Evaluation of the R4S post-analytical tool in suggesting inborn errors of metabolism among Sudden Infant Death Syndrome cases and controls

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Introduction

- **Current interpretation of tandem mass spectrometry (MS/MS) newborn screening (NBS) results**
  - MS/MS has been used in CA since July, 2005.
  - Screening decision is based on cut-off values.
  - Cut-off values vary from disorder to disorder and are rather subjective.
  - False positive and false negative are common.

Introduction

- **The R4S post-analytical tool**
  - A multivariate pattern-recognition tool developed by the Region 4 Stork (R4S) MS/MS data project.
  - A collaborative effort of 154 public health programs and private laboratories worldwide.
  - Objective was to minimize false positives and false negatives.
  - Determination is based on the degree of overlap between normal population and disease range.
  - Easy to use.

ORIGINAL RESEARCH ARTICLE | Genetics inMedicine

Enhanced interpretation of newborn screening results without analyte cutoff values

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R4S tool related presentations will be posted on:
http://www.myomedicallaboratories.com

Introduction

- **Sudden infant death syndrome (SIDS)**
  - Historically associated with metabolic disorders.
  - Remains the third leading cause of overall infant mortality and accounts for 8.4% of all infant deaths.
  - In pre-NBS era, 1-2% were attributed to inborn errors of metabolism (IEMs) especially fatty acid oxidation disorders using postmortem specimens.
  - In post-NBS era, could undiagnosed IEMs remain a contributor to SIDS?

Introduction

- **Study objectives**

    - To evaluate whether the R4S post-analytical tool is useful in suggesting IEMs that were not detected by regular NBS test among SIDS cases

    - To determine whether suggested IEMs are more common among SIDS cases compared to controls

Methods

- A matched case-control study

- All SIDS cases born during 2005–2008 with available MS/MS NBS testing results were included.

- Five controls were matched to each case on specimen collection date and laboratory code.

- Exclusion criteria
  - Known chromosomal and neural tube defects
  - Confirmed genetic disorders
  - Twin or multiple births
  - MS/MS analyte patterns implying a total parenteral nutrition (TPN) diet

Methods

- **Data sources**
  - California death record databases.

  - California NBS databases.

  - Patient Discharge and Emergency Department Visit databases from the Office of Statewide Health Planning and Development.

  - Probability matching was used for linking.

  - Linking variables included baby's date of birth, first name, last name, mother's maiden name, and residential address, city and zip code.

Methods

- **Definitions**
  - **SIDS:** ICD-10 code of R95 listed as underlying cause of death on death certificate.
  - **Potential IEM:** with a guideline score of ≥2.
  - **Potentially fatal IEMs (PFIEMs):** IEMs that were identified in the SIDS case group and might increase the risk of mortality.
  - **Low birth weight (LBW):** <2500 grams
  - **Small for gestational age (SGA):** having a weight for gestational age that was below the 10th percentile based on published smoothed birth weight for gestational age norms.
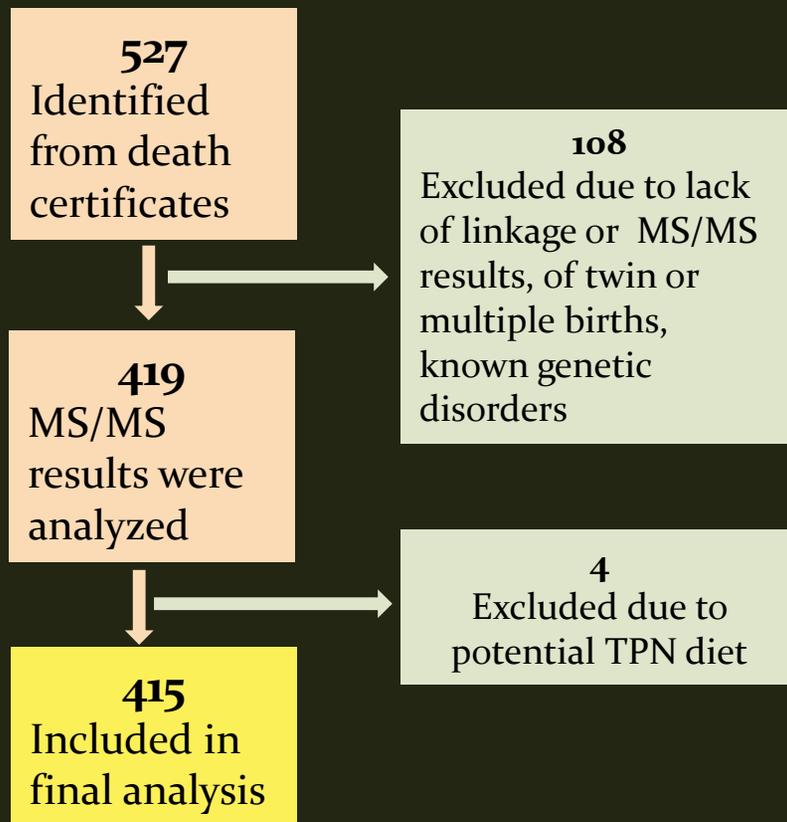
Methods

- **Data analysis**
  - Frequencies of PFIEMs were reported for both case and control groups.

  - Birth prevalence of PFIEMs was calculated and Chi-square test was used to compare between cases and controls.

  - Multivariable logistic regression was used to assess the association between PFIEMs and SIDS adjusting for LBW; the association between LBW and NICU admission and PFIEMs adjusting for case status.
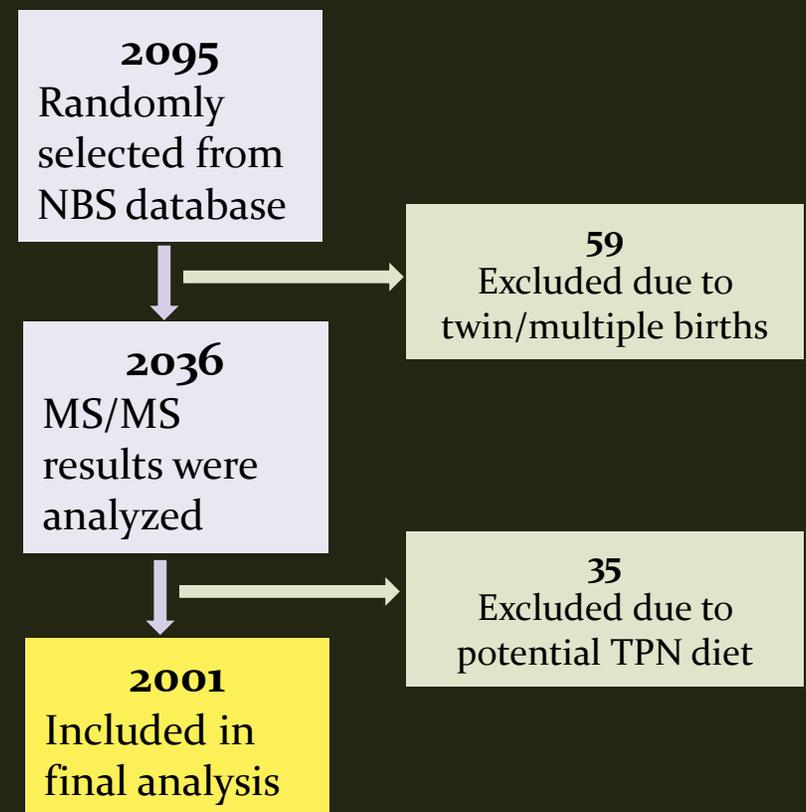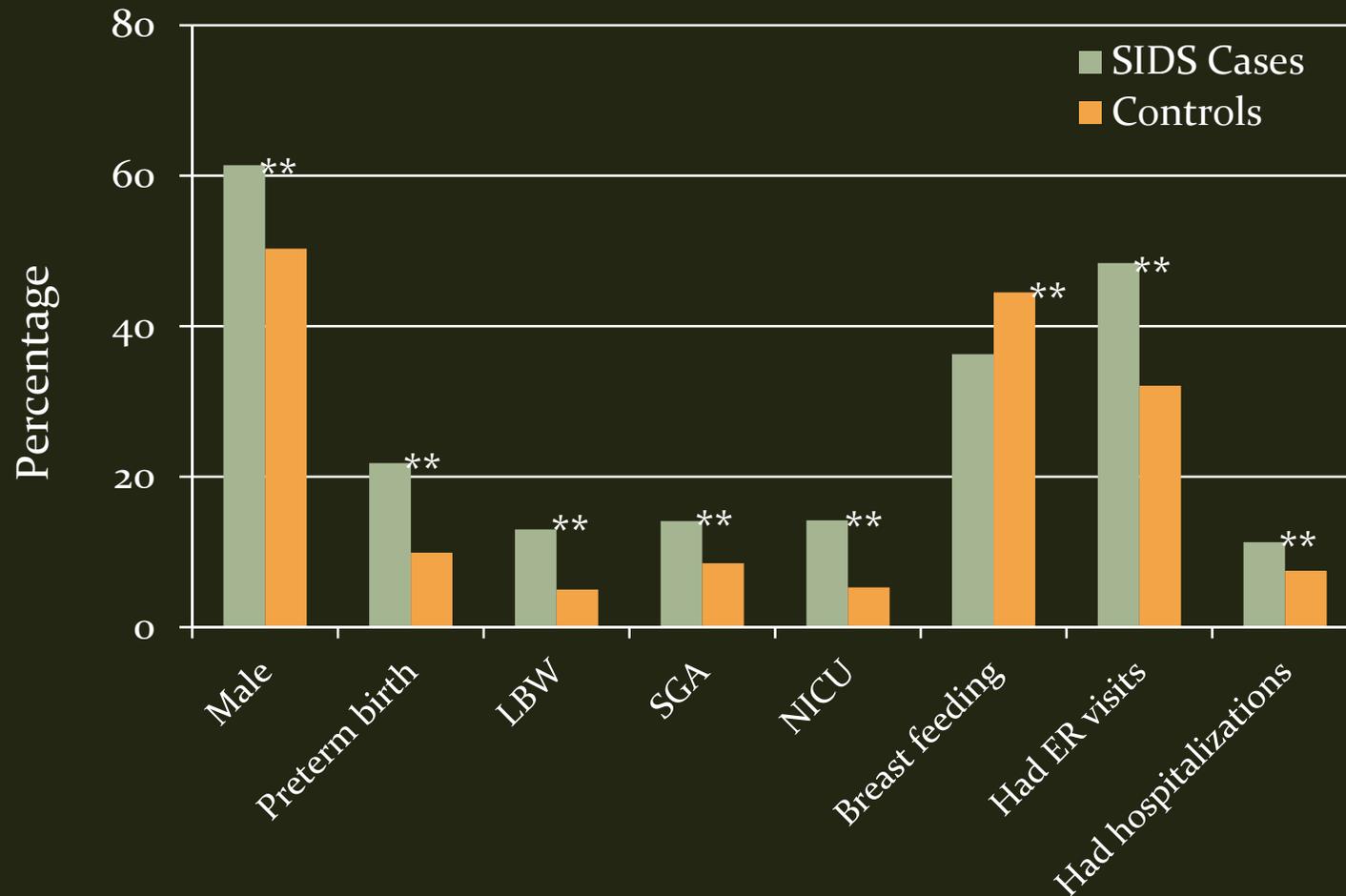
Results

- **Study sample**

SIDS cases

527 Identified from death certificates

419 MS/MS results were analyzed

415 Included in final analysis

108 Excluded due to lack of linkage or MS/MS results, of twin or multiple births, known genetic disorders

4 Excluded due to potential TPN diet

Controls

2095 Randomly selected from NBS database

2036 MS/MS results were analyzed

2001 Included in final analysis

59 Excluded due to twin/multiple births

35 Excluded due to potential TPN diet

Results

- **Characteristics of the study sample**

** P<0.01

Results

- **Frequency and prevalence of PFIEMs**

| Type of PFIEMs	SIDS Cases (n=415)	Controls (n=2001)
Citrullinemia Type II (CIT Type II)	1	1
Carnitine palmitoyl transferase deficiency-type 1 (CPT-1 deficiency)	3	10
Hypermethioninemia (MET)	1	4
Ornithine transcarbamylase /carbamoyl phosphate synthetase deficiency (OTC/CPS deficiency)	1	4
Argininosuccinic acid lyase deficiency (ASA)	1	2
Prevalence of all PFIEMs	1.5%	1.0%

Results

- **Multivariable analysis (SIDS Cases Vs. Controls)**

Characteristics	SIDS Cases Vs. Controls	
	OR	95% CI
Suggested PFIEMs	1.1	0.4, 2.8[a]
Low birth weight (LBW)	**2.8**	**2.0, 4.0[b]**
Small for gestational age (SGA)	1.3	0.9, 1.8 [c]
NICU admission	**2.3**	**1.5, 3.4 [c]**
Had emergency room visits during infancy	**2.0**	**1.6, 2.5 [c]**
Had hospital admissions during infancy	**1.4**	**1.0, 2.0 [c]**

[a] **Adjusted for LBW and NICU admission;** [b] **Adjusted for PFIEM status;**

[c] **Adjusted for LBW and PFIEM status**

Results

- **Comparison between PFIEMs and non-PFIEMs**
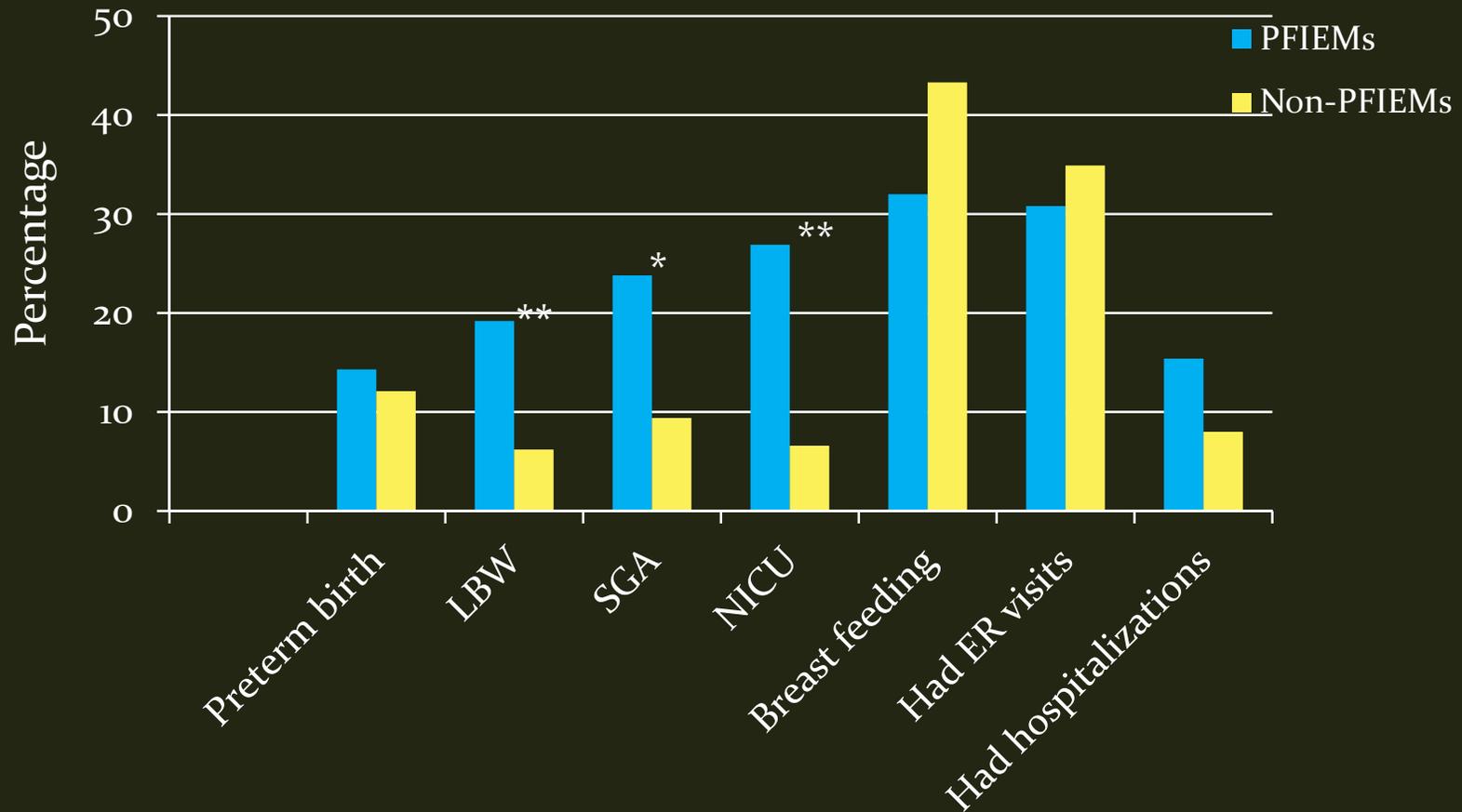
* P<0.05 ** P<0.01

Results

- **Multivariable analysis (PFIEMs Vs. Non-PFIEMs)**

Characteristics	PFIEMs Vs. Non-PFIEMs	
	OR	95% CI
Low birth weight	**3.4**	**1.2, 9.4**
Small for gestational age	2.1	0.6, 6.9
NICU admission	**4.4**	**1.4, 13.4**
Had emergency room visits during infancy	0.8	0.3, 1.8
Had hospitalizations during infancy	1.7	0.6, 5.2

Note: Adjusted for case status and LBW except for low birth weight variable

Conclusions

- The R4S tool suggested five types of PFIEMs among SIDS cases that were not previously reported.

- The PFIEMs were not more prevalent among SIDS cases compared to controls.

- These PFIEMs might have contributed to the sudden deaths among infants with the presence of other birth compromising conditions.

- The suggested PFIEMs might reflect serious metabolic dysfunction but did not reach diagnosis level.

Limitations and Next Step

- Nearly 20% of all identified cases were excluded, which might have reduced the statistical power of analysis.

- The sensitivity and specificity of the R4S tool for the suggested PFIEMs are unknown. It is unclear how many of the suggested PFIEMs are truly metabolically compromised.

- Further investigation is needed to evaluate the sensitivity and specificity of the R4S tool for the suggested conditions.

Acknowledgement

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- California Office of Statewide Health Planning & Development
- California Office of Vital Records

References

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- **Have a safe trip home!**
- **Contact information**
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Thank you!