California ALD Screening Experience

Identifying Standards of Care Conference

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ALD Screening in California

- Chapter 565, Statutes of 2014, Health & Safety Code Section 125001 (d) mandates that CDPH screen newborns for ALD after it is added to the national Recommended Uniform Screening Panel (RUSP)
- ALD was added to the RUSP on February 16, 2016
- Screening went live on September 21, 2016; testing of the "backlogged" specimens received by the lab starting on February 16, were stored by the California Biobank Program and screened retroactively

ALD Cases Screened: Feb 16, 2016 – Jan 2, 2018		
	Total Screened	Screen Positive
Backlog	294,398	74
Go Live	604,413	140
Total	898,811	214

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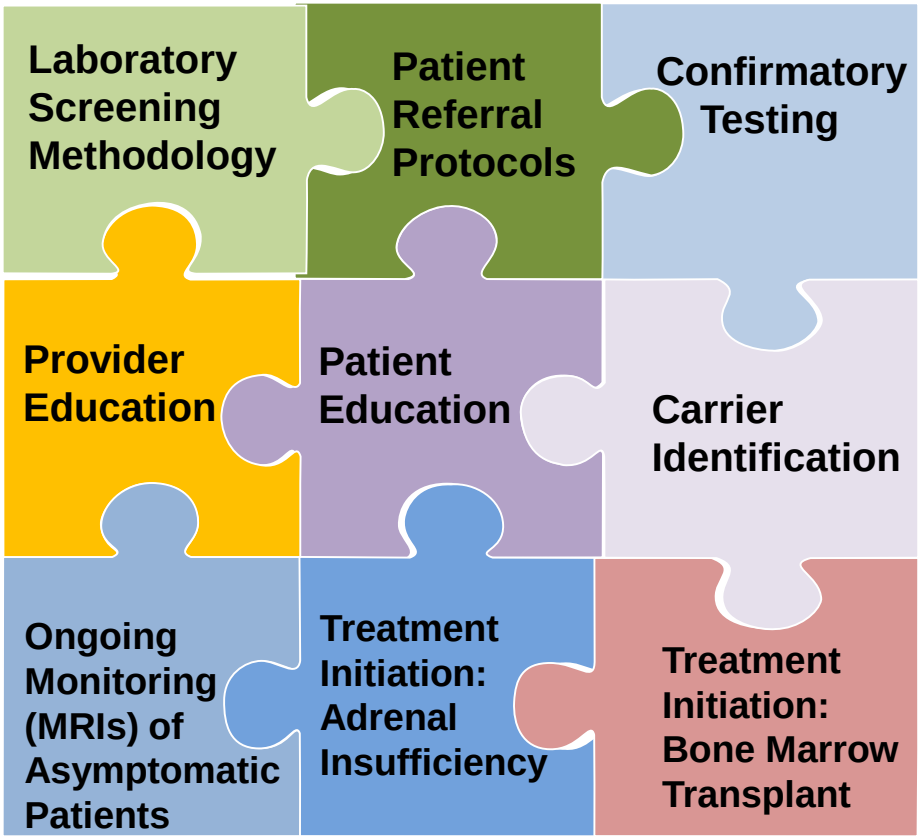
ALD Screening Implementation Challenges



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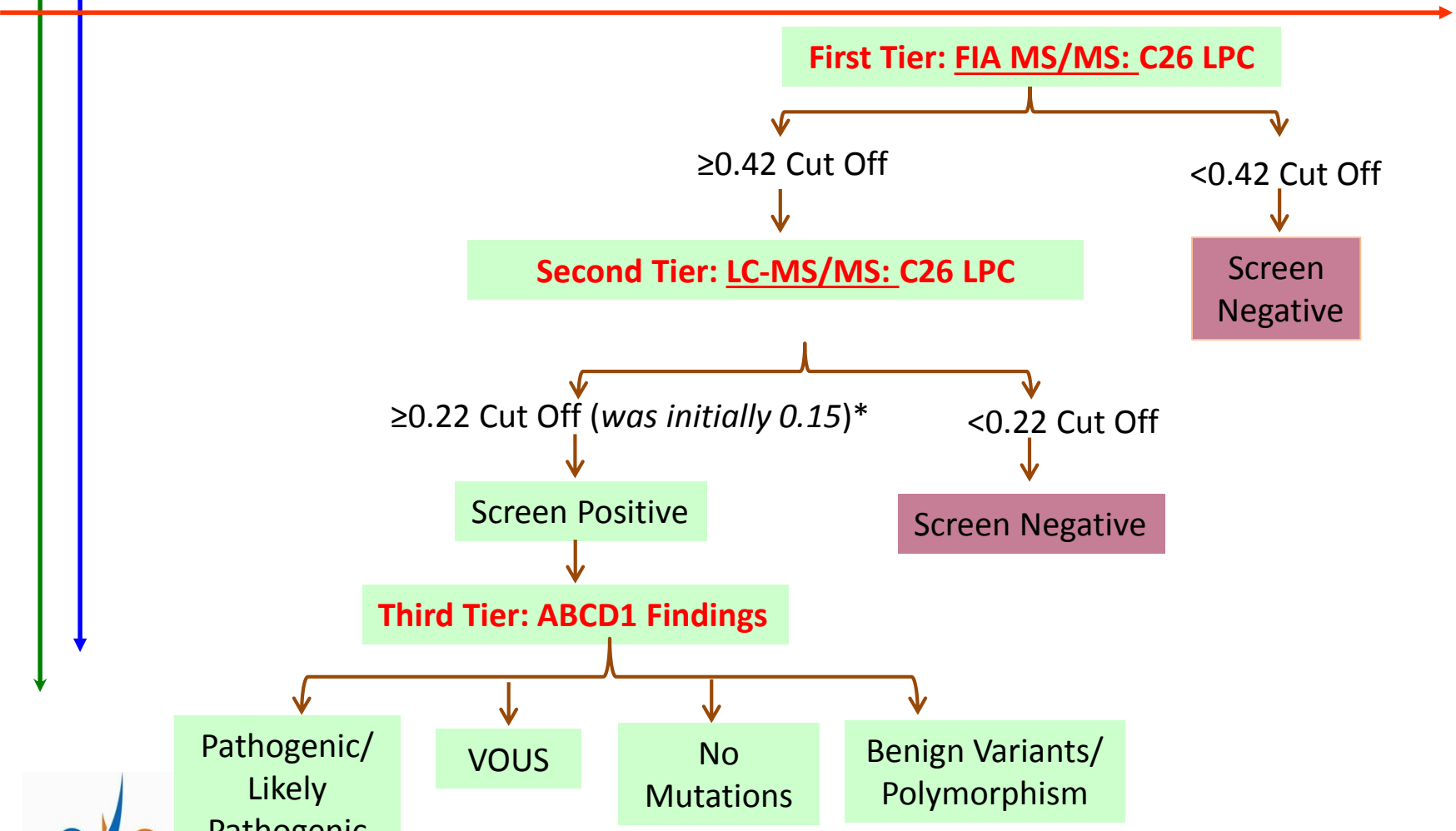
California ALD Screening Algorithm



** New Cut-Off Effective December 13, 2017*

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ALD Follow-up Approach

ALD Tier 2 Positive Cases Appear as "Headline Case" on Follow-up Coordinator Computer Screen:

- Coordinator notifies Primary Care Physician
- Primary Care Physician contacts family to arrange a referral to an approved metabolic center

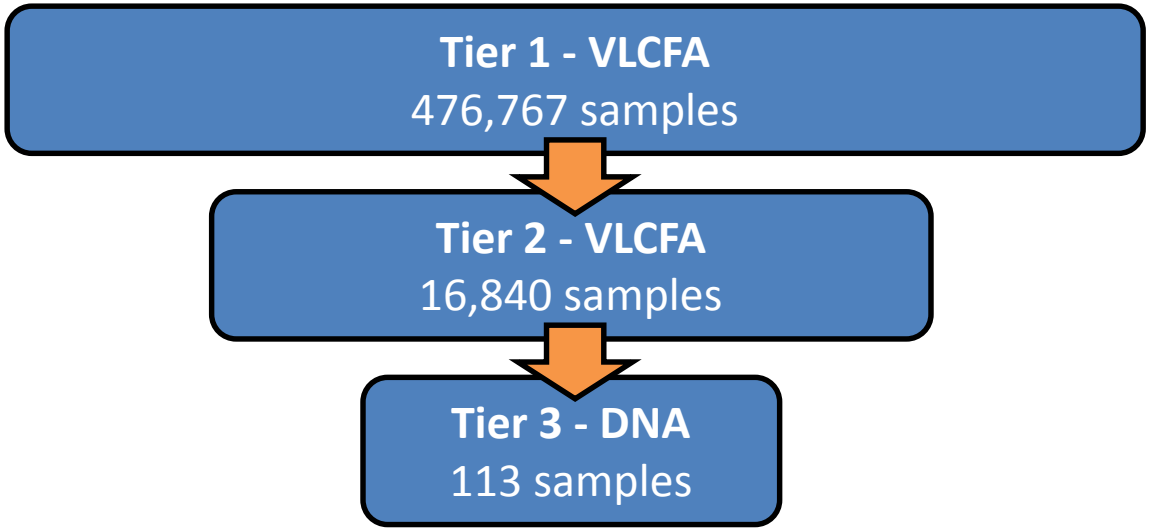
Metabolic Centers:

- Provide genetic counseling
- Confirmatory Testing
- Resolve as "disorder" or "no disorder"
- Long Term Follow-up (LTFU)
  - Annual patient summary reports submitted by specialty care centers - through age 21
  - *Data system allows patient to transferred an approved endocrine center for LTFU*

One Year of ALD Screening in California

(September 21, 2016 – September 20, 2017)

- Tier 1 measures elevation of very long chain fatty acids (VLCFA) in the same blood collected for routine newborn screening
- Tier 2 is a more precise measurement of VLCFA
- Tier 3 consists of DNA sequencing of the ABCD1 gene to identify genetic variants associated with ALD



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Initial Findings from Molecular Analysis

(Feb 16, 2016 – Jan 2, 2018)

Variant Interpretation		Count	Percent
Pathogenic/Likely Pathogenic			17%
	Boys	17	
	Girls	20	
VOUS			50%
	Boys	52	
	Girls	55	
Benign/Polymorphism			16%
	Boys	10	
	Girls	24	
No Mutations			17%
	Boys	22	
	Girls	14	
Interpretation Total		214	100%

	Pathogenic/Likely Pathogenic + Variants of Unknown Significance	Pathogenic/Likely Pathogenic Only
Affected Males/ Total Male Births	1 in 6,513	1 in 26,436
Female Carriers/ Total Female Births	1 in 5,992	1 in 22,470
Total Births	1 in 6,242	1 in 24,292

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Impact of New ALD Cut-off on Molecular Findings

Initial cut0ff (0.15) versus new cut-off (0.22)*

Variant Interpretation	Old Cutoff Count	Old Cutoff Percent	New Cutoff Count	New Cutoff Percent
Pathogenic/Likely Pathogenic		17%		31%
Boys	17		16	
Girls	20		19	
VOUS		50%		46%
Boys	52		21	
Girls	55		31	
Benign/Polymorphism		16%		11%
Boys	10		3	
Girls	24		10	
No Mutation		17%		12%
Boys	22		5	
Girls	14		9	
	214	**100%**	**114**	**100%**

** New Cut-Off effective December 13, 2017*

	Old Cutoff: Pathogenic/Likely Pathogenic + Variants of Unknown Significance	Old Cutoff: Pathogenic/Likely Pathogenic Only	New Cutoff: Pathogenic/Likely Pathogenic + Variants of Unknown Significance	New Cutoff: Pathogenic/Likely Pathogenic Only
Affected Males/ Total Male Births	1 in 6,513	1 in 26,436	1 in 12,146	1 in 28,088
Female Carriers/ Total Female Births	1 in 5,992	1 in 22,470	1 in 8,988	1 in 23,653
Total Births	1 in 6,242	1 in 24,292	1 in 10,331	1 in 25,680

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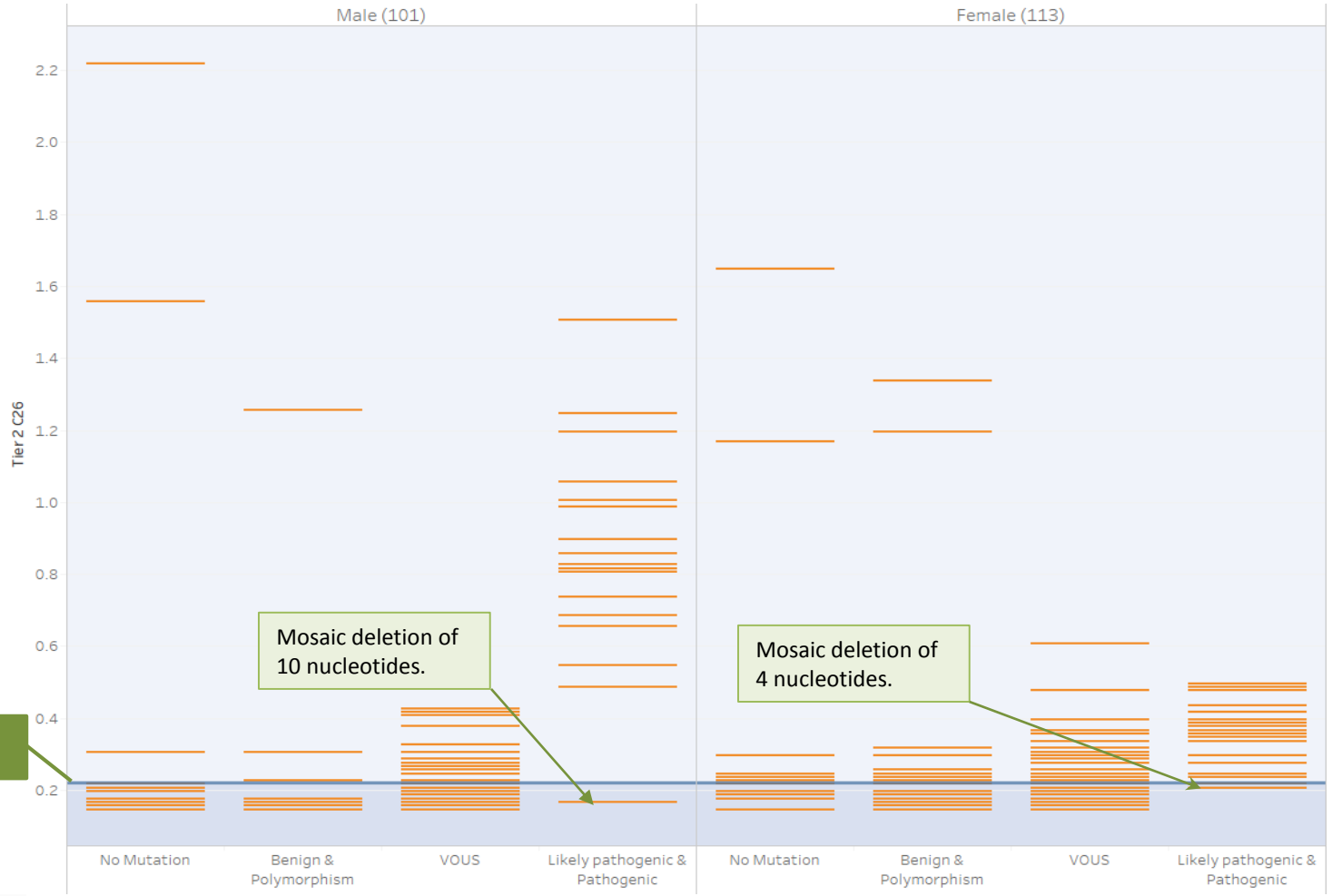
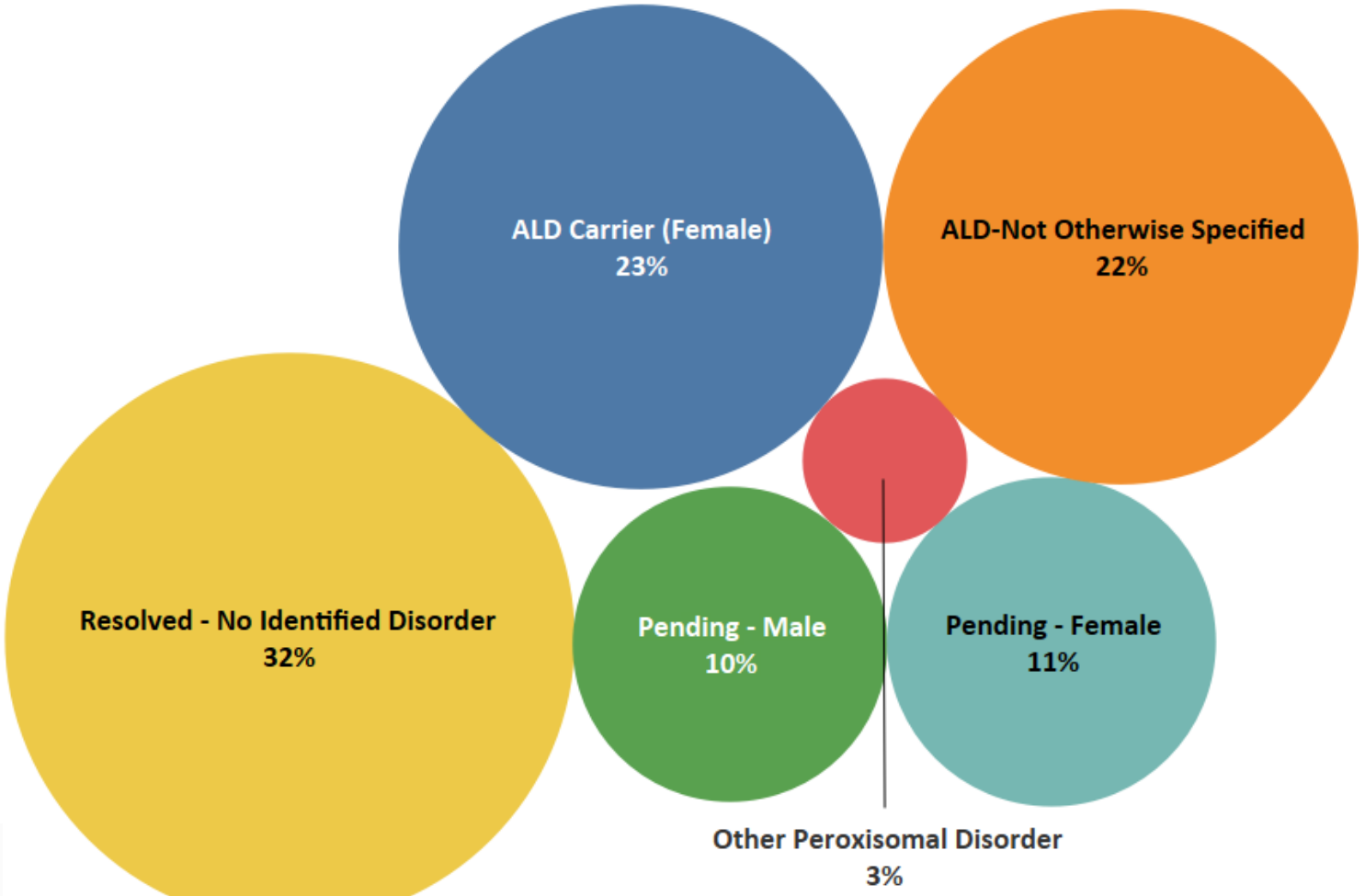
ALD Tier 2: C26 Levels by Sex & Presence of ABCD1 Variants



New Cutoff = 0.22*

** New Cut-Off effective December 13, 2017*

Case Resolution of Referred Cases in First Year



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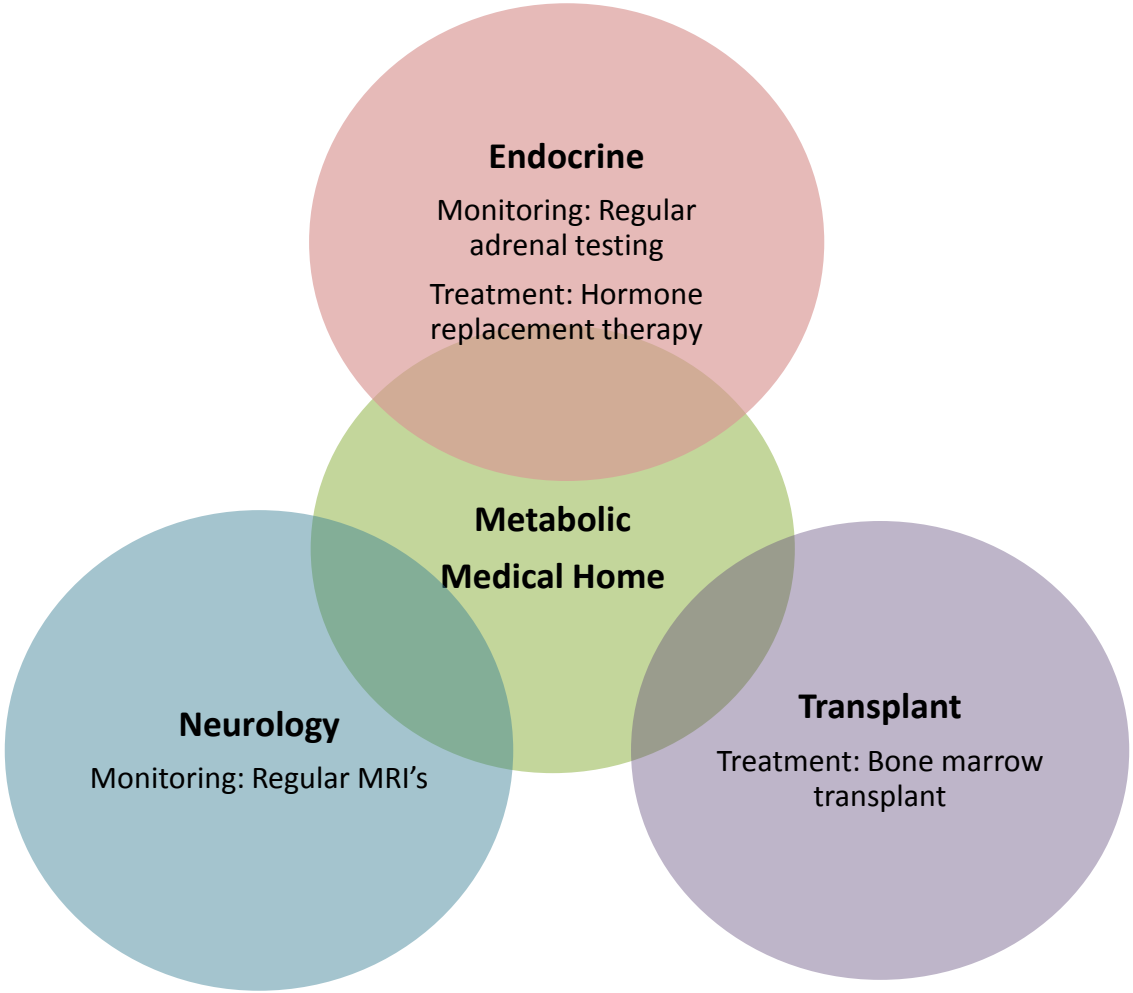
ALD Follow-up Care



ALD Short Term Follow-up Form

- Service Reports are entered by metabolic centers during diagnostic period after birth.
- Service Reports collects data on:
  - Resolution and follow-up status
  - Diagnostic information
  - Contacts with patients & child's primary care provider
  - Insurance coverage
  - Specialists providing services
  - Lab tests and procedures (results)
  - Interventions/treatments
  - Health status/clinical findings

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ALD Long Term Follow-Up Form

- Annual Patient Summary entered metabolic centers or endocrine centers when the child is between age 1 and 21 years old

- Annual Patient Summary collects data on:
  - Patient contact information
  - Diagnosis
  - Affected family members
  - Follow-up status
  - Interactions with the patient
  - Hospitalizations
  - Insurance
  - Anthropometrics
  - Specialists providing services
  - Lab tests and procedures (includes MRIs)
  - Interventions/treatments
  - Health status/clinical findings
  - Developmental assessment

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Questions from Specialists

- What age to do the first MRI?
- When to make the first referral to endocrinology?
- When should bone marrow matching be initiated?
- Case definitions: When to make a definitive diagnosis of ALD in boys?
- What are the appropriate age ranges for care guidelines? Age 0-3, age 4 -10, age 11-21 years, 21+? Other age groupings?
- Should radiologists seek out a second opinion if changes are found on MRI?
- Should Lorenzo's oil be removed from the list of treatments?