



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- Average 760,000 specimens (~400,000 newborns) annually
- ~90% of newborns have a second screen submitted
- In 2018, reported results for 732,915 specimens
 - Average 2,350 specimens per day; 6 days a week
 - 4,258 unsatisfactory specimens (~0.58%)
- In 2018, 3,173 (0.43%) specimens reported with amino acid, fatty acid oxidation or organic acid presumptive positive screening results



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The 'Big' Picture

- From December 6, 2006 to Dec 31, 2018: **9,143,353** specimens tested by tandem mass spectrometry
- Yes, we use 10 tandem mass spectrometers!



TQD's: Frodo, Sam, Legolas, Gimli, Aragorn, Boromir, Merry, Pippin, Gandalf and Bilbo



Xinru, Maria, John, Brian, Yasmine, Jeff, Ruth, Mercedes, Taylor and Danielle



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MS/MS

- From 2006 thru April 2010, used the NeoGram Derivatized Kit
- Since April 10, 2010, used the NeoBase Non-Derivatized Kit
- Screen for 22 core and report on 20 secondary amino acid, fatty acid oxidation and organic acid disorders (Secondary conditions added in May 2015)
- Use different cutoffs for 1st (to 167 hrs) and 2nd (168 hrs and older) screen
- Use separate reporting algorithms for 2nd screens for some disorders



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First Screen Normal

- Reviewed all true positive cases reported to the Texas NBS Program for specimens tested from December 6, 2006 thru 2018
 - 1225 True Positives (Core and Secondary Conditions) with presumptive positive screening results
 - 108 True Positives had a normal 1st screen result (9%)
 - 5 False Negatives (0.4%)

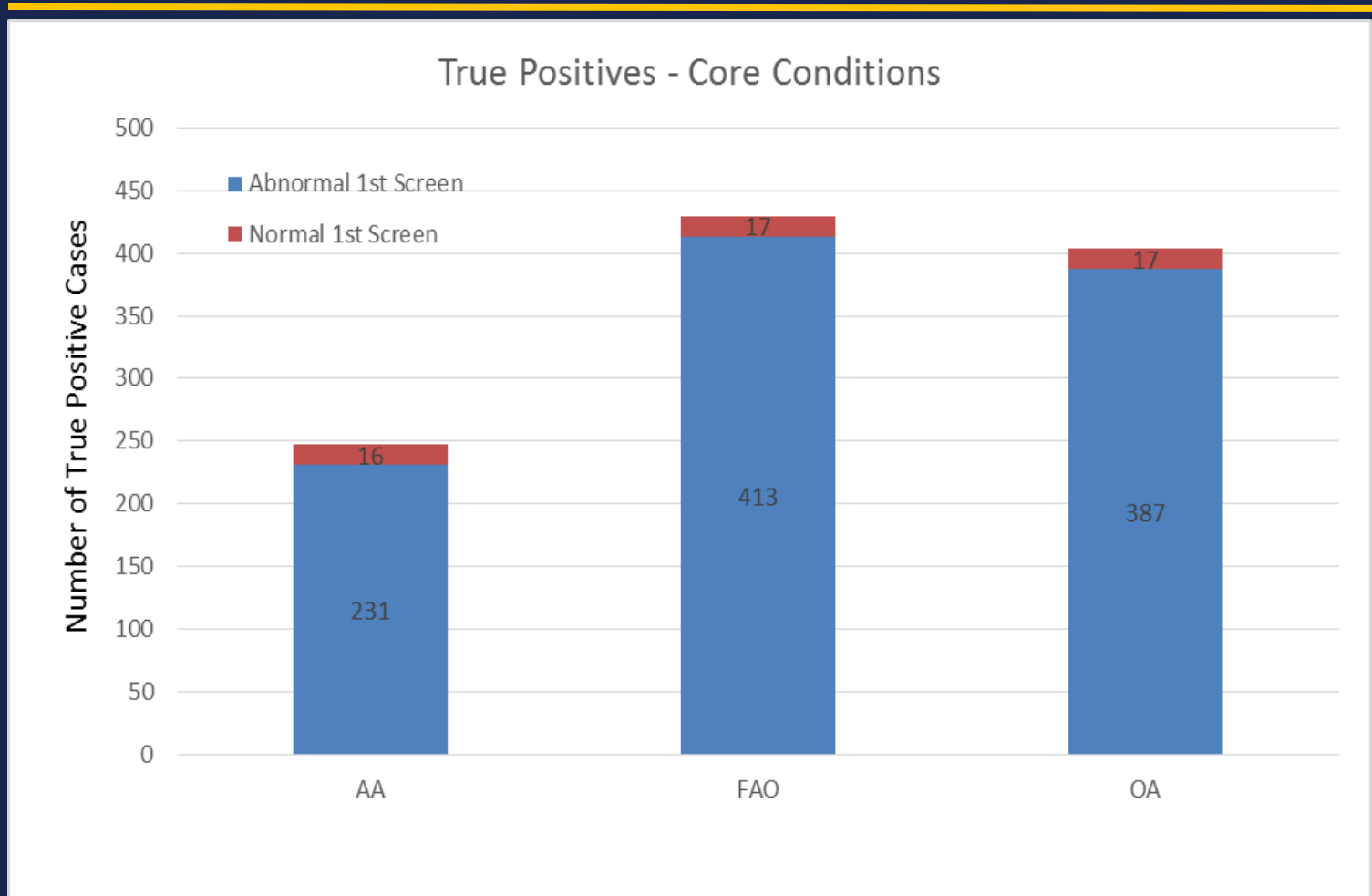
Core Conditions – First Screen Normal



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Core and Secondary Conditions – First Screen Normal

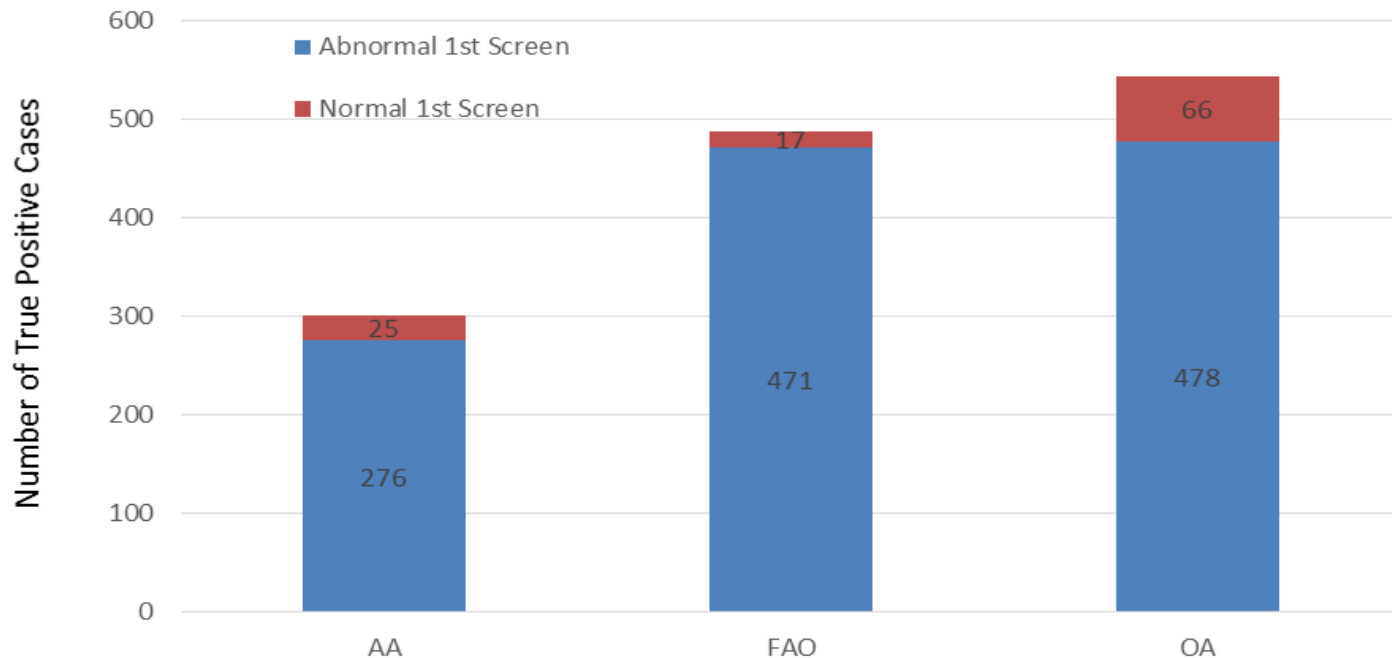


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True Positives - Core and Secondary Conditions



Secondary Conditions – First Screen Normal



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	Secondary Conditions (2007 - 2018)	Total
Organic Acid Disorders	MMA Cbl C	30
	2MBG	19
Amino Acid Disorders	CIT II	5
	ARG	1
	TYR III	3
	Total	58

Core Conditions – First Screen Normal



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	Core Conditions (2007-2018)	Total
Organic Acid Disorders	MMA Mutase	2
	MMA Cbl B	2
	PROP	4
	3MCC	8
	GA1 (low excretor)	1
Fatty Acid Oxidation Disorders	VLCAD	5
	MCAD	1
	CUD	11
Amino Acid Disorders	HCY	5
	MSUD	8
	CIT	1
	PKU	1
	ASA	1
	Total	49

Fatty Acid Oxidation Disorders



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Disorder	Total	Age at Collection	Birth Weight (g)
MCAD	1	At 24 hours	2128
VLCAD	5	1 at 13 hours, others at 24-48 hours	3020 - 3980
CUD	11	1 (1 st at 2 hours, 2 nd at 48, 3 rd at 6 days), others at 24-48 hours	1050 - 3595

MCAD

	Age at Collection	Birth Weight	C8	C6	C10:1	C10	C8/C2
1st Screen	35 hours	2128	0.06	0.07	0.06	0.05	0.00
2nd screen	9 days		0.69	0.33	0.33	0.26	0.03

Average (2018)		Birth Weight	C8	C6	C10:1	C10	C8/C2
1st Screen	1 day	3453	13.72	1.66	0.52	1.15	0.68



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Amino Acid Disorders



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Disorder	Total	Age at Collection	Birth Weight(g)
HCY	5	all between 24-30 hours	2800 - 3500
MSUD	8	1 at 23 hours, others 24-48 hours	2090 - 4090
PKU	1	at 2 hours	3053
ASA	1	at 24 hours	2952
CIT	1	at 25 hours	3285
CIT II	5	all between 24-30 hours	2090 - 3509
ARG	1	at 24 hours	2800
TYR III	3	all 24-30 hours	2640 - 3572

Maple Syrup Urine Disease



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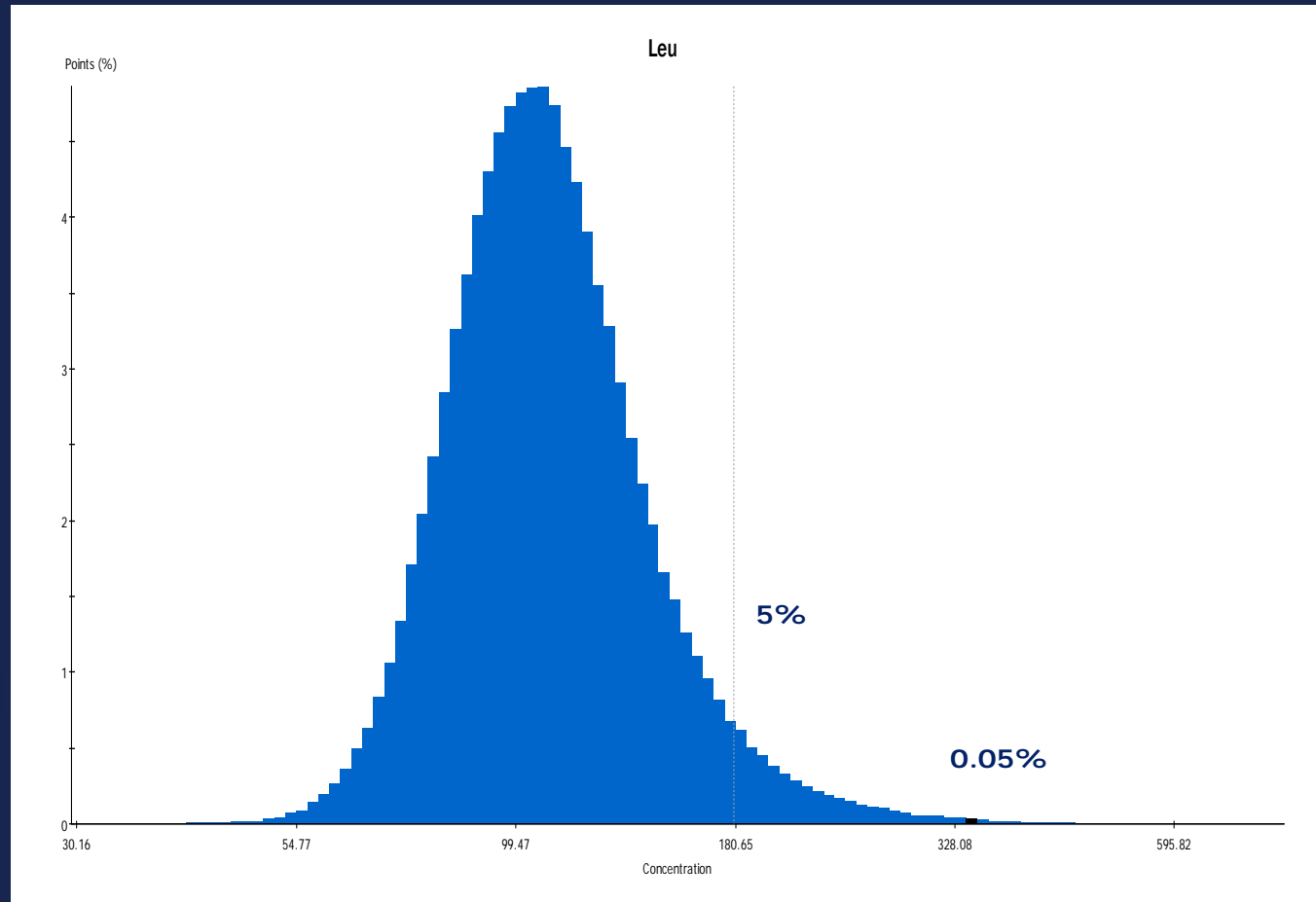
- 8 cases with Normal 1st screen
- Leucine value range = 180 - 349 $\mu\text{mol/L}$
- Average Leucine value = 274
- All collected 24 – 48 hours, except one at 23 hours
- All birth weights >2000 grams
- Current cutoff (BW >2000g) = 394 $\mu\text{mol/L}$

Example of Leucine value distribution (2017)



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Organic Acid Disorders



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Disorder	Total	Age at Collection	Birth Weight (g)
MMA Mutase	2	24 - 48 hours	3160 - 4027
MMA Cbl B	2	24 - 48 hours	2390 - 3840
PROP	4	24 - 48 hours	2473 - 3370
3MCC	8	24 - 48 hours	2481 - 3740
GA1 low excretor	1	32 hours	550
MMA Cbl C	30	24 - 48 hours	1710 - 3870
2MBG	19	24 - 48 hours	2466 - 4360

C3 Group

2007 - 2018	True Positive Cases	96
2007 - March 2010	Normal 1st Screen, Abnormal 2nd Screen	21%
April 2010 – 2018 (Algorithm Change for 2 nd Screens)	Normal 1st Screen, Abnormal 2nd Screen	41%



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C3 Group Algorithm – 1st and 2nd Screen



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C3 Elevated (99.9): Retest

C3 Elevated

C3 Borderline (99.95)
and C3/C2 Elevated

C3 Borderline
C3/C2 Normal

Diagnostic
testing

Repeat
Screen

C3 Group Algorithm – 2nd Screen



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C3 Elevated (99.7): Retest

C3
Elevated

C3 Borderline (99.95)
and C3/C2 Elevated

C3 btwn 99.7 and
99.95 and C3/C2
Elevated

Diagnostic
testing

C3 Borderline
C3/C2 Normal

Repeat
Screen



Conclusion

Is a second screen necessary to detect amino acid, fatty acid oxidation, and organic acid disorders ?

Considerations:

- NBS Program goals (ie. allow for phenotype variability, milder forms, detection of time critical disorders on 1st screen, case definitions)
- Program practices (ie. specimens collected prior to 24 hours are reported as unsat)
- Disorder algorithms/risk assessment scheme



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Thank you