# Public Health System Impact Assessment:
# Factsheet for X-Linked Adrenoleukodystrophy (ALD) Screening

| Condition | ALD |
|---|---|
| **Description** | Metabolic disorder affecting the adrenal glands and central nervous system. It is due to mutations in the ABCD1 gene and affects the metabolism of very long chain fatty acids (VLCFA). X-ALD presents as a spectrum of disease, typically with progressive neurological decline (Cerebral ALD) and/or adrenal insufficiency ("Addison's Disease") presenting across the lifespan. Most boys (~90%) with childhood cerebral ALD (CALD) also experience adrenal insufficiency. Neurological involvement and/or adrenal insufficiency may also occur later in adolescence or adulthood (adult-onset adrenomyeloneuropathy [AMN]), or as Addison's Disease, respectively. Females may be identified with a heterozygote ABCD1 mutation, and usually present with neurological symptoms in later adulthood. |
| **Expected Incidence** | Clinical detection= ~1 in 20,000 male births[1]<br>Detection by laboratory screening= 1 in 17,924 male infants screened; NYS NBS Program with data collected from 12/30/2013 to 4/30/2015; 316,016 infants screened including 161,321 males<br>Clinically 35-40% of patients have childhood onset of cerebral ALD[1] |
| **Screening Methods** | |
| **Measurement Method** | First tier- MS/MS (required for referral)<br>Second tier- HPLC MS/MS (required for referral)<br>Sequencing of ABCD1 gene is a next step toward diagnosis (optional as third tier for NBS program) |
| **Data Source(s)** | NY NBS Program uses a three-tiered screening approach and screens over 316,000 infants |
| **Screening Marker** | C26:0 lysophosphatidylcholine (C26:0 LPC) |
| **Screening Strategy** | Measurement of analyte |
| **Resources and Materials** | |
| **Minimum Instrumentation, Equipment and Requirements Necessary to Process 100,000 Specimens Annually (Includes Conventional Redundancies)** | • At least two MS/MS with one for back-up<br>• One liquid handler is helpful (can be done without liquid handler in smaller volume laboratory) |
| **Equipment Suppliers and Availability of Kits, Reagents and Consumables** | Tips and plates; HPLC column |
| **Workstation Resources and Capacity** | |
| **Tech Time to Prepare Specimens (Extraction and Loading Cartridges)** | Not Available |
| **Instrument Time** | 1.5 min. per run per specimen<br>2.5 hrs. per plate |

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| **Maximum Number of Specimens to Be Analyzed at One Workstation During An 8 Hour Shift** | Not Available |
| **Minimum Space Requirements (Supporting Equipment Not Included)** | Cu ft. for two MS/MS and liquid handlers and hood space for solvent and extraction (dependent on instrumentation) |
| **Personnel Requirements** | |
| **FTE Needed to Process 100,000 Specimens Annually (From Sample Receiving Through Result Interpretation)** | 1.5 FTE |
| **Other Considerations** | |
| **LIMs Adjustments** | Variable (dependent on vendor) |
| **Training** | MS/MS and chromatography |
| **QC and Reported Screening Results** | |
| **Availability of Quality-Control Specimens** | Yes |
| **Reported Rate of Second-Tier Test** | 5,939 samples of 346,506 samples received = 1.7% |
| **Reported Rate of Repeat Requests (Independent Specimen)** | 33 borderlines requiring second specimen out of 346,506 samples tested = 0.0095% |
| **Rate of Referrals** | 26 of 346,506 specimens = 0.0075% |
| **Reported Outcomes** | **# by type(s):**<br>(n=346,506 DBS)<br>Confirmed ALD = 9 boys with ABCD1 mutations<br>Carriers = 11 females heterozygous for an ABCD1 mutation<br>Zellweger spectrum disorder = 3<br>Possible peroxisomal disorder = 2<br>Possible Zellweger unconfirmed (likely PBD but baby expired)<br>Other = Aicardi-Goutieres syndrome determined using whole exome sequencing (elevated VLCFA and normal plasmalogen); may carry a deletion that was not detected (this is pending).<br>False positives = 0<br>Lost to follow-up = 0 |
| **Estimated $$ Costs** | |
| **Equipment Cost (Overhead)** | Two MS/MS- $400,000-$500,000<br>DNA Sequencer- $160,000 if purchasing (not required)<br>Liquid Handler- $100,000-$250,000 if purchasing (not required; used in NY because of LSD assay; varies by capacity; can use multi-channel pipettors) |

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| **Estimated Cost to Laboratory of Reagents or FDA-Approved Kit** | $35,000 annually |
| **Estimated Reagent Rental Cost** | N/A |
| **Estimated Personnel Cost To Screen 50,000 to 100,000 Specimens Annually (Follow-Up Not Included)** | $109,000-$135,000 (salary, fringe, and indirect) |
| **Estimated Diagnostic Assay Cost** | $160-$320 depending on laboratory (VLCFA only) |
| **Estimated Diagnostic Molecular Testing Costs** | $500 per sample (approximate actual reagent and personnel cost; not laboratory charge) |
| **Short-Term Follow-Up** | |
| **Description** | Confirmation of diagnosis of X-ALD and female ABCD1 carriers by determination of VLCFA levels; assessment of endocrine status, genetic analysis, and MRI/neurological exam. |
| **Case Definition Applicable to Neonatal Period** | X-ALD is a rare demyelinating disease of the central nervous system that is inherited as an X-linked recessive trait primarily affecting males in childhood; characterized by progressive neurological decline, blindness, deafness, tonic spasms, and mental deterioration. |
| **Diagnostic Method & Criteria** | • ABCD1 mutation (this is not necessary if screening program offers Tier 3 testing)<br>• Confirmatory VLCFA analysis<br>• Plasmalogen evaluation is performed if no mutation or an unknown variant is detected on DNA sequencing<br><br>ABCD1 mutation and elevated VLCFA in males suggests ALD; ABCD1 mutation in females and normal VLCFA and plasmalogen suggests carrier; clinical symptoms and high plasmalogen in females suggests peroxisomal disorder.<br><br>Multiple phenotypes of X-ALD can be seen in families. |
| **Availability of Diagnostic Testing Laboratories** | The diagnostic studies recommended at this phase of testing (VLCFA, plasmalogen, ABCD1) can be performed in a number of laboratories. |
| **Current Treatment(s)** | |
| **Description and Current Treatment Guidelines with Clinical Identification** | Hematopoietic stem cell therapy (HSCT) is recommended for males with cerebral X-ALD. This is generally NOT done in infants, rather, identified boys are followed closely in infancy and early childhood with serial MRI's to optimize time of HSCT. HSCT can prevent progressive cerebral demyelination.<br><br>Gene therapy research is currently experimental and not yet approved.<br><br>Corticosteroid replacement therapy is used for adrenal insufficiency. |

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| Current Treatment(s) | |
|---|---|
| **Specialty Providers or Centers** | Screen positive infants are referred to inherited metabolic disease specialists in NYS for evaluation and genetic counseling. Short term follow-up ends with a diagnosis of X-ALD, ABCD1 carrier, specific peroxisomal disorder or other condition. See “Reported Outcomes” above.<br><br>Once a diagnosis of X-ALD is made, the following specialists are involved:<br><br>• Endocrinologists- to conduct serial evaluations and treatment for adrenal insufficiency (usually at the specialty center).<br>• Neurologists- to conduct evaluations, arrange for se MRI’s beginning at 6 months of life, and refer for HSCT if appropriate.<br>• HSCT centers- there are very few centers specializing in pediatric HSCT for metabolic disorders; X-ALD patients may need to go out of state for treatment. Follow-up care may continue at a specialty care center. |

[1]Vogel BH et al., 2015. Newborn Screening for X-linked Adrenoleukodystrophy in New York State: Diagnostic protocol, surveillance protocol and treatment guidelines. *Molecular Genetics and Metabolism,* 114 (4), 599-603.