Newborn Screening Second Tier Molecular Testing is Critical for Identifying True Positives in Lysosomal Storage Diseases and X-linked Adrenoleukodystrophy

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BACKGROUND

Newborn screening (NBS) for infantile/childhood onset disorders for which early interventions can significantly improve the clinical outcome have been expanded to include lysosomal storage diseases (LSD) and X-linked adrenoleukodystrophy (X-ALD) in many states. However, due to pseudodeficiency, transportation, and other reasons, the positive predicted value is low. Therefore, second tier gene sequencing is often required to increase clinical sensitivity.

LSDs are multisystem disorders involving cardiovascular and neurological systems that can lead to irreversible damage and even premature death.

X-ALD is the most common leukodystrophy characterized by the progressive deterioration of the adrenal glands, spinal cord, white matter of the nervous system. Phenotypes range from adrenocortical insufficiency (Addison disease), to a progressive adult on-set paraparesis with adrenal gland dysfunction (adrenomyeloneuropathy, AMN), to the most severe and fatal cerebral form of XALD.

In the past five years, we have performed 2286 dry blood spot (DBS) specimens that are positive or inconclusive for NBS for LSD and X-ALD.

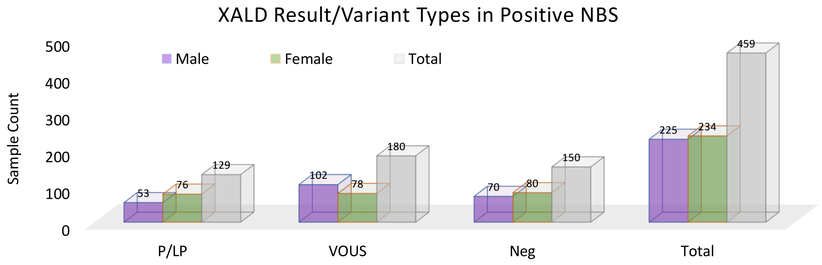
RESULTS - Lysosomal storage diseases

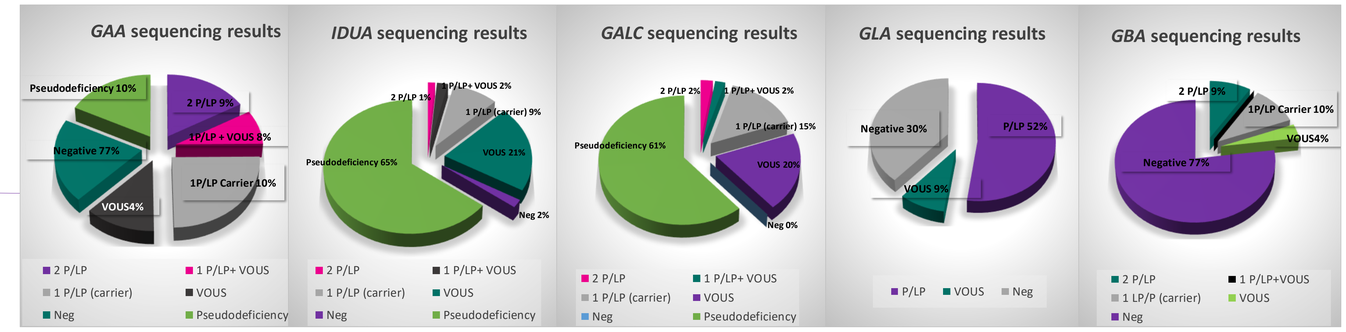
PKIG Sequenced 1843 DBS for the states of PA, CA, TN, NB, FL, MS, IL, DC, well as other states through Lantern program since 2016.

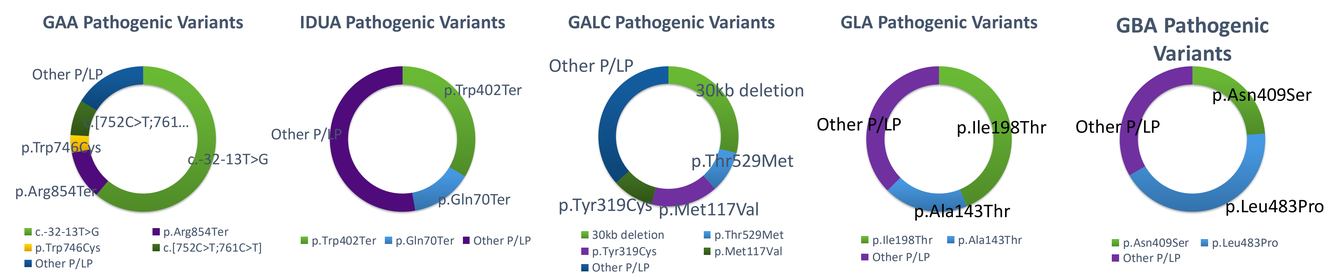
- Pompe disease/GAA
  - 17.6% confirmed with two P/LP variants and 97% of these possess at least one late-onset pathogenic variant
- MPSI/IDUA (mucopolysaccharidosis type I)
  - Very few (2%) are truly affected with two P/LP variants
  - Majority (82%) due to pseudodeficiency allele(s)
- Krabbe disease/GALC
  - Very few (3.5%) are truly affected with with two P/LP variants
  - Majority (84%) due to pseudodeficiency allele(s)
- Fabry disease/GLA
  - Over half are truly affected with (52%) P/LP variant
  - Over one third (39%) are negative
- GBA (Gaucher disease)
  - Majority (80%) are negative
  - Very few (6%) were truly affected with two P/LP variants

RESULTS – X-linked Adrenoleukodystrophy

- Sequenced 434 DBS samples for *ABCD1*
- 28% yielded a pathogenic/likely pathogenic (P/LP) variant.
- 33% returned no reportable *ABCD1* variant.
- Three confirmed with a partial gene deletion
- Among those with parental testing
  - 6% occurred de novo
  - 26% maternally inherited







CONCLUSION

- Second-tier confirmatory NBS testing is essential to identify and ascertain affected individuals with positive biochemical NBS for LSDs and XALD by
  - Ruling out pseudodeficiency allele
  - Differentiate carriers and late-onset disease
  - Proceed with unreliable/inconclusive biochemical screening results
- The molecular confirmatory data is critical in
  - Assessing the NBS biochemical cut-off values for calling positive result
  - Establishing genotype-phenotype correlation to aid clinical management.
- NBS second tier molecular testing is one of the most economic and efficient approach to improve clinical outcomes.