Developing Short- and Long-term Follow-up for X-linked Adrenoleukodystrophy

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Outline

- Review of X-linked Adrenoleukodystrophy
- Newborn screening for ALD
- New York State (NYS) method
- Follow-up preparations
  - Diagnostic algorithm and case definitions
  - Medical management
  - Considerations for treatment
  - Genetic counseling considerations
  - Long-term follow-up
  - Educational materials

ALD Review

- ALD is a peroxisomal disorder
- Caused by mutations in the *ABCD1* gene
- X-linked inheritance
- 1 in 21,000 males (~12 per year in NYS)
- Two phenotypes
  - Childhood cerebral onset and adult onset (adrenomyeloneuropathy)

Symptoms
Childhood Onset

- 35 to 50% of males
- Onset varies from three to ten years
- Symptoms: Addison disease, cognitive disturbances, hyperactivity, seizures, psychosis, vision and hearing loss
- Vegetative state and death within two to four years of the onset of neurological symptoms

Adrenomyeloneuropathy (AMN)

- Onset of symptoms from the second to fourth decade
- Progressive weakness of the legs, paresis, sphincter disturbance and sexual dysfunction
- About 70% also have Addison disease

Carriers

- Approximately 10 to 50% of females with an *ABCD1* gene mutation have neurological symptoms
- Similar presentation to AMN
- Milder and more slowly progressive
- Onset of symptoms in the 30s

NYS Method of Screening for ALD

- 1st and 2nd tier: C26:0 lysophosphatidylcholine (C26:0 LPC)
  - 1st tier: MS/MS
  - 2nd tier: MS/MS with selective HPLC
- 3rd tier: sequencing of *ABCD1* gene
- More details from Joe Orsini, PhD

Differential Diagnoses

(1) X-linked adrenoleukodystrophy(X-ALD)

(2) Carrier of X-linked adrenoleukodystrophy

(3) Adrenomyeloneuropathy (AMN)

(4) Zellweger Spectrum Disorders (ZSD)

(5) Single-enzyme deficiency (SED) of the peroxisomal β-oxidation enzymes

   (1) D-bifunctional protein (D-BP)

   (2) acyl-CoA oxidase (AOx)

(6) CADDS

Follow-up Preparations

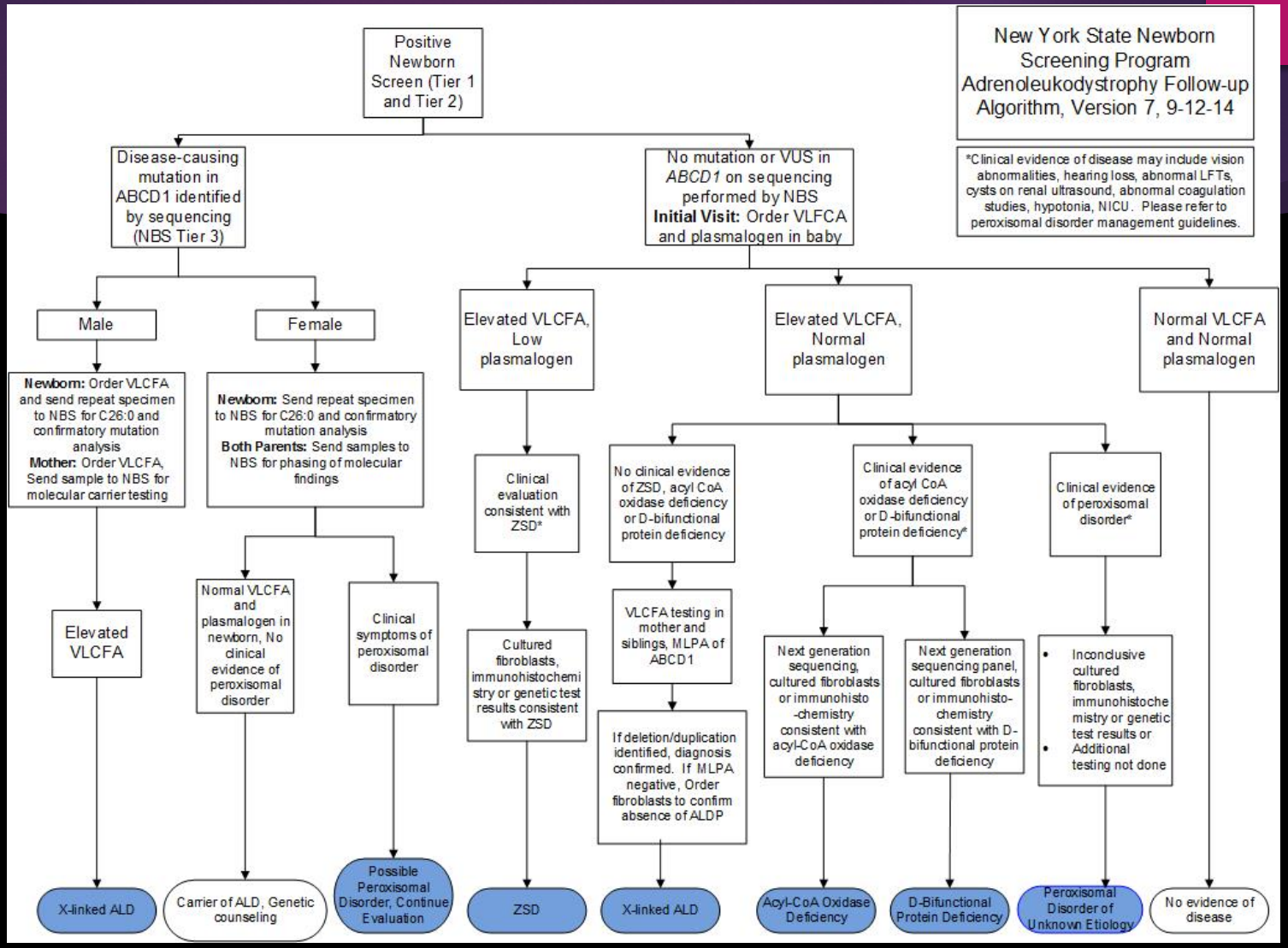
- Series of conference calls
  - metabolic geneticists
  - NBS Program Staff
  - Disorder expert – Dr. Gerald Raymond
- Separate calls with endocrinologists, neurologists and genetic counselors

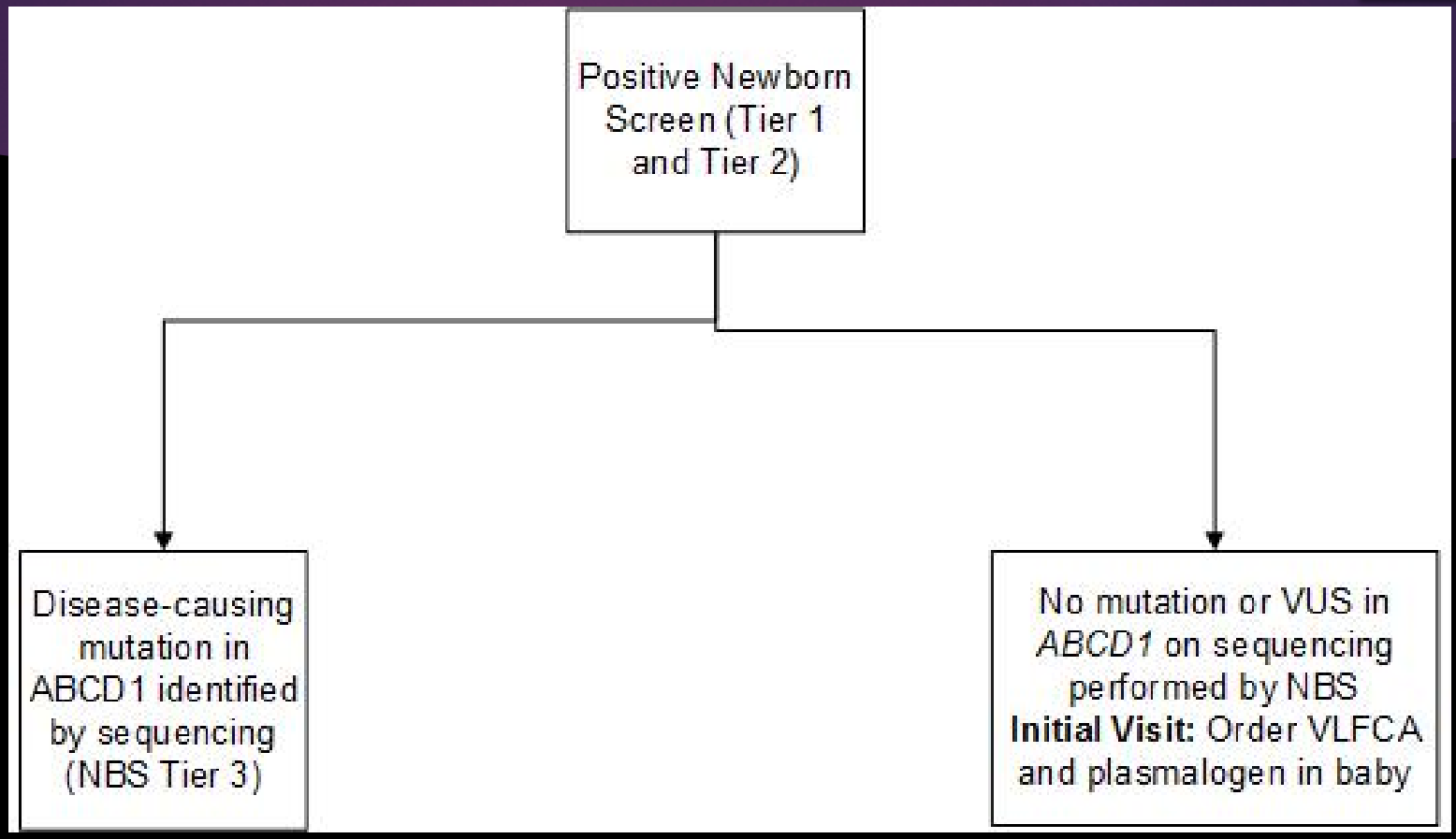
Follow-up Preparations

1. Preliminary diagnostic algorithms and management recommendations were created prior to calls
2. These were reviewed and revised with the group on conference calls

Diagnostic Algorithm

- Goals of the algorithm:
  - To answer the question, does this baby have ALD
  - To recommend the minimum lab work and evaluations necessary in order to answer that question


New York State Newborn Screening Program Adrenoleukodystrophy Follow-up Algorithm, Version 7, 9-12-14
*Clinical evidence of disease may include vision abnormalities, hearing loss, abnormal LFTs, cysts on renal ultrasound, abnormal coagulation studies, hypotonia, NICU. Please refer to peroxisomal disorder management guidelines.
Positive Newborn Screen (Tier 1 and Tier 2)
Disease-causing mutation in ABCD1 identified by sequencing (NBS Tier 3)
No mutation or VUS in ABCD1 on sequencing performed by NBS
Initial Visit: Order VLFCA and plasmalogen in baby
Male
Female
Newborn: Order VLCFA and send repeat specimen to NBS for C26:0 and confirmatory mutation analysis
Mother: Order VLCFA, Send sample to NBS for molecular carrier testing
Newborn: Send repeat specimen to NBS for C26:0 and confirmatory mutation analysis
Both Parents: Send samples to NBS for phasing of molecular findings
Elevated VLCFA
Normal VLCFA and plasmalogen in newborn, No clinical evidence of peroxisomal disorder
Clinical symptoms of peroxisomal disorder
X-linked ALD
Carrier of ALD, Genetic counseling
Possible Peroxisomal Disorder, Continue Evaluation
Elevated VLCFA, Low plasmalogen
Elevated VLCFA, Normal plasmalogen
Normal VLCFA and Normal plasmalogen
Clinical evaluation consistent with ZSD*
Cultured fibroblasts, immunohistochemistry or genetic test results consistent with ZSD
ZSD
No clinical evidence of ZSD, acyl CoA oxidase deficiency or D-bifunctional protein deficiency
VLCFA testing in mother and siblings, MLPA of ABCD1
If deletion/duplication identified, diagnosis confirmed. If MLPA negative, Order fibroblasts to confirm absence of ALDP
X-linked ALD
Clinical evidence of acyl CoA oxidase deficiency or D-bifunctional protein deficiency*
Next generation sequencing, cultured fibroblasts or immunohisto-chemistry consistent with acyl-CoA oxidase deficiency
Acyl-CoA Oxidase Deficiency
Next generation sequencing panel, cultured fibroblasts or immunohisto-chemistry consistent with D-bifunctional protein deficiency
D-Bifunctional Protein Deficiency
Clinical evidence of peroxisomal disorder*
Inconclusive cultured fibroblasts, immunohistochemistry or genetic test results or
Additional testing not done
Peroxisomal Disorder of Unknown Etiology
No evidence of disease


Positive Newborn Screen (Tier 1 and Tier 2)
Disease-causing mutation in ABCD1 identified by sequencing (NBS Tier 3)
No mutation or VUS in *ABCD1* on sequencing performed by NBS
Initial Visit: Order VLFCA and plasmalogen in baby

Case Definitions

- Developed for
  - ALD
  - Zellweger spectrum disorders
  - Acyl CoA oxidase deficiency
  - D-bifunctional protein deficiency
  - Peroxisomal disorder of unknown etiology

Category	VLCFA	Plasmalogen	Clinical symptoms	Mutation analysis	Fibroblast studies	Additional Comments
Definite	Elevated	Untested or unknown	Not present	Disease-causing mutation in ABCD1	Untested or unknown	
Definite	Elevated	Normal	Not present	Deletion/duplication on MLPA	Untested or unknown	
Definite	Elevated	Normal	Not present	No mutation, deletion or duplication	ALDP Absent	
Probable	Elevated	Normal	Not present	No mutation on sequencing, deletion/duplication not done	Untested or unknown	Family history or family VLCFA studies suggestive of X-linked ALD
Possible	Elevated	Normal	Not present	Variant of unknown significance inherited from the mother	Untested or unknown	
Possible	Elevated	Normal	Not present	No mutation on sequencing, deletion/duplication not done	Untested or unknown	
No disease	Normal	Normal	Not present	No mutation on sequencing	Untested or unknown	

Management Protocols

- At the time of diagnosis
- Asymptomatic boys in childhood
- Asymptomatic men after age 18

At the Time of Diagnosis

	Timing
Endocrine	
Enter practice and Initial clinical evaluation	At Diagnosis
Serum ACTH	At Diagnosis
Cortisol	At Diagnosis
Neurology	
Enter practice and Initial clinical evaluation	At Diagnosis
Genetic Counseling	
Referral	At Diagnosis

Asymptomatic Boys in Childhood

	Timing	Frequency
Endocrine		
Clinical evaluation	Age 12 months - 18 years	At least annually
Serum ACTH	Age 6 months- 18 years	Every 6 months
Cortisol	Age 6 months- 18 years	Every 6 months
Neurology		
Clinical evaluation	Age 6 months - 18 years	Annually
Brain MRI without contrast	Age 6 months	Initial
Brain MRI without contrast	Age 18 months - 30 months	Annually
Brain MRI without contrast	Age 36 months - 10 years	Every 6 months
Brain MRI without contrast	Age 10 years - 18 years	Annually
Genetics		
Clinical evaluation and counseling	Age 12 months - 18 years	At discretion of specialist

Asymptomatic Men After Age 18

	Timing	Frequency
Endocrine		
Transition to adult Endocrinology and have clinical evaluation	Starting at 18 years	At least every other year
Serum ACTH	Starting at 18 years	Annually
Cortisol	Starting at 18 years	Annually
Neurology		
Enter adult practice and have clinical evaluation	Starting at 18 years	Annually
Brain MRI without contrast	Starting at 18 years	Annually
Genetics		
Clinical evaluation and counseling	Starting at 18 years	At discretion of specialist

Considerations for Referral to HCT

- HCT only recommended during early stages of cerebral disease due to mortality rate
- ALD MRI Score
  - ALD MR severity score is greater than one and less than nine
- performance IQ of greater than 80

Genetic Counseling Considerations

- Identification and counseling of potentially affected family members
- Identification of female carriers and males with AMN
  - Grief, anxiety, depression, despair
  - Life and long-term care insurance
  - Only give results to fathers with AMN in-person

Long-term Follow-up

- Data elements determined by the group
- 40 data elements
- Data includes general elements, endocrine, neurology, family history and prenatal history

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Questions?

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