The X (ALD) Factor: Follow-Up and Clinical Perspectives After One Year of Screening in Minnesota

TWO YEARS

Amy Gaviglio MS LCGC | Genetic Counselor/Follow-Up Coordinator

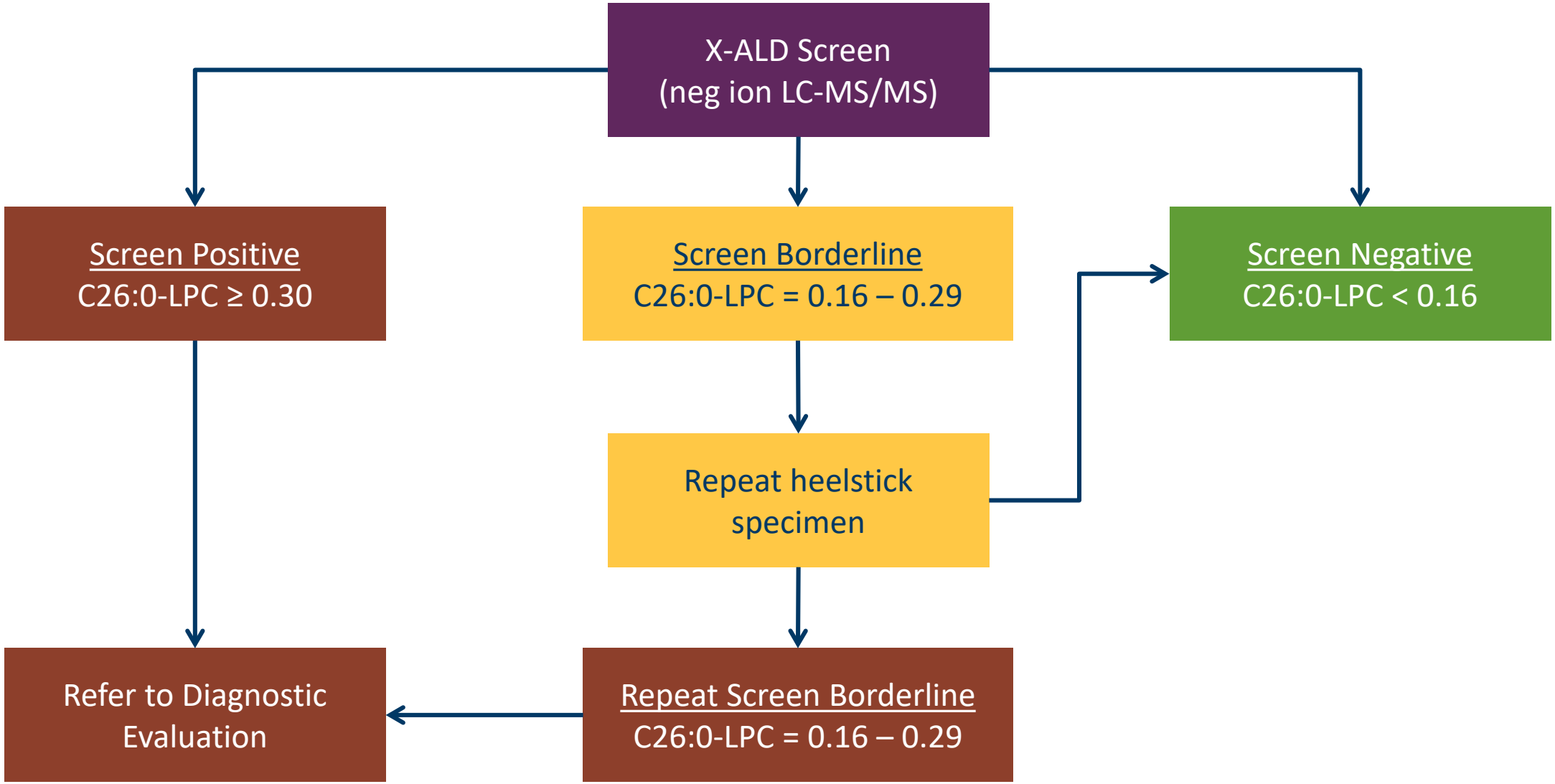
DEPARTMENT OF HEALTH

X-ALD: Background and Testing

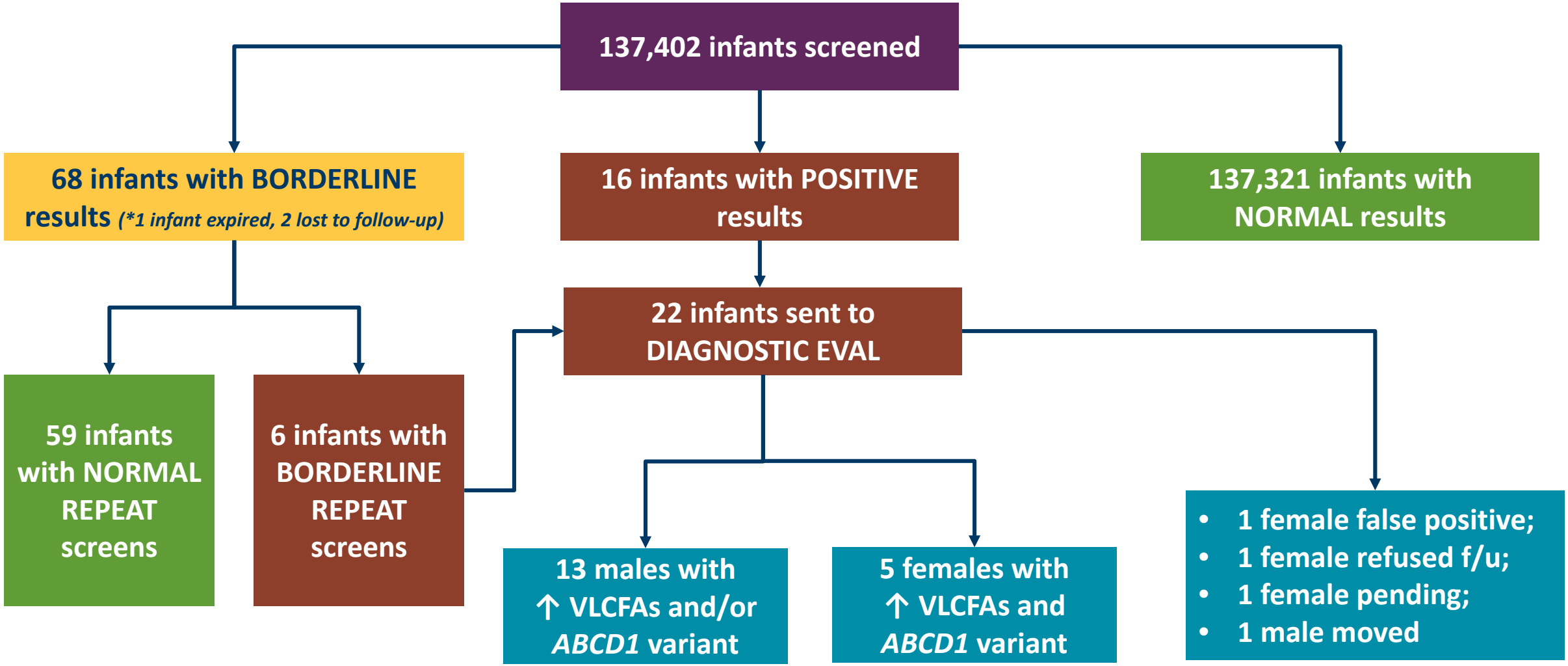
X-ALD Overview

X-ALD Types/Characteristics	Details
• **Childhood Cerebral**	• ~ 35%-50% of males • Onset from around 4-10 yrs • Adrenal, cognitive, and developmental issues • Death within 2-4 yrs after onset of cerebral symptoms
• **Adrenal Insufficiency**	• ~ 80% of affected individuals
• **Adrenomyeloneuropathy (AMN)**	• Seen in most older men with X-ALD • Onset around 20s to 40s • Progressive weakness
• **Symptomatic Females**	• ~10-50% have neurological symptoms • Onset around 30s • Similar to AMN, but slower progression

Screening Algorithm



Performance and Outcomes: 2/06/2017 to 2/28/2019



Performance and Outcomes: 2/06/2017 to 2/28/2019

- **Screen-Borderline Rate** ~ 1 in 2,114 infants
- **Screen-Positive Rate** ~ 1 in 6,245 infants

- **Birth Prevalence*** ~ 1 in 7,633 infants
- **Male Birth Prevalence*** ~ 1 in 5,427 males
- **Female Birth Prevalence*** ~ 1 in 13,416 females

** A case is considered confirmed upon elevated VCFAs and ABCD1 variant identification*

DEPARTMENT OF HEALTH

X-ALD: Follow-Up and Clinical Considerations

Challenges for the NBS System

- **High rate of variants of uncertain significance in *ABCD1* gene**
- **Inability to predict phenotypic severity**
- **X-linked inheritance**
  - Downstream family member diagnoses
  - Detect females who will not be symptomatic for years (if ever)
  - Heightened need to check unscreened older siblings (especially males)

Variants of Uncertain Significance (*and one unknown Variant*)

- **17 had an *ABCD1* variant detected**
  - 11 classified as likely pathogenic/pathogenic
  - 4 variants of uncertain significance
    - ALL were eventually reclassified as likely pathogenic
  - 4 variants never seen before

- **One male case did not have a detectable *ABCD1* variant**
  - Family history consistent with X-linked inheritance
  - Functional ALDP expression study on fibroblasts pending in Amsterdam

= novel variants

Clinical Findings: Male X-ALD Cases

Case	NBS C26:0-LPC (umol/L)		VLCFA C26:0 (umol/L)		*ABCD1* Variant	Classification *(as reported by specialists)*
M1	0.26		3.34		None Found	N/A
M2	0.72	**0.9**	10.6	**7.72**	c.293C>T	Pathogenic
M3	1.06		7.38		c.900+1G>A	Pathogenic
M4	0.74		6.43		c.1028G>T	Pathogenic
M5	1.12		8.07		c.1973C>T	Pathogenic
M6	0.76	**0.415**	6.9	**2.27**	c.487C>T	Likely Pathogenic
M7	0.4		2.17		c.1597A>G	Likely Pathogenic
M8	0.43		1.92		c.593C>T	Likely Pathogenic
M9	0.31		2.37		c.593C>T	Likely Pathogenic
M10	0.16	**0.41**	1.53	**3.18**	c.80A>C	VUS*
M11	0.35		3.18		c.823C>T	VUS*
M12	0.47		N/A		c.823C>T	VUS*
M13	0.49		3.73		c.1747G>A	VUS*

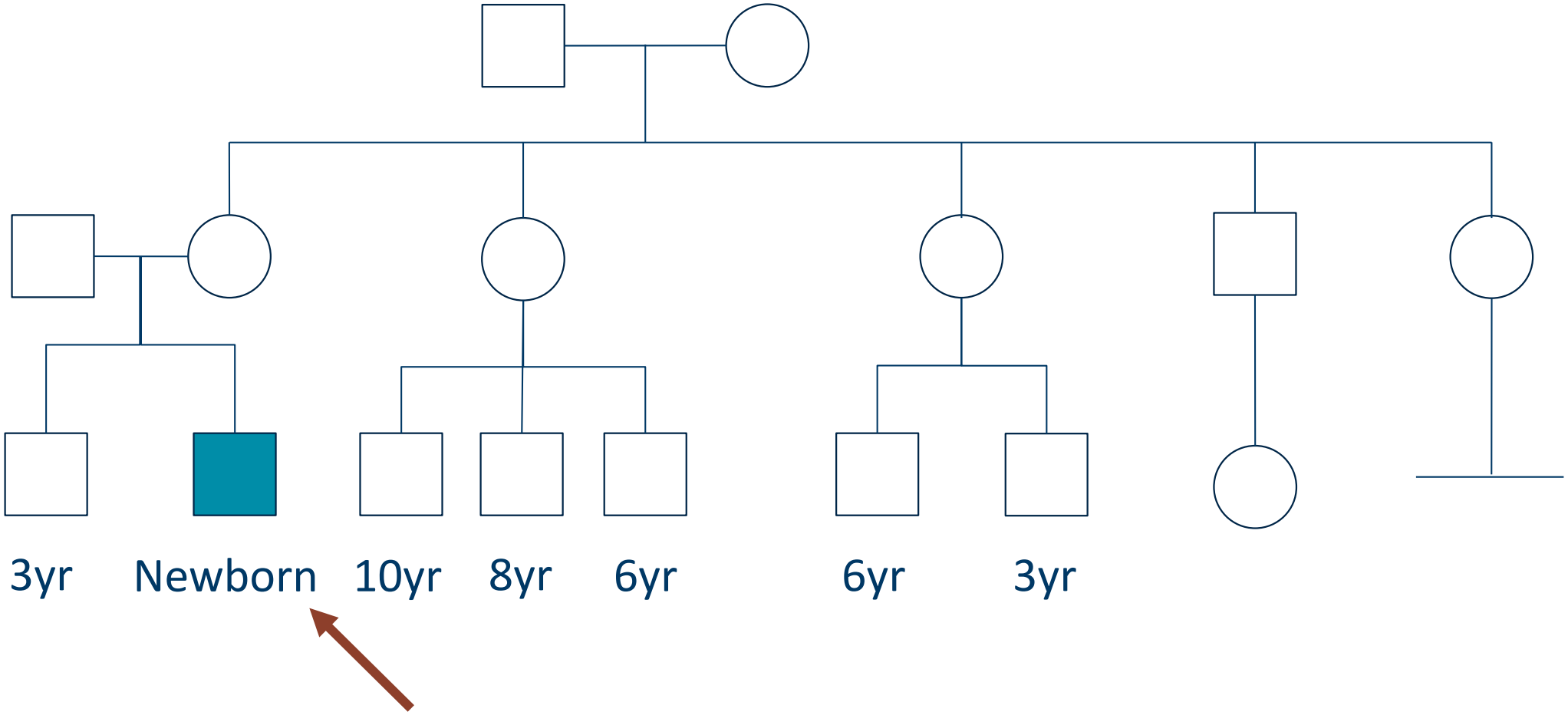
* reclassified as likely pathogenic

Case Example I

= male

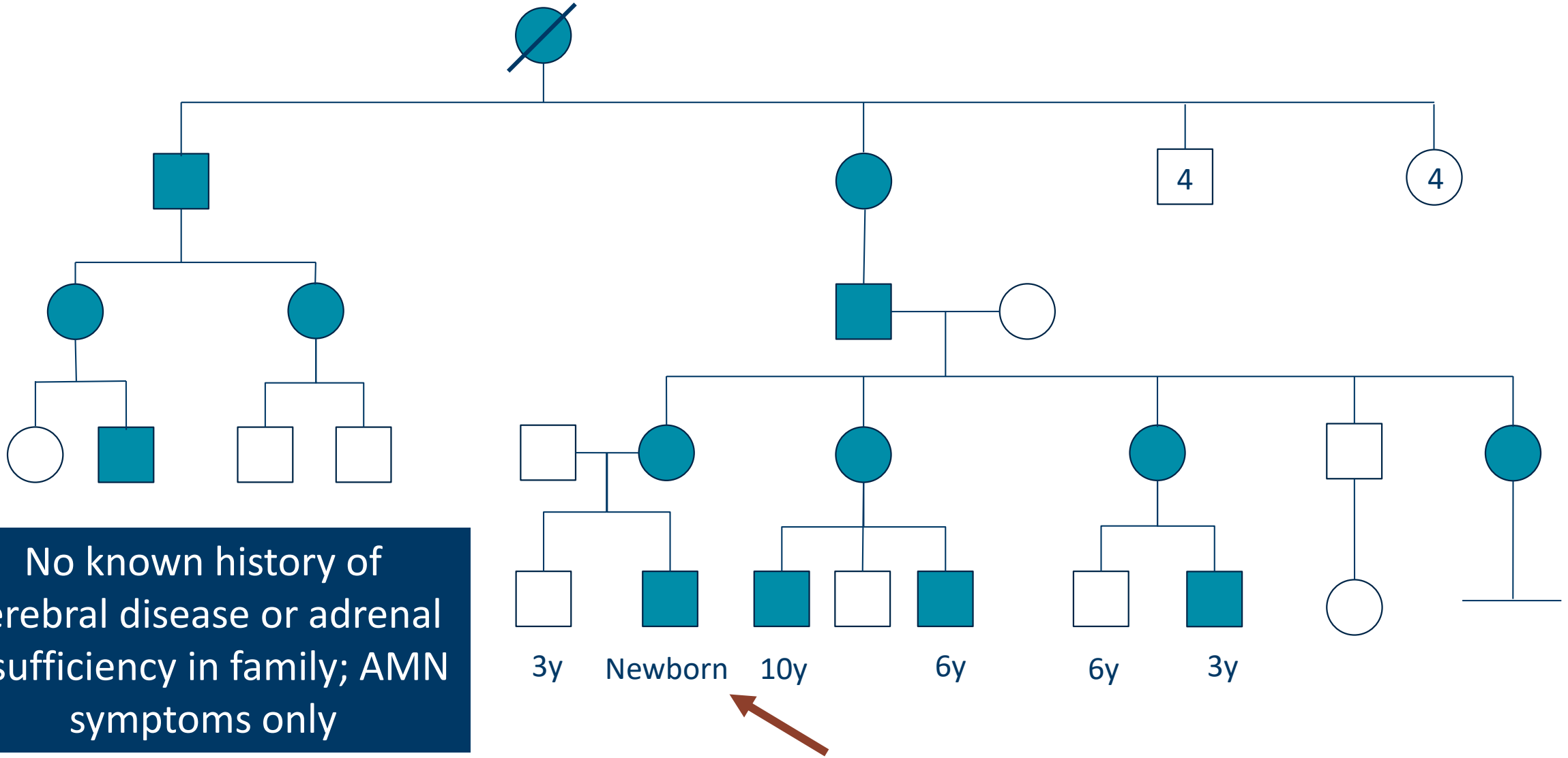
= female

= affected



Shared with permission from UMN and family

Case Example I: Further Familial Analysis



No known history of cerebral disease or adrenal insufficiency in family; AMN symptoms only

Variant Re-classifed from VUS to Likely Pathogenic

The c.823C>T variant in ABCD1 results in the p.Arg275Trp substitution. This variant has been reported as likely pathogenic by a single submitting laboratory without supporting evidence. This variant is present in one hemizygous individual in the gnomAD database of 140,000 controls. In silico prediction models estimate this variant to be pathogenic; however, the accuracy of such models is limited. Due to insufficient data to clearly classify this variant as pathogenic or benign, this variant is categorized as a variant of uncertain significance.

- Co-segregation of variant with VLCFA elevations
- Variant identified in other families following X-linked inheritance

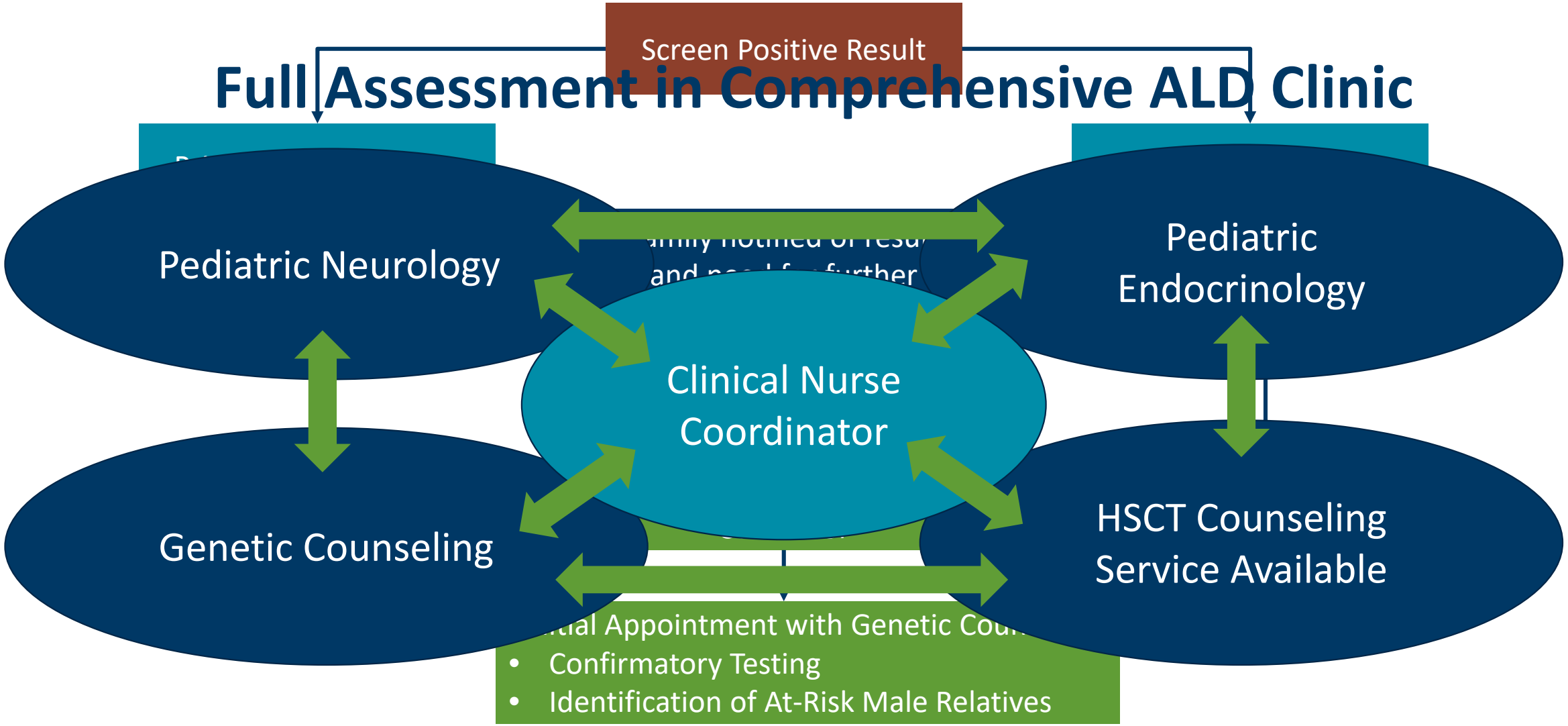
This addendum is issued to reflect additional evidence regarding the c.823C>T (p.Arg275Trp) variant in the ABCD1 gene. Since this patient's report was originally issued, this variant has been identified in additional probands with X-linked adrenoleukodytrophy by other laboratories and the variant has also been shown to segregate with an X-linked ALD phenotype in another family tested in this laboratory. Based upon this additional evidence, this variant is now classified as likely pathogenic. Genetic counseling regarding these results is recommended.

Downstream Diagnoses (*first year cases only*)

- **Approximately 4 family members are being detected for every newborn**
  - Age Range = 1 to 67 years
  - Median = 10 years

Phenotypes	Percentage of Identified Family Members
Males with cerebral disease	~6%
Males with adrenal insufficiency	~6%
Males with AMN symptoms	~12% (~67% of males > 18 years)
Females with AMN symptoms	~30%

Clinical Care Process



Conclusions

- **X-ALD incidence may be more common than previously observed**
- **Can expect numerous subsequent family member diagnoses**
    - Phenotypic spectrum may be broader/more mild than expected
- **Challenges include:**
    - Delayed understanding of true clinical picture of detected cases
    - Numerous VUS' and reclassifications based on biochemical/molecular findings only
    - Inability to predict phenotypic severity
- **Given the above, thoughtful planning and coordination by dedicated specialists is imperative for successful implementation of population-based screening for X-ALD**

Acknowledgements

- Katie Wiens, MS, LCGC
- Paul Orchard and Troy Lund, MDs
- Amy Dahle, MPH
- Amy Hietala, MS
- Holly Winslow

amy.gaviglio@state.mn.us