The Genetic Scale Panel: Newborn screening for inborn errors of metabolism (IEM) with whole exome sequencing (WES)

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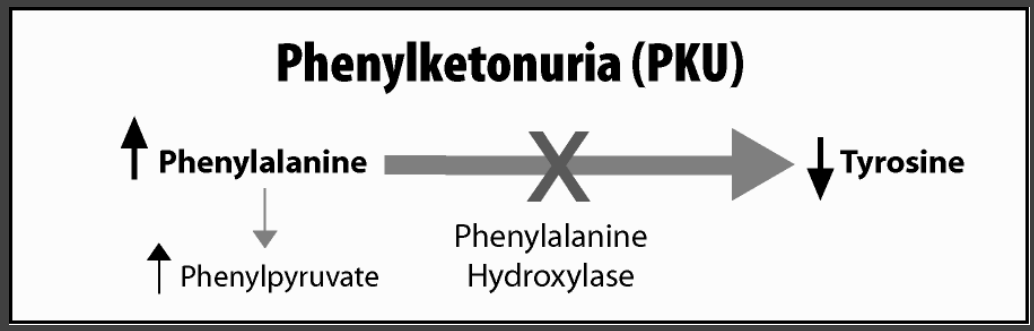
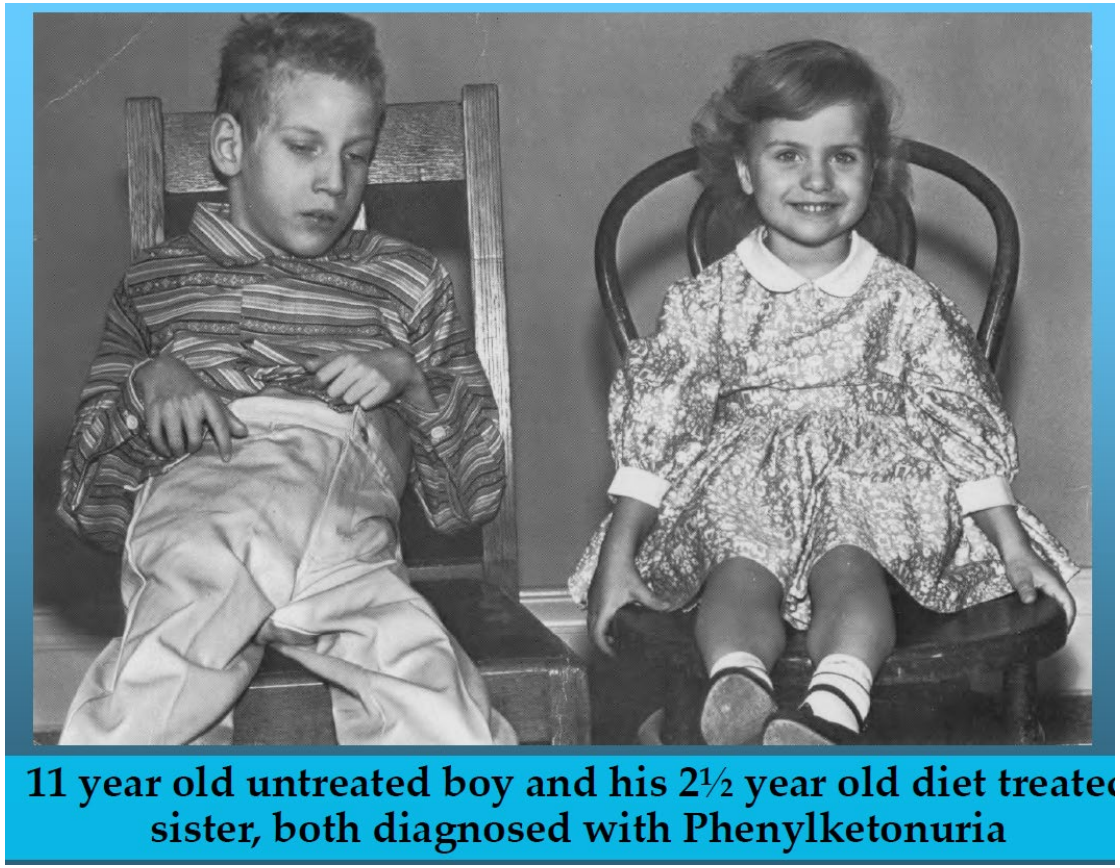
No conflicts of interest to declare.

PKU: Poster child for precision nutrition



- **Profound cognitive impairment due to untreated PKU is rare in developed world**
  - Mandated newborn screening programs, by 1970
  - Initiation of low-Phe diet (devised in 1953) within first week of life

PKU is the first human genetic disease to have population-based newborn screening coupled with an effective nutritional therapy!



11 year old untreated boy and his 2½ year old diet treate sister, both diagnosed with Phenylketonuria

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The role of exome sequencing in newborn screening for inborn errors of metabolism

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WES: genomic technique for sequencing the protein-coding regions of genes (~1% genome) where most known mutations that cause disease are thought to occur.

NBS for IEM: ideal model for evaluating the role of sequencing in population screening

Analyzed variants within an “exome slice” of 78 genes linked with 48 IEM ascertained by NBS in California using archived dried blood spots from 4.5 million births, 2005-2013.

Population-level NBS: It is imperative to identify all positive cases of IEM (life threatening) while minimizing false positives (undue stress on the family and medical resources).

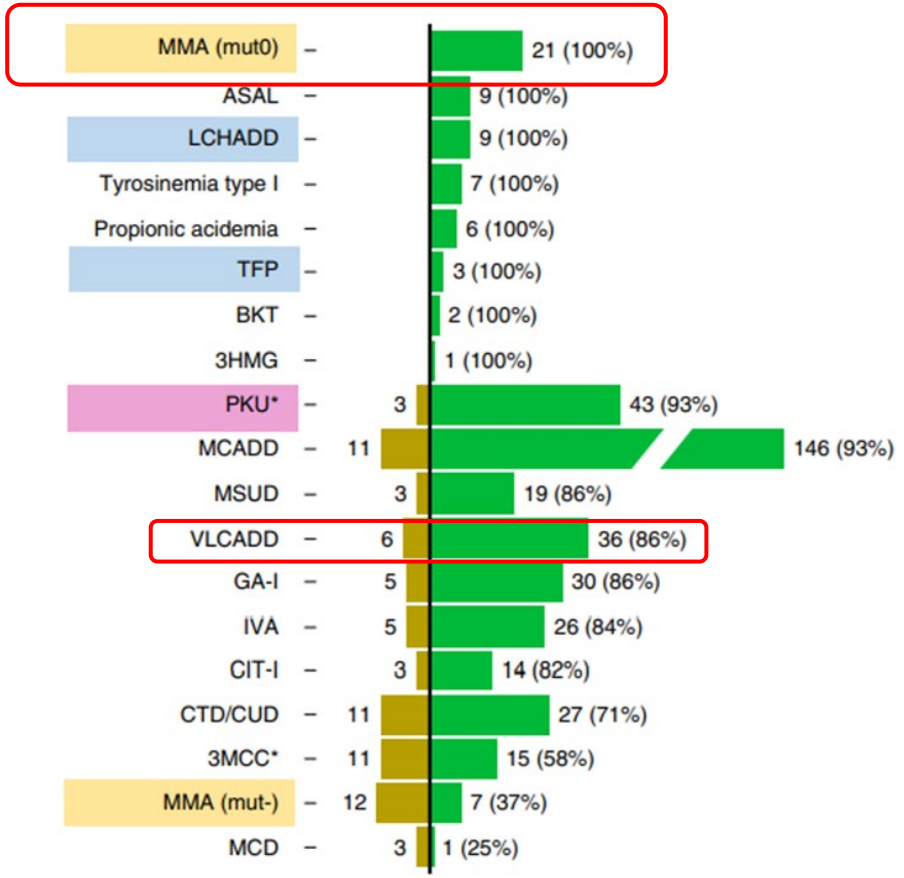
MS/MS (tandem mass spectrometry) NBS:

Sensitivity=99.0% and Specificity=99.8%.

Conclusion #1: WES alone is insufficiently sensitive or specific to be the primary screen for most NBS IEMs.

- Sensitivity = 88% overall
  - 571 cases identified & 103 cases missed
  - Varied among IEM
    - 100% MMA, known genes
    - 86% VLCADD

- Specificity = 98.4% overall
  - 11 cases were false positives
  - Extrapolates to 8,000 cases/yr
  - MS/MS yielded 1,362 false positives in 2015



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Green bar=correct ID; Brown bar=missed ID; parentheses indicate sensitivity

Conclusion #2: WES has advantages as a secondary test for infants with abnormal MS/MS screens before further biochemical/clinical studies.

- ▶ reduces false "+" cases
- ▶ may reveal new genetic variants and suggest the need for WGS

Table 2 | Performance of WES as a follow-up test after positive MS/MS for six selected IEMs, assuming an individual would not be referred for additional evaluation without at least one reportable variant identified for that IEM

Abnormal MS/MS screen result reported for	Number of MS/MS false positives	Number of exome false negatives (missed cases)	Number of exome true negatives	Specificity % (95% CI) (reduction in false positives)	NPV % (95% CI)
VLCADD	108	1	48	44.4 (34.9–54.3)	98.0 (89.1–100)
LCHADD	72	0	68	94.4 (86.4–98.5)	100.0 (94.7–100.9)
PKU	27	2	6	22.2 (8.6–42.3)	75.0 (34.9–96.8)
IVA	16	4	15	93.8 (69.8–99.8)	78.9 (54.3–93.9)
MSUD	16	1	16	100.0 (79.4–100)	94.1 (71.3–99.9)
GA-II	1	2	1	100.0 (2.5–100)	33.3 (0.8–90.6)
All of above	240	10	154	**64.2 (57.7–70.2)**	**93.9 (80.0–97.0)**

PKU, phenylketonuria. Two-sided Clopper–Pearson confidence interval (CI) was calculated using the 'exactci' function from R package PropCIs (https://github.com/shearer/PropCIs).