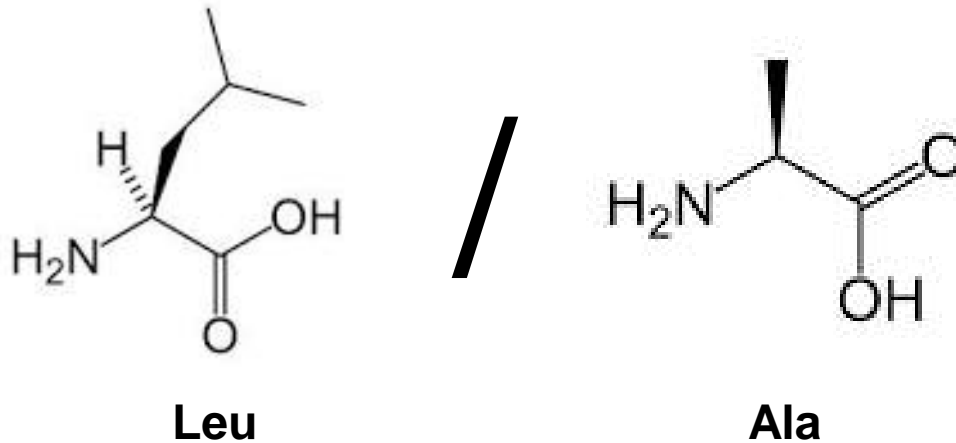


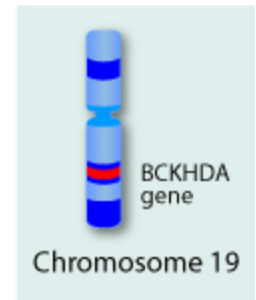
# Variant MSUD:

## A Strategy to Increase Detection through Newborn Screening



Bill Hoffman, BS – presenting on behalf of  
Sheila Weiss, MS, CGC  
WA State Newborn Screening Program

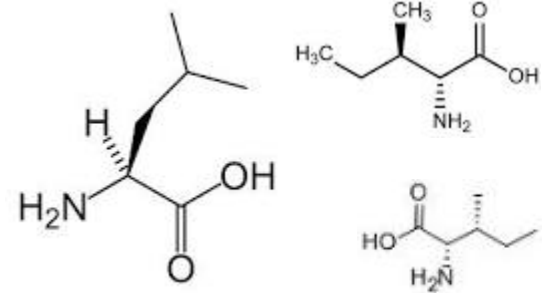
# MSUD Basics



- Deficiency of the branched chain alpha-keto acid dehydrogenase (BCKD) complex
- Results in the buildup of leucine, isoleucine, alloisoleucine, valine & their toxic by-products (ketoacids)
- Classic form will result in severe neurological damage and death if untreated
- Variant forms are less severe, but can still result in intellectual disability & physical problems if untreated

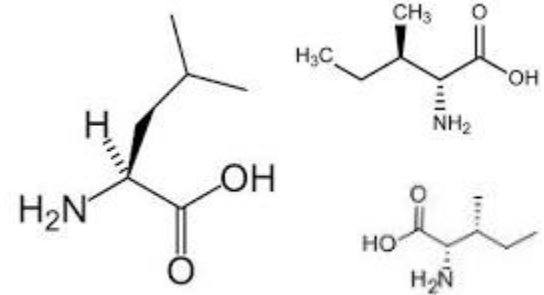
# MSUD Screening

- Primary marker – Leu (“Xle”)
- Secondary markers
  - leu/alanine (>1.5)
  - valine (>220 mmol/L )
  - leu/phenylalanine (>3.65)
  - valine/phenylalanine (>3.0)



# MSUD Screening

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XLE mmol/L blood	Age at collection $\leq$ 6 days		Age at collection $>$ 6 days	
	not all secondary markers* elevated	all secondary markers* elevated	not all secondary markers* elevated	not all secondary markers* elevated
<b>&lt; 236</b>	<b>normal</b>	<b>normal</b>	<b>normal</b>	<b>normal</b>
<b>236 – 321</b>	<b>borderline</b>	<b>borderline</b>	<b>normal</b>	<b>normal</b>
<b>322 – 465</b>	<b>borderline</b>	<b>presumptive</b>	<b>borderline</b>	<b>presumptive</b>
<b><math>\geq</math>466</b>	<b>presumptive</b>	<b>presumptive</b>	<b>borderline</b>	<b>presumptive</b>

# Results of Screening

- **200** babies with elevated leucine (in 5 $\frac{1}{3}$  yrs)
- **11** referred for diagnostic testing
  - 6 confirmed – 3 classic, 3 variant (55% PPV+)
  - 5 false positives (**only one with a leu/ala ratio >1.0**)
- Disease prevalence: **~1 in 75,000**
  - Classic - ~1 in 150,000
  - Variant - ~1 in 150,000

Leu  $\geq$  236  $\mu$ M  
Leu/Ala  $>$ 1.5

# Classic MSUD Cases

Age (hrs)	LEU	Leu/Ala
24	441	2.29
21	338	1.83
16	246	1.02

Leu  $\geq$  236  $\mu$ M  
Leu/Ala  $>$ 1.5

# Variant MSUD Cases - 1<sup>st</sup> NBS

Age (hrs)	LEU	leu/ala
24	218	1.16
27	173	1.08
23	179	1.25

Leu  $\geq 322$   $\mu\text{M}$   
Leu/Ala  $> 1.5$

# Variant MSUD Cases - 2<sup>nd</sup> NBS

Age (hrs)	LEU	leu/ala	Age (d)	LEU	leu/ala
24	218	1.16	16	428	2.42
27	173	1.08	15	386	1.61
23	179	1.25	11	355	1.57



# Babies with normal Leucine and elevated leu/ala

subset	leu/ala >1.0	True +
non-NICU	6	1

1 year of data (during 2013-2014), AAC  $\leq$  6d  
~85,000 babies screened

# Babies with normal Leucine and elevated leu/ala

subset	leu/ala >1.0	True +
non-NICU	6	1
NICU, non-HA/TPN	8	0

1 year of data (during 2013-2014), AAC  $\leq$  6d  
~85,000 babies screened

# Babies with normal Leucine and elevated leu/ala

subset	leu/ala >1.0	True +
non-NICU	6	1
NICU, non-HA/TPN	8	0
NICU & HA/TPN	23	0

Minor impact to identify babies with elevated leu/ala ratios and monitor for routine 2<sup>nd</sup> NBS

1 year of data (during 2013-2014), AAC  $\leq$  6d  
~85,000 babies screened

# Summary

- **Observations**
  - leu/ala ratio is the strongest secondary screening marker in predicting the likelihood of a true positive MSUD
  - there is a very small number of babies, with a NBS specimen collected  $\leq 6$  days, with a leu/ala ratio  $> 1.0$
- **Plan:** to create a result code or a query that will trigger a response for follow-up to monitor for a 2nd NBS on babies whose 1<sup>st</sup> NBS has a leu/ala ratio  $> 1.0$  (non-HA/TPN, NBS collected  $\leq 6$  days)
- **Goal:** to ensure that no baby with a variant form of MSUD goes undetected due to a normal leucine on a 1<sup>st</sup> NBS

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