State of California—Health and Human Services Agency
Department of Health Care Services

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DIRECTOR

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TO: COUNTY CALIFORNIA CHILDREN'S SERVICES (CCS) ADMINISTRATORS, MEDICAL DIRECTORS, AND MEDICAL CONSULTANTS, INTEGRATED SYSTEMS OF CARE DIVISION (ISCD) STAFF, CCS PROGRAM-APPROVED SPECIAL CARE CENTERS (SCC)

SUBJECT: AUTHORIZATION OF DIAGNOSTIC AND TREATMENT SERVICE FOR INFANTS REFERRED BY THE CALIFORNIA NEWBORN SCREENING (NBS) PROGRAM FOR X-LINKED ADRENOLEUKODYSTROPHY (ALD)

I. PURPOSE

The purpose of this Numbered Letter is to establish CCS policy on the authorization of diagnostic and treatment services for X-linked ALD for individuals with a positive NBS test.

II. BACKGROUND

X-linked ALD is an inherited peroxisomal disorder in which accumulation of very long chain fatty acids (VCLFA) in the brain, spinal cord and adrenal glands leads to demyelination in the brain and spinal cord, and impaired adrenal corticoid function in the adrenal cortex.

The condition results from the mutations of the ABCD1 gene on the X chromosome. The ABCD1 gene codes for the ALD protein, which facilitates transport of VLCFA into peroxisomes. Absence of the protein results in an inability to transport and degrade VLCFA. Over 1,000 mutations associated with ALD have been identified. The incidence is between 1 in 20,000 and 1 in 50,000 births.

There are multiple presentations of ALD, including childhood cerebral ALD, adolescent cerebral ALD, 'Addison's disease only' and adrenomyeloneuropathy (AMN). Childhood cerebral ALD most commonly presents in boys between the ages of four to eight years old, with intellectual or behavioral impairments. The condition may also present as clumsiness, seizures, or loss of vision or hearing. As the disease progresses, additional neurologic deficits develop, including cerebellar

ataxia, dysphagia, loss of ambulation, hemiparesis and progressive dementia. Most individuals succumb to the disease within a few years of diagnosis.

The cerebral childhood ALD presentation affects approximately 31 percent of individuals with ABCD1 mutations (Burtman, 2016). Around 4 – 7 percent of individuals with the ABCD1 mutation present with adolescent cerebral ALD, which begins between 11 and 21 years of age and progresses more slowly.

The other neurologic presentation of ALD is AMH. This form generally appears in adulthood between the ages of 18 and 60 years. It is estimated to occur in 40 – 46 percent of individuals with ABCD1 mutation, and is the most common presentation for women with ALD.

The non-neurologic presentation of ALD is 'Addison's disease only', which is present in around 10 percent of cases. Adrenal insufficiency is usually not the only manifestation of ALD, however; the majority of males with adrenal insufficiency develop childhood cerebral ALD or other neurologic sequaelae in subsequent years. Rarely, female carriers with ABCD1 mutation develop adrenal insufficiency

The only established curative treatment for childhood cerebral ALD is hematopoietic stem cell transplantation (HSCT). It is most effective only when boys have no or minor symptoms of cerebral demyelination. For this reason, brain magnetic resonance imaging (MRIs) is recommended at any time when there is a new symptom suggestive of ALD, and every 6 months from two years up to age ten years. Another promising therapy is a gene therapy, specifically HSCT transduced with Lenti-D antiviral vector. Other treatments include oral steroid replacement therapy and supportive care for neurologic, behavioral and other manifestations.

ALD NBS identifies individuals at risk of developing clinical ALD. Screening for ALD was added to the Recommended Uniform Screening Panel (RUSP) on February 16, 2016 and was mandated by California Assembly Bill 1559 (Pan). Screening for ALD was initiated in California on September 21, 2016 (including re-testing of specimens dating back to February 16, 2016). At this time, all births in California are routinely screened for ALD.

The NBS Program provides mutation analysis of the ABCD1 gene for all infants who are positive in the first two tiers of screening. All infants, regardless of the sequencing results, will require testing of their Plasma VLCFA to confirm the elevated VLCFA found in screening. Infants with pathogenic mutations and Variants of Unknown Significance (VOUS) may require regular SCC follow up until adulthood. Infants with benign polymorphisms or no mutation may require further diagnostic workup, which could include biochemical and additional genetic testing. The additional testing will clarify whether they have another peroxisomal disorder, like

Zellweger Syndrome spectrum (PBS-ZSS), which may be associated with loss of sight and hearing, and liver and bone disease.

Genetic testing and metabolic testing for VLCFA is recommended for siblings in order to assure timely diagnosis and treatment of siblings. In addition, testing of mothers is recommended to determine if they are carriers, as rarely the ALD results from a *de novo* mutation in the affected newborn. Sibling and maternal screening for ALD may also result in the identification of PBS-ZSS.

When an infant is identified as NBS positive for ALD, the Genetic Disease Screening Program (GDSP) NBS coordinator initiates the referral by:

1. Contacting the infant's primary care provider (PCP) to verify that the state coordinator had informed the PCP of positive confirmatory test results, and to confirm that the baby needs to be referred to one of the CCS metabolic genetic centers for follow-up;

2. Notifying the specialist at the CCS-approved metabolic center of the positive NBS result and requesting that the specialist contact the primary care provider to discuss the diagnostic evaluation;

3. Contacting the family to verify notification from the primary care provider, and providing information; and

4. Submitting a copy of the positive NBS report to the SCC and the county CCS Program.

<u>When the SCC receives the request to evaluate the client with the ALD+ screen, the SCC will:</u>

1. Contact the primary care provider to discuss the diagnostic evaluation;

2. Schedule the appointment with the family at the SCC;

3. Report the final diagnostic test results and the diagnosis to the NBS Coordinator and the CCS Program;

4. Assist the family in completing and signing the CCS application, and faxing the completed application to the local CCS office; and

5. Submit request for authorization to the county CCS office.

III. Policy

A. Effective the date of this policy, the following clients shall be eligible for CCS Program for diagnostic and treatment services:

1. Client has a positive NBS for ALD, pathogenic mutation or Variant of Unknown Significance. In this case, the GDSP Program staff will identify the SCC to which the infant will be referred and will submit the following to the county CCS Program:

   a. An “Expedited Diagnostic Service Request” form (attachment 3);

   b. The positive NBS report;

   c. A “New Referral CCS/GHPP Client SAR form; and

   d. A signed CCS application for infants who do not have full scope, no share of cost Medi-Cal.

Note: Females with positive newborn testing shall be open for diagnostic testing including further genetic testing and VLCFA levels.

2. Client is a male sibling of NBS positive infant between the ages of two and nine, these clients should be opened for diagnostic testing including neurologic and endocrine evaluation, genetic testing and VLCFA analysis.

3. Asymptomatic ABCD1 screen-positive male clients shall remain open up to the age of ten years or when the client develops symptoms or signs consistent with ALD.

4. Screening guidelines from New York State (BH, 2015) recommend annual screening with MRI from age 10 – 18 years. This may be implemented by the primary health insurance, but without signs or symptoms of ALD at this age, the client is not eligible for CCS. It is expected that the asymptomatic client will continue to be assessed periodically by the primary care provider after the age of ten years, with referrals to endocrine or neurology.

B. Services shall be authorized to CCS approved SCCs as described below:

1. Metabolic SCC for the diagnosis and treatment of ALD through the age of three years.

2. Endocrine SCC for assessment of asymptomatic ABCD1 positive clients with pathogenic or VOUS ABCD1 mutation. Services may include cosyntropin stimulation test during infancy, and adrenocorticotropic hormone (ACT) stimulation and/or cortisol testing at least annually up to age ten years to assess for adrenal insufficiency.

3. Neurology center assessment of asymptomatic of male clients with pathogenic or VOUS ABCD1 mutation including brain MRI at age 24 months, at 36 months, and every every 6 months to screen for childhood cerebral ALD up to age 10 years.

4. For some clients diagnosed with ALD, treatment will include specific therapies. For others, treatment will be primarily once-a-year follow-up with the SCC or specialist, consisting of assessment of the client and instruction/teaching for the family. For ALD, ongoing evaluations by a CCS-approved metabolic center, regular MRIs, and endocrine evaluation to monitor disease progression are essential. For infants/children without full scope, no share of cost Medi-Cal, program eligibility will need to be confirmed annually.

C. Information on CCS coverage of genetic testing can be obtained by contacting the ISCD medical consultant.

D. Authorization for primary care physicians may be issued for treatment and follow-up of the CCS eligible condition, in conjunction with the SCC or specialist, using a SAR with medical SCG 01.

E. Transportation to the CCS approved SCC is covered under All Plan Letter 17-010 and the CCS Program may cover additional maintenance and transportation services when required.

F. Families of infants who are not eligible for full scope, no share of cost Medi-Cal must complete program eligibility requirements prior to the issuance of treatment authorizations.

IV. Policy Implementation

A. Authorizations for diagnosis and treatment services should be issued to CCS Program-approved Metabolic, Endocrine, Neurology or Hematology/Oncology SCCs for clients who have full scope, no share of cost Medi-Cal using SCG 02 to the center, SCG 01 to the metabolic physician, neurologist, endocrinologist or hematologist/oncologist as requested.

B. Laboratory tests for genetic testing should be authorized with SCG01 and the specific CPT 81405, molecular pathology procedures.

C. Authorizations shall be for up to one year.

D. Authorizations shall include the following information:

Provider must bill other health insurance first; submit Explanation of Benefits with claim.

If you have any questions regarding the above policy or policy implementation, please contact the CCS Program Medical director or designee.

Sincerely,

ORIGINAL SIGNED BY

Sarah Eberhardt-Rios, Division Chief
Integrated Systems of Care Division

Enclosures: Recommended Uniform Screening Panel.
Adrenoleukodystrophy (ALD) Fact Sheet
Expedited Diagnostic Service Request

Recommended Uniform Screening Panel[1] (RUSP)
Core Conditions[2]
(As of September 2017)

Category	Condition	Included in California Newborn Screening
Organic Acid Disorders	Propionic Acidemia	☐
	Methylmalonic Acidemia (Methylmalonyl-CoA Mutase)	☐
	Methylmalonic Acidemia (Cobalamin Disorders)	☐
	Isovaleric Acidemia	☐
	3-Methylcrotonyl-CoA Carboxylase Deficiency	☐
	3-Hydroxy-3-Methylglutaric Aciduria	☐
	Holocarboxylase Synthase Deficiency	☐
	β-Ketothiolase Deficiency	☐
	Glutaric Acidemia Type I	☐
Fatty Acid Oxidation Disorders	Carnitine Uptake Defect	☐
	Medium-chain Acyl-CoA Dehydrogenase Deficiency	☐
	Very Long-chain Acyl-CoA Dehydrogenase Deficiency	☐
	Long-chain L-3-Hydroxyacyl-CoA Dehydrogenase Deficiency	☐
	Trifunctional Protein Deficiency	☐
	Carnitine Uptake Defect	☐
	Medium-chain Acyl-CoA Dehydrogenase Deficiency	☐
	Very Long-chain Acyl-CoA Dehydrogenase Deficiency	☐
Amino Acid Disorders	Argininosuccinic Aciduria	☐
	Citrullinemia Type I	☐
	Maple Syrup Urine Disease	☐
	Homocystinuria	☐
	Classic Phenylketonuria	☐
	Tyrosinemia Type I	☐
Endocrine Disorders	Primary Congenital Hypothyroidism	☐
	Congenital Adrenal Hyperplasia	☐
Hemoglobin Disorders	S,S Disease (Sickle Cell Anemia)	☐
	S, β-Thalassemia	☐
	S,C Disease	☐
Other Disorders	Biotinidase Deficiency	☐
	Cystic Fibrosis[3]	☐
	Classic Galactosemia	☐
	Severe Combined Immunodeficiencies	☐
	X-linked Adrenoleukodystrophy	☐
	Critical Congenital Heart Disease	☐
	Hearing Loss	☐
	Glycogen Storage Disease Type II (Pompe)	Planning for 2018
	Mucopolysaccharidosis Type I	Planning for 2018

1. https://www.hrsa.gov/advisorycommittees/mchbadvisory/heritabledisorders/recommendedpan el/uniformscreeningpanel.pdf
2. Due to biological variability of newborns and differences in detection rates for the various disorders in the newborn period, the California Newborn Screening Program will not identify all newborns with these conditions. While a positive screening result identifies newborns at an increased risk to justify a diagnostic work-up, a negative screening result does not rule out the possibility of a disorder. Health care providers should remain watchful for any sign or symptoms of these disorders in their patients. A newborn screening result should not be considered diagnostic, and cannot replace the individualized evaluation and diagnosis of an infant by a well-trained, knowledgeable health care provider
3. ☐ Point-of-care screening tests performed under the auspices of the California Department of Health Care Services

Recommended Uniform Screening Panel[1] (RUSP)
Secondary[2] Conditions[3]
(California Newborn Screening Panel, as of September 2017)

Category	Condition	Included in California Newborn Screening
Organic Acid Disorders	2-Methyl-3-Hydroxybutyric Aciduria	☐
	2-Methylbutyrylglycinuria	☐
	3-Methylglutaconic Aciduria	☐
	Methylmalonic Acidemia with Homocystinuria	☐
	Isobutyrylglycinuria	☐
	Malonic Acidemia	☐
Fatty Acid Oxidation Disorders	Carnitine Acylcarnitine Translocase Deficiency	☐
	Carnitine Palmitoyltransferase I Deficiency	☐
	Carnitine Palmitoyltransferase II Deficiency	☐
	Medium/Short-Chain L-3-Hydroxyacyl-CoA Dehydrogenase Deficiency	☐
	Glutaric Acidemia Type II	☐
	Short Chain Acyl-CoA Dehydrogenase Deficiency	☐
Amino Acid Disorders	Argininemia	☐
	Biopterin Defect in Cofactor Biosynthesis	☐
	Biopterin Defect in Cofactor Regeneration	☐
	Citrullinemia Type II	☐
	Benign Hyperphenylalaninemia	☐
	Hypermethioninemia	☐
	Tyrosinemia Type II	☐
	Tyrosinemia Type III	☐
Hemoglobin Disorders	Various Other Hemoglobinopathies	☐
Other Disorders	T-Cell Related Lymphocyte Deficiencies	☐

1. https://www.hrsa.gov/advisorycommittees/mchbadvisory/heritabledisorders/recommendedpa nel/uniformscreeningpanel.pdf
2. Disorders that can be detected in the differential diagnosis of a core disorder
3. Due to biological variability of newborns and differences in detection rates for the various disorders in the newborn period, the California Newborn Screening Program will not identify all newborns with these conditions. While a positive screening result identifies newborns at an increased risk to justify a diagnostic work-up, a negative screening result does not rule out the possibility of a disorder. Health care providers should remain watchful for any sign or symptoms of these disorders in their patients. A newborn screening result should not be considered diagnostic, and cannot replace the individualized evaluation and diagnosis of an infant by a well-trained, knowledgeable health care provider

California Newborn Screening Panel
Additional Secondary[1] Conditions[2]
(As of September 2017)

Category	Condition	Included in California Newborn Screening
Organic Acid Disorders	Ethylmalonic Encephalopathy	☐
	Formiminoglutamic acidemia	☐
Amino Acid Disorders	Carbamoylphosphate Synthetase Deficiency	☐
	Gyrate Atrophy of the Choroid and Retina	☐
	Hyperornithinemia-Hyperammonemia-Homocitrullinuria Syndrome	☐
	Hyperprolinemia Type I	☐
	Hyperprolinemia Type II	☐
	Ornithine Transcarbamylase Deficiency	☐
	Remethylation Defects (MTHFR, MTR, MTRR, Cbl D v1, Cbl G Deficiencies)	☐
	Tyrosinemia, Transient	☐
Other Disorders	Congenital Adrenal Hyperplasia (11β- Monooxygenase Deficiency)	☐
	Duarte Galactosemia	☐

1. Disorders that can be detected in the differential diagnosis of a core disorder
2. Due to biological variability of newborns and differences in detection rates for the various disorders in the newborn period, the California Newborn Screening Program will not identify all newborns with these conditions. While a positive screening result identifies newborns at an increased risk to justify a diagnostic work-up, a negative screening result does not rule out the possibility of a disorder. Health care providers should remain watchful for any sign or symptoms of these disorders in their patients. A newborn screening result should not be considered diagnostic, and cannot replace the individualized evaluation and diagnosis of an infant by a well-trained, knowledgeable health care provider

California Newborn Screening Panel
Secondary[1] Conditions[2] Hemoglobinopathies)
(As of September 2017)

Category	Condition	Included in California Newborn Screening
Alpha Thalassemias	Alpha Thalassemia Major	☐
	Hemoglobin H Disease	☐
Beta Hemoglobin Variants	Hemoglobin C Disease	☐
	Hemoglobin D Disease	☐
	Hemoglobin E, E	☐
	Hemoglobin SD Disease	☐
	Hemoglobin SE Disease	☐
	Hemoglobin S, Variant	☐
	Hemoglobin Variant, Variant	☐
Beta Thalassemias	Beta Thalassemia Major	☐
	Hemoglobin C Beta-Thalassemia	☐
	Hemoglobin D Beta-Thalassemia	☐
	Hemoglobin E Beta-Thalassemia	☐
	Hemoglobin E Delta-Beta- Thalassemia	☐
	Hemoglobin Variant/Beta-Thalassemia	☐
Hereditary Persistence of Fetal Hemoglobin	HPFH/HPFH	☐
	S/HPFH	☐

1. Disorders that can be detected in the differential diagnosis of a core disorder
2. Due to biological variability of newborns and differences in detection rates for the various disorders in the newborn period, the California Newborn Screening Program will not identify all newborns with these conditions. While a positive screening result identifies newborns at an increased risk to justify a diagnostic work-up, a negative screening result does not rule out the possibility of a disorder. Health care providers should remain watchful for any sign or symptoms of these disorders in their patients. A newborn screening result should not be considered diagnostic, and cannot replace the individualized evaluation and diagnosis of an infant by a well-trained, knowledgeable health care provider.

California Department of Public Health – Genetic Disease Screening Program

Adrenoleukodystrophy (ALD) Fact Sheet

Our record shows that a baby in your care has tested positive for ALD on the Newborn Screening panel. Please see enclosed test results. More testing is indicated.

What is ALD?

ALD is an X-linked peroxisomal disorder affecting the metabolism of very long chain fatty acids (VLCFAs). ALD occurs when there is a mutation in the *ABCD1* gene, which encodes the transmembrane protein that transports VLCFAs from the cytosol into the peroxisome for catabolism. Over 700 mutations have been identified. In patients with ALD, excess VLCFAs accumulate in body fluids and tissues, including the brain and adrenal cortex. The accumulation of VLCFAs disrupts normal cell function, resulting in many health complications, including adrenal insufficiency alone, or in combination with varying neurological symptoms. The overall incidence of ALD is one in every 17,000 births. Since ALD is X-linked, males are mainly affected – exhibiting varying degrees of symptoms ranging from mild to severe and/or life-threatening that can develop at different times over the lifespan. Female carriers, however, can develop mild to moderate symptoms, typically between the fourth and fifth decades of life.

ALD Screening in California

Governor Brown signed Assembly Bill (AB) 1559 into law in 2014. This bill stated that California would be required to expand statewide screening of newborns to include screening for adrenoleukodystrophy (ALD) as soon as ALD was adopted by the federal Recommended Uniform Screening Panel (RUSP). On February 16, 2016, the U.S. Department of Health and Human Services announced the addition of ALD to the RUSP.

What do I need to know and do as the primary care physician of a baby that tested positive for ALD on their newborn screen?

- ALD is a potentially fatal, but treatable genetic disorder.
- Although some children with ALD can remain free of complications for the first few years of life, they are at high risk for developing neurologic injury and adrenal insufficiency in childhood.
- The Metabolic Special Care Center of your and the family's choice in your region will be notified and will help you manage the care of this patient.
- This patient will require regular visits with at least three specialists (Metabolic, Neurology, and Endocrinology) over the coming months and years.
- Although your subspecialty colleagues will see the patient regularly for early signs of ALD, you will still need to remain informed and alert for early signs of adrenal insufficiency or neurologic involvement.
- Prompt treatment of these complications can be life-saving.
- Baby girls who inherit the *ABCD1* mutation are carriers and can develop AMN symptoms in adulthood and can pass the affected gene to their offspring.

ALD Backlog Testing
In compliance with AB 1559, beginning September 21, 2016, the CDPH Genetic Disease Screening Program (GDSP) will retroactively screen all newborn specimens received on or after February 16, 2016 for ALD. Backlog testing may take up to one year to complete and only positive cases will be called out to primary care providers.

How is newborn screening done for ALD?
ALD screening is done by performing biochemical testing for elevated VLCFA levels in the newborn's dried blood specimen collected through newborn screening. If the initial screen (Tier 1) is positive, a more specific assay for VLCFAs (Tier 2) will be conducted. If the Tier 2 screening is positive, the *ABCD1* gene will be sequenced for mutations (Tier 3). The Newborn Screening (NBS) Program will notify the primary care provider of the results after the sequencing of the *ABCD1* gene (Tier 3) is completed.

Baby tested positive, what happens next?
If a mutation in *ABCD1* is found in baby boys, they are presumptively diagnosed with ALD. If a mutation in *ABCD1* is found in baby girls, they are carriers and have 50% chance of passing down this defective gene to any of her children. The primary care provider, with the assistance of the NBS Program, will notify the family about the selection of the Metabolic Special Care Center. The specialist at the Metabolic Special Care Center will explain the ongoing monitoring and treatment process for the baby and initiate a referral for California Children's Services. Genetic counseling is recommended for all potentially affected family members and carriers.

If there is no mutation in *ABCD1*, but an elevated VLCFA level is present in the baby's blood sample, then this indicates that the baby may have another type of peroxisomal disorder, such as the Zellweger spectrum disorder (ZSD), neonatal adrenoleukodystrophy (NALD), acyl-CoA oxidase deficiency, D-bifunctional protein deficiency (DBP), infantile Refsum disease (IRD), or other peroxisomal disorder of unknown etiology. To identify which peroxisomal disorder the baby might have, the NBS program will make a referral for the baby to visit the metabolic center where further evaluation will be done.

ALD Phenotypes in Boys
There are four ALD phenotypes: cerebral ALD (cALD), adrenomyeloneuropathy (AMN), Addison's disease/adrenal insufficiency and asymptomatic. Since there is no correlation between genotype and phenotype, doctors will not know which form a child has until the symptoms develop.

Cerebral ALD (cALD)
Cerebral ALD is the most severe form of ALD. The severe inflammatory response to the accumulation of VLCFA in the brain destroys the myelin sheath and the symptoms are a result of this demyelination process. Demyelination starts and brain lesions develop rapidly in most cases, causing neurological deterioration and death within 2 – 4 years after onset. Brain lesions typically start without warning and may not manifest obvious symptoms until it is too late to treat. Regular MRI studies are essential because they can detect the brain lesions long before symptoms appear. With timely and proper treatment, further neurological deterioration can be halted and death can be prevented.

Onset of Symptoms in cALD
cALD typically occurs in childhood (~40% of males with ALD), but can present in adolescence and adulthood.

Childhood cALD: Symptoms don't normally appear until about 3 – 12 years of age. The common signs and symptoms are similar to attention deficit hyperactivity disorder, which is due to the gradual loss of visuospatial and visuomotor functions. Patients show clumsiness, ataxia, poor handwriting, hyperactivity, inattention, and language comprehension problem. Behavioral problems, such as aggression or inappropriate behavior are also observed. Seizures can be the first symptom in some patients. As the disorder progresses, untreated patients will eventually lose all sight, hearing, and muscle control before succumbing to the illness.

Adolescent cALD: The age of onset is between 13 and 19 years of age. Patients have shown similar symptoms to childhood cALD, but with slower initial progression.

Adult cALD: Approximately 20% of males develop cALD in adulthood. The typical age of onset is between 20 and 39 years of age. Symptoms typically include cognitive decline associating with psychological disorders, such as psychosis, which are not obvious initially.

Treatment for cALD
The only current treatment that can arrest further cerebral demyelination is allogeneic hematopoietic stem cell transplant (HSCT) taken either from a human leukocyte antigen (HLA)-matched bone marrow donor or cord blood. This procedure is only beneficial to patients with mild MRI abnormalities who show no physical signs of cerebral demyelination. Autologous hematopoietic stem cell gene therapy is actively being studied, as well as several additional gene therapy trials that could provide alternative treatments in the future.

Adrenomyeloneuropathy (AMN)
Nearly every patient with ALD will develop adrenomyeloneuropathy in adulthood, and the onset of symptoms usually occurs between the second and fourth decades of life. AMN is a slowly progressive axonopathy. Initial symptoms involve mainly the spinal cord and peripheral nerves marked by slowly progressive stiffness and pain in the lower limbs, loss of coordination with impaired vibration sense, bowel and bladder dysfunction, and impotence. Patients may also experience mild to moderate weakness of the arms and hands. Balding at a young age is not uncommon for AMN patients. Approximately 70% of AMN patients develop Addison's disease and 20% develop secondary cerebral demyelination.

Treatment for AMN
There is no cure for AMN. However, some treatments are available to help alleviate the symptoms. If the patient has adrenal insufficiency, then adrenal steroid replacement therapy would be appropriate. Physical therapy can help build and maintain muscle strength.

Addison's disease or Adrenal Insufficiency
Addison's disease is an endocrine disorder characterized by adrenocortical insufficiency often before the onset of neurological symptoms. Some ALD patients can present with Addison's disease and not show any neurological symptoms for decades. Addison's disease is commonly observed in individuals with cALD or AMN and it can be the only clinical manifestation in patients with ALD.

The typical characteristics of adrenocortical insufficiency are weight loss, muscle weakness, fatigue, low blood pressure, and darkening of the skin. The onset of adrenocortical insufficiency is typically between 2 years of age and adulthood, but usually by 8 years of age. Addison's disease is treatable, and prompt treatment can prevent serious morbidity and mortality caused by adrenal crisis. Since about 1/3 of Addison's disease is attributable to ALD, not every patient who has Addison's disease has ALD.

Treatment for Addison's disease or Adrenal Insufficiency
Adrenal hormone replacement therapy can alleviate symptoms of Addison's disease and prevent a potentially life-threatening adrenal crisis.

Asymptomatic ALD: The Importance of Ongoing Monitoring
Ongoing monitoring of the child with ALD is essential. All the evidence indicates that the primary available treatment for the disease -- stem cell transplantation -- only works during a very narrow window either before neurological symptoms develop, or very early after their onset. Once the disease has progressed and symptoms have become severe, there are currently no treatments that can repair the brain injury and the only treatments available are palliative. Early brain MRI changes in cerebral ALD are usually readily recognized by experienced pediatric neurologists, and currently brain MRI remains the only tool to detect the progression of brain demyelination. Thus ongoing monitoring of asymptomatic children is critical to assure that treatment can be initiated in a timely manner.

The metabolic center following the baby diagnosed with ALD will develop a follow-up plan, which includes periodic laboratory testing and brain imaging. Consultations with a pediatric endocrinologist and neurologist will be coordinated as indicated.

California pediatric metabolic, neurology, and endocrine specialists will work with parents of children with ALD to develop a timeline for ALD follow-up procedures and specialty evaluations in California.

Female Carriers
Some female carriers of ALD can develop AMN symptoms, usually in later years of life. It is very rare, however, for female carriers to develop cALD or Addison's disease. Counseling at a Metabolic Special Care Center is available for female carriers.

If you have questions about ALD screening in California, please contact the Newborn Screening Program at **510-412-1502**.

For more information about ALD, please visit the following sites:
X-linked Adrenoleukodystrophy Database: www.x-ald.nl
The Myelin Project: myelin.org
ALD Connect: www.aldconnect.org/index.php
National Institute of Neurological Disorders and Stroke:
www.ninds.nih.gov/disorders/adrenoleukodystrophy/adrenoleukodystrophy.htm
Fight ALD: www.fightald.org (ALD information from the parent's perspective)

3.19 B **Expedited Diagnostic Service Request**

For Infants with a Positive Newborn Screening (NBS) Test

To: The Special Care Center (SCC)

- ❑ Metabolic
- ❑ Endocrine
- ❑ Hemoglobinopathy/Sickle Cell Disease
- ❑ Cystic Fibrosis/Pulmonary
- ❑ Immunology

The purpose of this request is to expedite the diagnostic evaluation for an infant with a positive newborn screening test. **The California Children's Program (CCS) will authorize these evaluations**, **but due to the scheduled appointment occurring quickly, the SCC may not have the authorization at the time of the visit.** The authorization will be forthcoming.

The infant named below will be scheduled for a diagnostic evaluation with the following:

SCC _____ Physician _____

SCC Contact _____ Fax _____

Date of Visit (If known) _____

Infant's Name _____ AKA _____
(as on the positive newborn screening report) (when applicable)

Infant's Date of Birth _____ NBS Number _____
(intitial NBS screening test accession #)

Mother's Name _____ AKA _____
(as on the positive newborn screening report) (when applicable)

Mother's Date of Birth _____

Primary Care Provider _____ Phone _____

The attached application* must be completed by the parent/legal guardian at the time of the SCC visit and then faxed to the appropriate CCS program.

The CCS program will issue an authorization to cover the diagnostic services within five working days of receipt of all necessary documents. **The SCC shall not charge the infant's family for any services (including room fees) related to this diagnostic evaluation.**

If you have any questions, please contact the following:

NBS Coordinator _____ Phone _____

Area Service Center _____ Phone _____

Attachments: (1) CCS Application (2) Copy of the positive NBS report

*The application can also be downloaded from
http://www.dhs.ca.gov/pcfh/cms/ccs/publications.htm Click on DHS 4480 (English or Spanish)

cc: _____ County CCS Program _____ Fax