

# Evaluating appropriate cut-offs for methionine levels in premature newborns by gestational age and nutritional status

Sam Marcellus, MPH



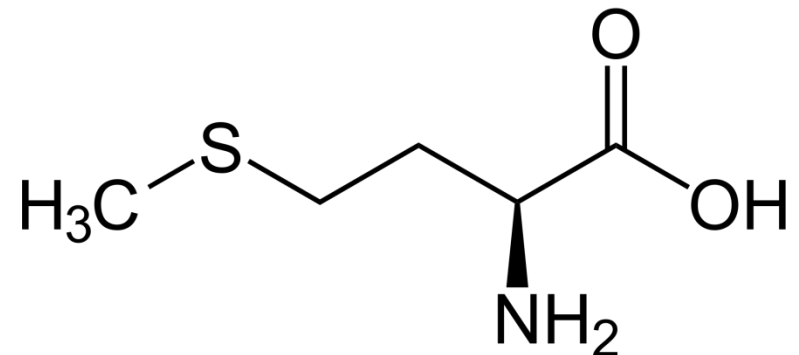


# Conflicts of Interest

- I have no conflicts of interest
- I have nothing to disclose

# Introduction

- Iowa screens for 50+ conditions on the newborn screen (NBS)
- Current methionine cut-off is 60  $\mu\text{mol/L}$  in Iowa, 50-75<sup>th</sup>ile compared to other Midwest states
- Elevated methionine on NBS associated with:
  - Homocystinuria
  - Methionine adenosyltransferase I/III deficiency
  - Glycine n-methyltransferase deficiency
  - Adenosylhomocysteine hydrolase deficiency
  - Liver disease
  - Hyperalimentation



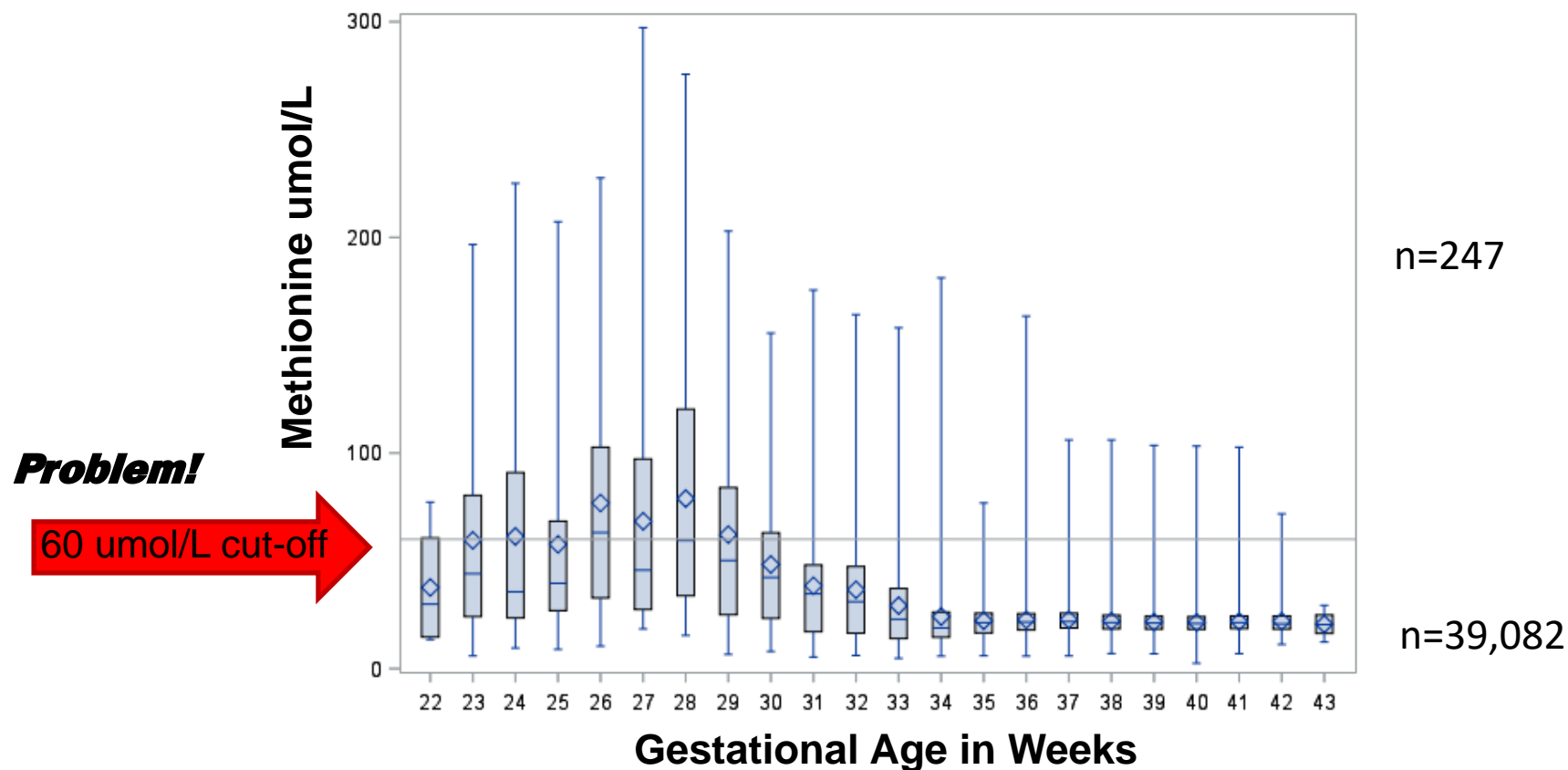
# Study Objectives

1. Evaluate the number of newborns in Iowa with hypermethioninemia
2. Assess the strain isolated hypermethioninemia newborn screens place on the Iowa Newborn Screening Program
3. Create new cut-off values for methionine screening based on gestational age and TPN status
  - Utilizing categorical bins similar to bins used for CAH screening

# Current Problem

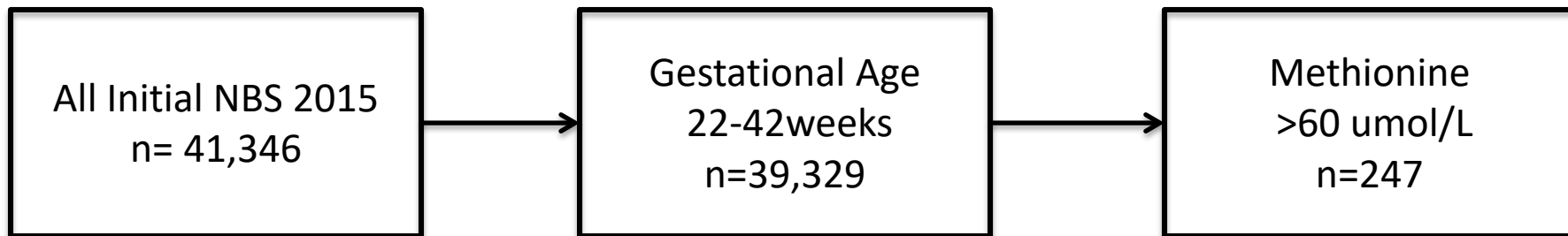
- Elevated methionine also associated with:
  - Low birth weight
  - Low gestational age
  - Total parenteral (TPN) status
- Methionine levels normalize as babies grow, age, and come off TPN in false positive cases
  - Pre-term newborns metabolize methionine up to **5x** slower than full-term newborns due to liver immaturity
- Newborns with high methionine levels due to weight, gestational age, and/or TPN status place strain on NBS short-term follow-up staff
  - Most common elevated single analyte in Iowa
  - Only 4 true positives in the history of the Iowa Newborn Screening Program
  - High methionine cases tend to “pile up”

# Methionine, All Initial Screens

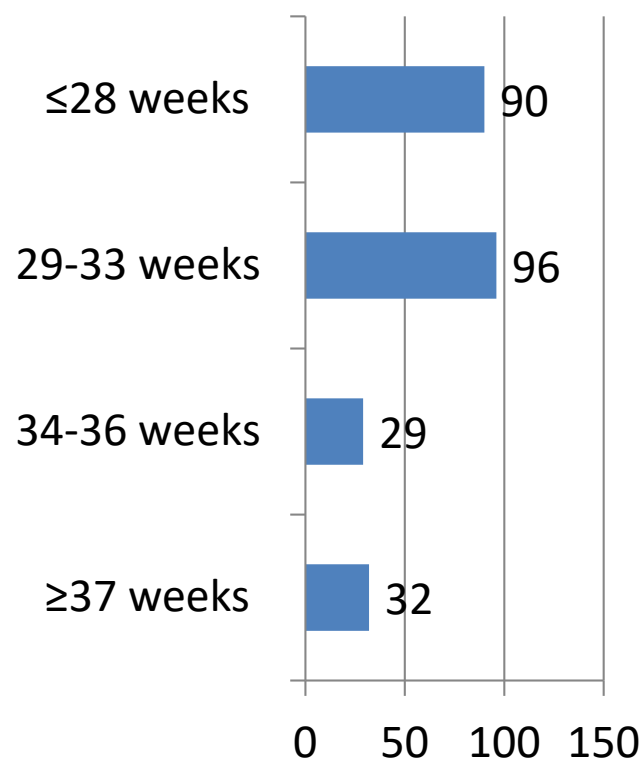
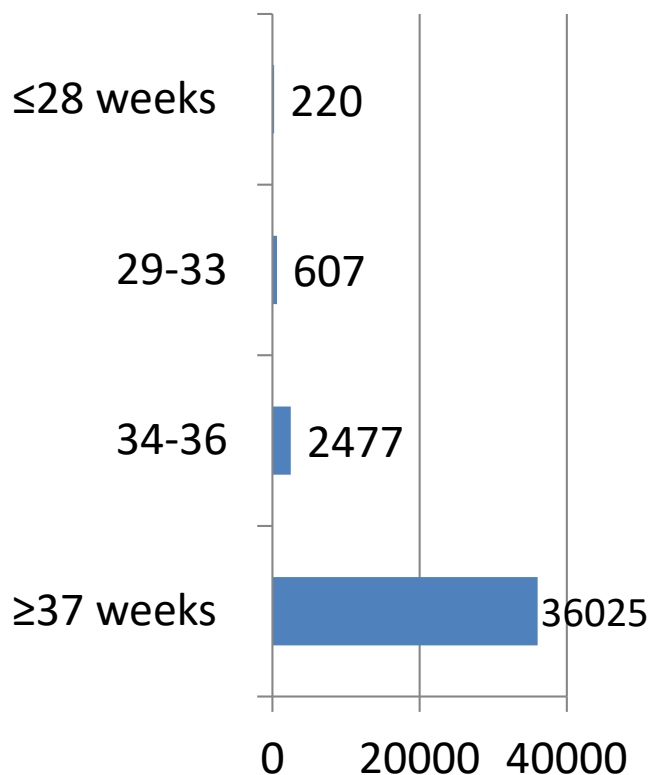


- Median (—) at or above the reference line for 26 and 28 weekers
- Mean (◇) at or above the reference line for 23-29 weekers

# Sample Selection for Data Analysis

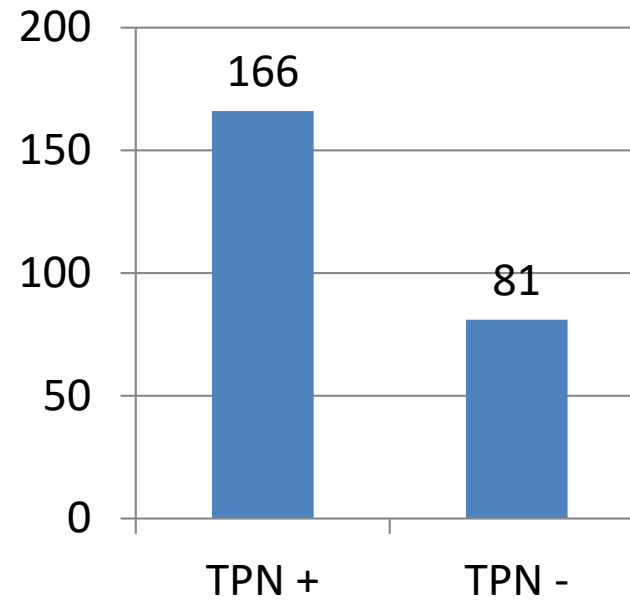
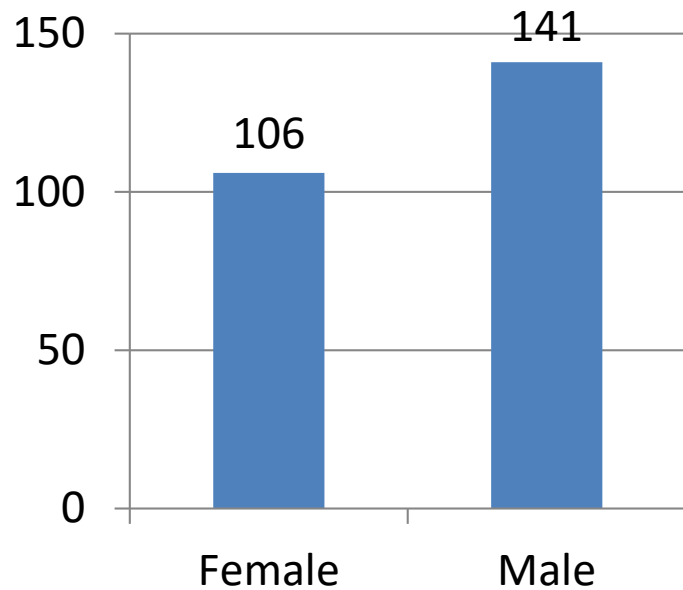


- Repeat screens excluded due to de-identified data set





# Demographics of Met >60 $\mu\text{mol/L}$




- Normal birth weight >2500 grams
- Mean birth weight of 1666.9 grams
- Median birth weight was 1430 grams



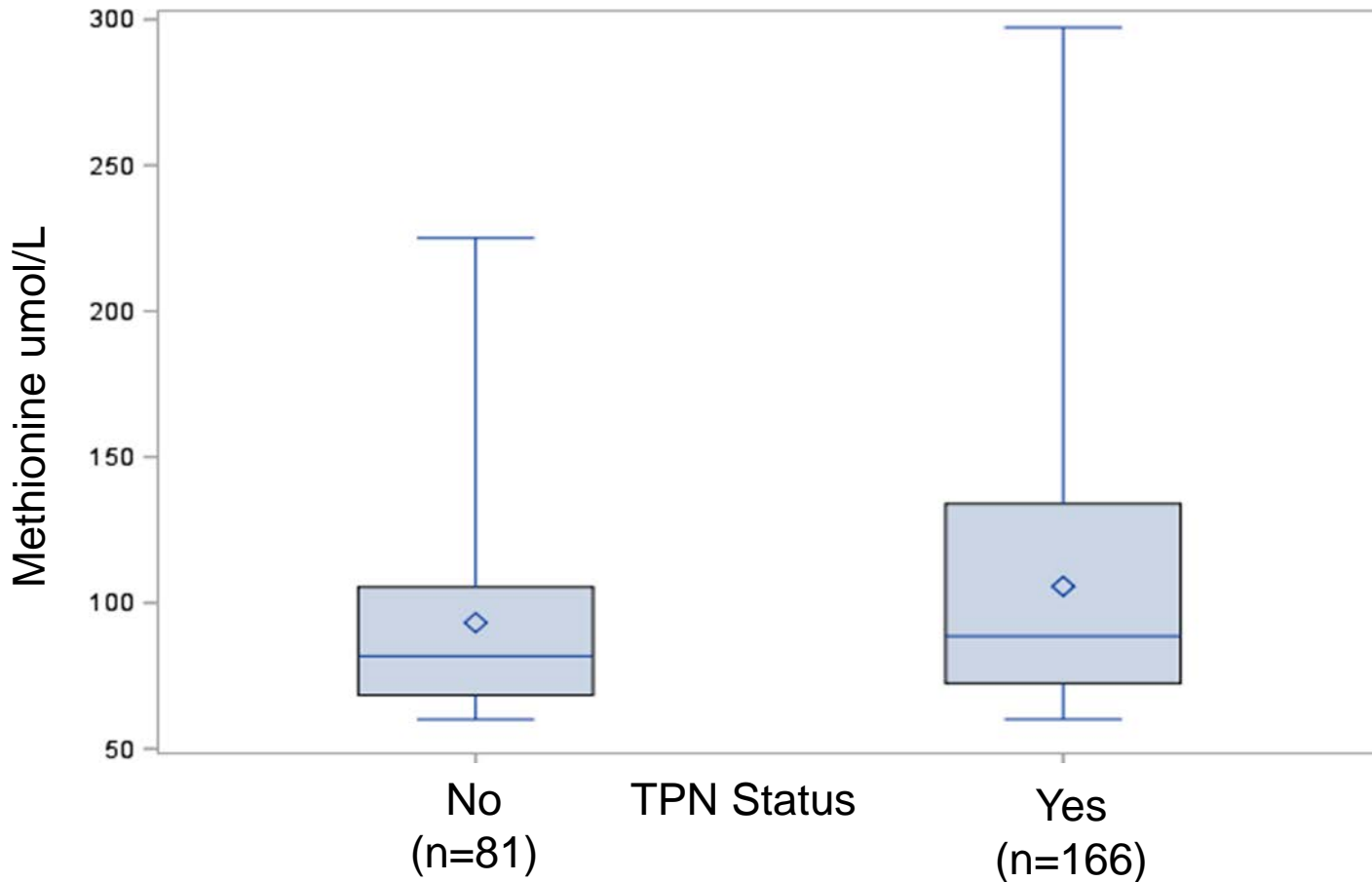


# TPN (Total Parenteral Nutrition)

- Feeding method that bypasses the GI tract
  - Used when person cannot receive feedings/fluids orally
- Nutritional fluid given into the veins via IV line or central line
- Can contain:
  - Electrolytes
  - Amino acids 
  - Vitamins
  - Minerals
- Unique to each NICU
- Unique to the patient and their needs



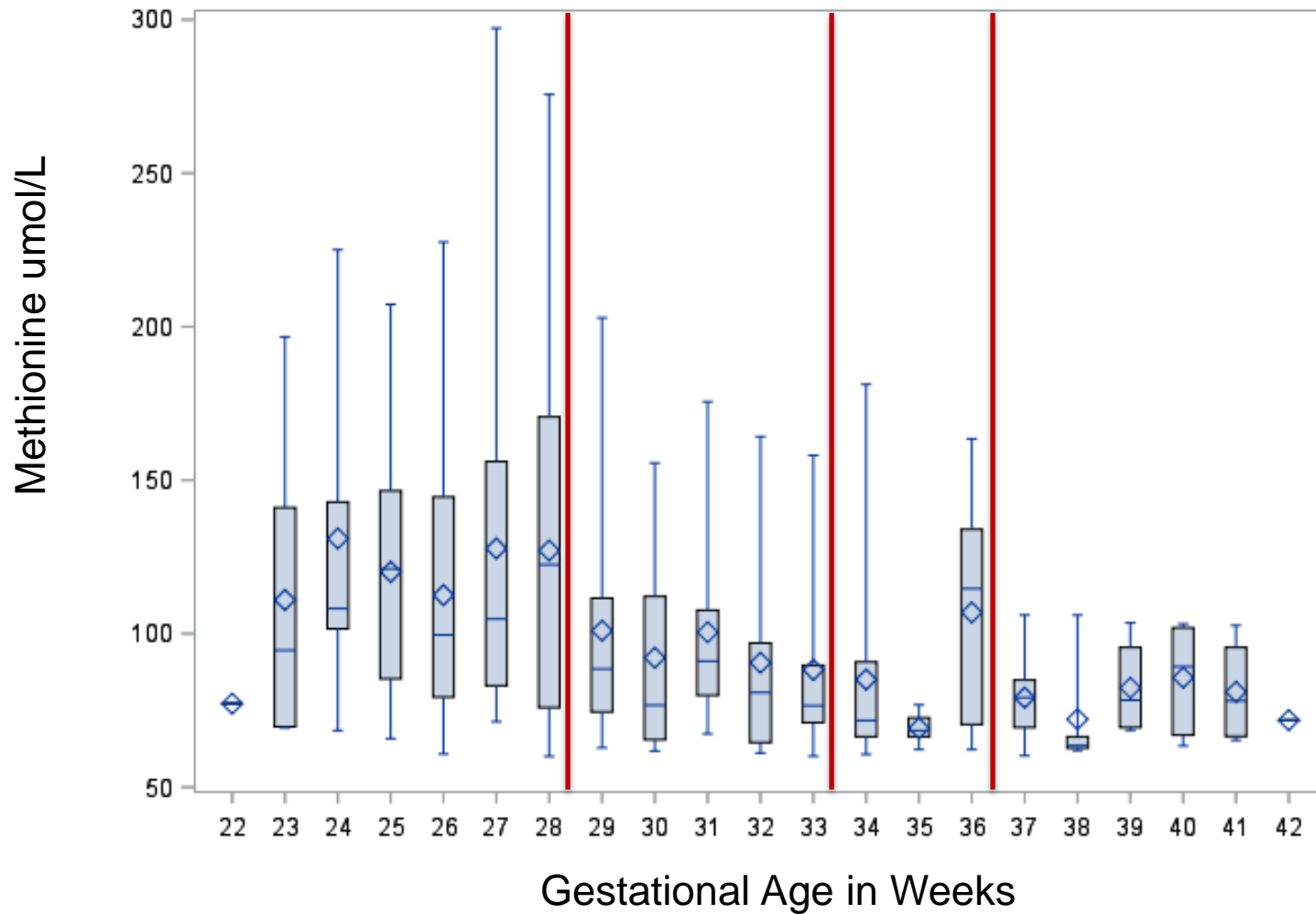
# Methionine by TPN Status



- Gestational age significantly related to methionine levels in babies on TPN ( $p=0.0138$ )
- Relationship not significant in babies off TPN ( $p=0.0693$ )



# Met >60 umol/L by Gestational Age



- 36 weeks was also an outlier in other years



# Recommendations

- Propose raising cut-offs for methionine through categorical bins
  - One set of bins for babies on (+) TPN, another set for babies not on (-) TPN
  - Bins based on gestational age
- Recommend implementation of the screening bins in the table below

Gestational Age (weeks)	≤28	29-33	34-36	≥37
Methionine (umol/L) + TPN	116	104	83	70
Methionine (umol/L) - TPN	102	93	76	70

## False Positive Rate (FPR)

- 2015 false positive rate for methionine on original newborn screens was 0.75%
- New bins would have reduced false positives from 247 to 112 in 2015
  - Lowering the FPR to 0.27%

# Next Steps

- Working on implementation in the Iowa Newborn Screening Program
- Create similar bins for other metabolic analytes
  - Valine
  - Leucine
  - Valine/Leucine Ratio

# Acknowledgements

- Special thanks to:
  - Beth Tarini, MD, MS
  - Amy Calhoun, MD
  - Anne Atkins, MPH
  - Emily Phillips, BSN, RN, CCRC
  - The Iowa Newborn Screening Program Team
  - The University of Iowa College of Public Health

