Public Health Impact Assessment Fact Sheet for Krabbe Disease (KD) Newborn Screening

This fact sheet provides newborn screening programs with background information on Krabbe Disease (KD) so they can complete a public health impact assessment survey that evaluates their program's readiness and feasibility to add Krabbe Disease onto their newborn screening panels. The factsheet discusses background information pertaining to the condition, screening methods, resources/materials, personnel requirements, screening results, costs, short-term follow up, and treatment for Krabbe Diesease. Contact Jelili Ojodu (jelili.ojodu@aphl.org) for more information.

Condition	Krabbe Disease
Description	Krabbe disease (KD) is an autosomal recessive disorder caused by mutations in the *GALC* gene. It is considered a lysosomal storage disorder and leukodystrophy. KD is characterized by a deficiency in the lysosomal enzyme glactocerebrosidase (GALC) which is necessary for myelin turnover. Low GALC enzyme activity can lead to elevated psychosine levels, which is toxic to cells. Some infants develop KD in the first few years of life, known as infantile KD. Newborn screening can lead to earlier hematopoietic stem cell transplant, which can extend life and improve other outcomes. Without screening, infantile KD typically presents in the first year of life with irritability, feeding difficulties, seizures, and progressive spasticity. Infantile KD can progress quickly, with progressive neurologic decline leading to death.
Expected Incidence	Based on clinical detection, about 1/100,000 live births have infantile KD.

First-Tier Screening Methods	
Screening Strategy and Markers	The first-tier screen is to measure GALC enzyme activity using either tandem mass spectrometry (MS/MS) or fluorometry. Both tests have been multiplexed with other lysosomal storage disorders.

Second-Tier Screening Methods	
Screening Strategy and Markers	Psychosine concentrations in dried-blood spots can be measured as a second-tier test to reduce false-positive results and assist with assessing risk (e.g., > 10 nmol/L high-risk for infantile KD, 2-10 nmol/L “at risk” for late onset KD and need for follow-up). Psychosine concentration can be measured in-house or by a contracted laboratory. This testing is offered by the Mayo Clinic, Nationwide Children’s Hospital, and PerkinElmer. Some NBS programs also routinely conduct molecular testing after an initial positive screen. The supplemental information can be helpful for referrals and clinical follow-up, but is not necessary for screening.

Resources and Materials	
Minimum Instrumentation, Equipment and Requirements Necessary to Process 100,000 Specimens Annually	First-tier GALC enzyme activity screening MS/MS or fluorometry. Second-tier psychosine concentration testing in-house or as a send-out.
Equipment Suppliers and Availability of Kits, Reagents and Consumables	Reagents are available as an FDA approved kit from PerkinElmer for MS/MS. Some NBS programs originally used the analyte specific reagents from PerkinElmer and then converted to NeoLSD. Other NBS programs that rely on fluorometry use reagents from Baebies.

Workstation Resources and Capacity	
Instrument Time	NBS programs that screen for other LSDs can analyze results using existing instrumentation since the GALC enzyme activity is multiplexed.
Maximum Number of Specimens to Be Analyzed at One Workstation In A Day	NBS programs that screen for other LSDs can analyze the same number of samples that they currently analyze each day since the test is multiplexed.
Minimum Space Requirements	If a NBS program is screening for other LSDs, no additional space is required since this test can be multiplexed.

Personnel Requirements	
FTE Needed to Process 100,000 Specimens Annually	The laboratory may not require additional FTEs assuming that the assay is multiplexed with existing assays and incorporated into the workflow. Additional FTEs for follow-up may be minimal.

Other Considerations	
LIMs Adjustments	Variable (dependent on vendor). LIMs revisions for new conditions may require additional staff time and cost for initial set up.
Availability of Quality Control Materials	CDC has QC materials available.

Screening and Diagnostic Results Among Nine States Screening for KD After the Introduction of Psychosine to Some Algorithms [2016-2022]	
Rate of Referrals	With psychosine second-tier testing: 0.6-13.8 per 100,000 live births. *Some of the newborn screening programs refer based on GALC enzyme activity before second-tier test results are available, increasing referral rates.* Without psychosine second-tier testing: 28.8-54.0 per 100,000 live births.
Range of Infantile KD	0-1.8 per 100,000 live births
Range of Infants "At Risk" For Late-Onset KD	0-2.3 per 100,000 live births
Age At Hematopoietic Stem Cell Transplant (HSCT) for Infantile KD	Age to transplant collected for 8 babies identified with infantile KD from states using psychosine as second-tier test (n=5): 5 infants received HSCT between 24-36 days after birth, 2 between 101-150 days after birth, and the family of one infant elected not to have HSCT. *Transplants did not all occur in state where baby was identified.*

Estimated Costs from Two NBS Programs	
Estimated Total Program Costs	▪ Annually $430,000-$693,224 ▪ One-time costs $30,730
Estimated Cost of Equipment	▪ MS/MS: $582,874 ▪ Biotek fluorimeter provided through reagent rental ➢ Integra Viaflo = $20,450 ➢ Integra Viaflo maintenance agreement = $2,970 ➢ Ultra-low freezer = $9,650 ➢ Microplate shaker = $630
Estimated Cost of Consumables and Disposable Supplies	▪ MS/MS: $9,000/yr. ▪ Fluorometry: $34,000/yr
Estimated Cost of Reagents	▪ MS/MS: Included in reagent rental ▪ Fluorometry: $320,000/yr
Estimated 2nd Tier Testing Costs	▪ Avg 8.7 samples/month @ $60each +$60 shipping = $1041.82/month or $12,500/yr ▪ Avg. 10 samples/year @ $99each+$9.17 shipping= $1081/yr
Estimated Personnel Cost	▪ 0.73-1.0 FTE for Krabbe testing, labor cost (salary + fringe) = $53,000/yr -$57,000/yr ▪ 0.05-.17 FTE is used for Krabbe follow-up, labor cost = $3,000/yr-$17,852/yr
Other Cost Considerations for Implementation	▪ $5,000 - $10,000 per year in contracts with genetic specialty centers

*High range of cost estimate includes Krabbe Disease screening and 4 other LSDs.
*Costs estimates come from one state using MS/MS and another using fluorometry.

Short-Term Follow-Up	
Description	A clinician will perform KD confirmatory testing including measuring GALC enzyme activity and psychosine concentration in a new sample of blood, and additional neurologic testing. Molecular testing of the *GALC* gene will be done if not completed previously.
Case Definition	The case definition of early-onset Krabbe disease includes: GALC enzyme activity in peripheral blood leukocytes AND either ▪ 30-kb deletion in both alleles of the GALC ▪ Elevated psychosine level
Diagnostic Method & Criteria	Enzyme activity, psychosine level, mutations, neurodiagnostic/clinical abnormalities.

Current Treatment	
Description and Current Treatment Guidelines with Clinical Identification	Hematopoietic stem cell transplantation (HSCT) is recommended for infantile KD. Infants with the most severe form, early infantile KD, may require HSCT within 30 days after birth for best outcomes. Gene therapy trials are underway but not widely available. Some infants will be identified with KD that does not require HSCT before 3 years but does require frequent clinical follow-up. KD screening and clinical follow-up can also identify infants with Saposin A Deficiency, a very rare neurodegenerative lysosomal storage disorder that has similar laboratory findings and clinical presentation as KD.