

## Diagnostic Testing Algorithm

## **Lysosomal Acid Lipase Deficiency**

## **Clinical Suspicion in Infants:**

Abdominal Distension Hepatosplenomegaly Failure To Thrive, Cachexia Watery Diarrhea/Steatorrhea **Emesis** 

Anemia (microcytic, hypochromic) Thrombocytopenia Dyslipidemia

Adrenal Calcification (in ~50% of patients) Cholesteryl ester accumulation (spleen, liver, lymph nodes) Triglyceride Lipid Accumulation in Liver, Enterocytes, Spleen

## **Clinical Suspicion in Adults:**

Hepatomegaly with or without splenomegaly **Elevated Transaminases (ALT, AST) Elevated Total Serum and LDL Cholesterol Low HDL Cholesterol** Atherosclerosis, Coronary Artery Disease Cerebrovascular Disease

Orange-yellow Colored Liver Specimen Microvesicular Steatosis Micronodular Cirrhosis

Pathognomonic Birefringent Cholesteryl esters in hepatocytes

Test Lysosomal Acid Lipase (LAL) Enzyme Activity

LAL Enzyme **Activity is Normal** STOP No further testing is indicated\*

\*If the LAL enzyme activity is not deficient, and ultrastructural birefringent cholestryl ester accumulation was noted on pathology, or there is a high index of suspicion, an assay that is not specific to lysosomal acid lipase may have been used. Re-testing of LAL enzyme activity should be done by a laboratory utilizing using 4-methylumbelliferyl-palmitate, Lalistat 2 or another

competitive acid lipase

inhibitor. \*\* It is not requisite to wait for molecular testing results to begin enzyme replacement therapy (ERT). Genetic testing is of prognostic value and prenatal and carrier testing requires that the mutations in the proband are identified, but LAL enzyme deficiency is diagnostic. Molecular testing takes several weeks. In severe infantile LAL-D any delay in treatment may result in mortality.

LAL Enzyme Activity is Deficient-The Patient is Affected with LAL-D

Molecular LIPA Gene Testing is Indicated for Prenatal Testing, Family Carrier Testing, Prognostic Information and to Confirm Diagnosis

Initiate Treatment with Sebelipase Alfa Enzyme Replacement Therapy Immediately\*\*

Patient is European Ancestry 🔿 **Mutation Analysis for the** common European E8SJM-1

Patient is of Iranian Jewish or Bukharin Jewish Ancestry > **Mutation Analysis for the** common Mizrahi Jewish G87V Mutation \*\*\*

Patient is neither Mizrahi Jewish nor **European Jewish** 

Two LIPA gene mutations are identified **STOP** No further genetic testing is indicated.

\*\*\*The common Mizrahi

(Iranian and Bukharan)

Jewish G87V mutation is

sometimes called the G66V,

depending on the starting

\*\*\*\*Deletion studies such

Ligation-dependent Probe

Hybridization) may identify

deletions that would not be

Amplification) or CGH

(Comparative Genomic

place of the molecular

as MLPA (Multiplex

mutations, such as

detectable using

sequencing methods.

probe used.

One or No Mutation Identified on Mutation Analysis

Two LIPA gene mutations are identified STOP No further genetic

testing is indicated.

One or No LIPA gene mutations are identified -> LIPA gene Deletion Studies\*\*\*\*

**May Identify Mutations** Undetectable on Sequencing.