

# The Compelling Benefits of Routine 2<sup>nd</sup> NBS: A Fifteen-Year Review in Washington State



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*Saving lives with a simple blood spot*

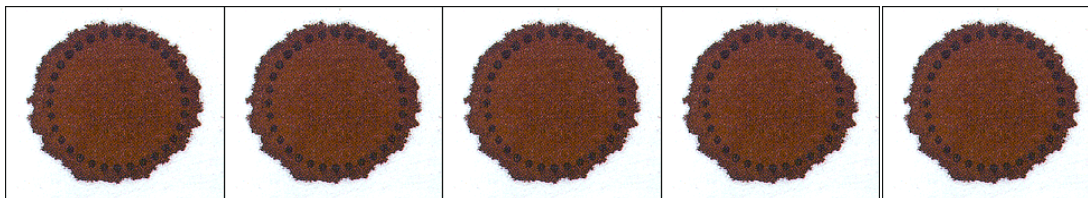


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HEALTHIER COMMUNITY



# Background

- ◆ 2<sup>nd</sup> NBS standard of care in WA
- ◆ Recommended between 7-14 days
- ◆ 95% compliance (though not mandated)
- ◆ 14 states in US collect routine 2nd
- ◆ (AL, AZ, CO, CT, DE, MD, NV, NM, NY, OK, OR, TX, UT, **WA**)



# What does Washington Screen for?

Phenylketonuria (PKU) - 1967

Congenital Hypothyroidism - 1977

Congenital Adrenal Hyperplasia - 1984

Sickle Cell Disease & other hemoglobinopathies - 1991

Biotinidase Deficiency - 2004

Galactosemia - 2004

Homocystinuria - 2004

Maple Syrup Urine Disease - 2004

MCAD Deficiency - 2004

Cystic Fibrosis - 2006

Isovaleric Acidemia - 2008

Glutaric Acidemia type I - 2008

Methylmalonic Acidemia - 2008

Propionic Acidemia - 2008

Long-chain L-3-OH Acyl-CoA Dehydrogenase Deficiency - 2008

Trifunctional Protein Deficiency - 2008

Very-long-chain Acyl-CoA Dehydrogenase Deficiency - 2008

Citrullinemia type I - 2008

Argininosuccinic Acidemia - 2008

Carnitine Uptake Defect - 2008

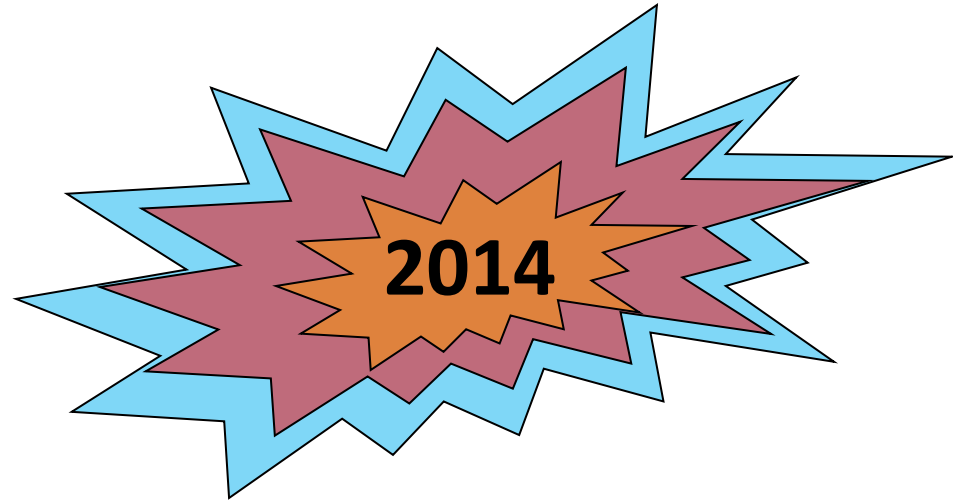
Holocarboxylase Synthetase Deficiency - 2008

b-Ketothiolase Deficiency - 2008

3-hydroxy-3-methylglutaric aciduria - 2008

Tyrosinemia type I - 2008

**Severe Combined Immunodeficiency - 2014**



# Newborn Screening Stats in WA



**~85,000 newborns are screened each year**

**~170,000 specimens are processed**

**~5,500 abnormal results**

**(~2,100 false +/-year)**

**Prevents death or disability for  
150 - 200 babies/year**

- \* **Coverage: DBS received from Jan. 1, 2000 to June 30, 2014**
- \* **Limitations: Excluded hemoglobin traits & other hemoglobinopathies**
- \* **Disorder data** reported by number of **infants** screened and number of confirmed **cases**
- \* **Unsuitable data** reported by number of **specimens** received and tested

# Non-MSMS Disorders

Disorder	# True Positive	Severe or Classic	# Infants Screened	Prevalence rate	# False negative
CH	945	580	1,153,274	1:1,220	3
CAH	91	60	1,153,274	1:12,673	4
CF	142	133	708,224	1:4,987	4
BIO	28	7	855,881	1:30,567	0
GALT	94	12	855,881	1:9,105	0
SCID	1	1	40,924	1:40,924	0

<b>MSMS Disorder</b>	<b># True +</b>	<b>Severe or Classic</b>	<b># Infants Screened</b>	<b>Prevalence rate</b>	<b># False Negative</b>
PKU	57	36	1,153,274	1:20,232	0
MSUD	7	4	825,084	1:117,869	0
HCYS	1	1	825,084	1:825,084	0
MCADD	36	29	825,084	1:22,919	0
VLCAD	11	6	495,021	1:45,000	0
CUD	1	0	495,021	1:495,021	0
MMA/PA	9	8	495,021	1:55,002	0
GA-1	3	3	495,021	1:165,007	0
IVA	2	2	495,021	1:247,510	0
CIT/ASA	3	2	495,021	1:247,510	1
TYR-1	2	2	495,021	1:247,510	0
BKT	1	1	495,021	1:495,021	1
Non-panel	16	N/A	495,021	1:30,938	N/A

## True + on 2<sup>nd</sup> NBS - Increase in Sensitivity

Disorder	# True positive	Detected on 2 <sup>nd</sup> NBS	Severe or Classic	Mild	Increase in sensitivity with 2 <sup>nd</sup> or subsequent
CH	945	268	182	86	28.4%
CAH	91	30	9	21	33.0%
CF	142	7	6	1	5.0%
PKU	57	15	0	15	26.3%
MCADD	36	3	2	1	8.3%
MSUD	7	3	0	3	43.0%
HCYS	1	1	1	0	100.0%
Total	1279	327	200(61%)	127(39%)	25.5%

**\*CH & CAH are the biggest bang for our buck!**



## True + on 2<sup>nd</sup> NBS - Increase in Sensitivity

Disorder	# True positive	Detected on 2 <sup>nd</sup> NBS	Severe or Classic	Mild	Increase in sensitivity with 2 <sup>nd</sup> or subsequent
CH	945	268	182	86	28.4%
CAH	91	30	9	21	33.0%
CF	142	7	6	1	5.0%
PKU	57	15	0	15	26.3%
MCADD	36	3	2	1	8.3%
MSUD	7	3	0	3	43.0%
HCYS	1	1	1	0	100.0%
Total	1279	327	200(61%)	127(39%)	25.5%

**\*Overall sensitivity is increased by 26% !**

## PPV of True + Based on # of Referrals

Disorder	# True positive	Detected on 2 <sup>nd</sup> NBS	Severe or Classic	Mild	Number Referrals	PPV based on # Referrals
CH	945	268	182	86	1193	79.2%
CAH	91	30	9	21	144	63.2%
CF	142	7	6	1	311	45.7%
PKU	57	15	0	15	114	50.0%
MCADD	36	3	2	1	55	65.5%
MSUD	7	3	0	3	19	36.8%
HCYS	1	1	1	0	32	3.1%
Total	1279	327	200(61%)	127(39%)	1868	68.5%

## TRUE + on 2<sup>nd</sup> NBS: Age @ Dx & Tx

Disorder	Detected on 2 <sup>nd</sup> NBS	Severe or Classic	Mild	Median Age @ dx	Median Age @ tx
CH	268	182	86	15	17
CAH	30	9	21	21	22
CF	7	6	1	11	16
PKU	15	0	15	31	20
MCADD	3	2	1	(18,73,86)	(26)
MSUD	3	0	3	22	25
HCYS	1	1	0	28	48
Total	327 (26%)	200(61%)	127	18	18

\*Prior to GALT screening in 2002, Phe was flagged on 2<sup>nd</sup> NBS, final diagnosis was Classic Galactosemia! (*incidental finding*)

## False + Resolved by 2<sup>nd</sup> NBS w/o FU

Disorder	# False + cases	# Resolved by 2nd	No FU (%)
CH	5454	3783	69%
CAH	3376	2154	64%
CF	5264	1857	35%
BIO	446	229	51%
GALT	434	276	64%
PKU	237	142	60%
AA	569	319	56%
FAO	1459	800	55%
OA	1198	697	58%
SCID	33	6	18%
Total	18,470	10,263	56%

## Unsuitable Data – Tested and Resolved

Total # specimens	# Hb traits	Confirmed cases	Resolved w/o FU	No FU (%)
51,114	414	112	20,967	41%

\*Although **unsuitable**, we still test and flag out-of-range values!

\***41%** of **unsuitable specimens** were resolved without active follow-up (*this would be an underestimate of the resolved unsuitable cases due to open cases without final disposition codes*)

# Unsuitable specimens - Breakdown of Disorders detected

Total # specimens	# Hb traits	Confirmed cases	Resolved w/o FU	No FU (%)
51,114	414	112	20,967	41%
True Positive cases detected on unsuitable specimens				
Endocrine	SCD/Hb	CF	PKU/MSMS	GALT
76	17	10	8	1 (DG)

**\*About 8 cases of True+ per year have at least one unsuitable specimen!**

**\*Recently on Oct. 17, 2014, our 1st confirmed LCHAD/TFP case was detected on a layered specimen!**

# Unsuitable & Refusals – Tested and Resolved

Total # specimens	# Hb traits	Confirmed cases	Resolved w/o FU	No FU (%)
51,114	414	112	20,967	41%
Total # Refusals	Hb trait	Confirmed cases	RBLT	RBLT (%)
2699	14	0	1376	51%

**\*Although 1<sup>st</sup> NBS was refused, eventually 51% are screened on 2<sup>nd</sup> NBS!  
*RBLT – refused but later tested***

# Results & Conclusions:

- ◆ Practice of routine 2<sup>nd</sup> NBS increased detection rate (sensitivity) by 26%
- ◆ Overall PPV of 68.5% for True + cases based on the number of referrals (*with positive results on 2<sup>nd</sup> NBS*)
- ◆ Affected infants missed on 1<sup>st</sup> NBS, detected on 2<sup>nd</sup> or subsequent NBS were diagnosed between 15-30 days and treated between 16-48 days of age



# Results & Conclusions:

- ◆ 56% of False Positive cases & 41% of unsuitable specimens were resolved with 2<sup>nd</sup> NBS without active follow-up
- ◆ 51% of Refusals were screened on 2<sup>nd</sup> NBS
- ◆ A significant number of true positive cases were still detected on unsuitable specimens

# Quality Improvements Implemented:

- ◆ Cut-offs, protocols & algorithms are modified to increase sensitivity and reduce false negative rates
- ◆ Monitoring steroid use for CAH to minimize false negative
- ◆ Second tier threshold algorithm for CF increases detection on 2<sup>nd</sup> NBS
- ◆ Monitoring Leu:Ala ratios increases detection of MSUD on 2<sup>nd</sup> NBS

# Bottomline: Compelling Benefits of 2<sup>nd</sup> NBS

- ◆ Enables complete and timely testing at the Newborn Screening Laboratory
- ◆ Allows prompt diagnosis and treatment of affected infants
- ◆ **Ultimately prevents death and disability for affected infants!**
- ◆ Reduces staff workload to resolve abnormal (false positive) & unsuitable specimens
- ◆ Increases probability of screening for refusals

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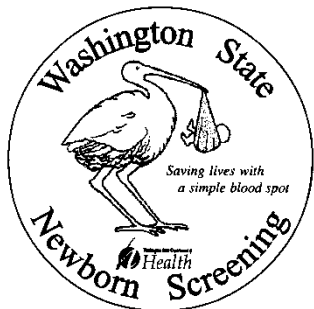
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# Washington State

## Newborn Screening

[www.doh.wa.gov/nbs](http://www.doh.wa.gov/nbs)

(206) 418-5410

or

1-866-660-9050

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