LAL-D: A LIFE-THREATENING GENETIC DISEASE WITH ONGOING, PROGRESSIVE, MULTIORGAN DAMAGE LEADING TO PREMATURE DEATH[1]

Suspected heterozygous familial hypercholesterolemia (HeFH) with no confirmed genetic mutation, or persistently elevated alanine aminotransferase (ALT), or no family history?[2,3]

TEST FOR LAL-D

ALEXION®

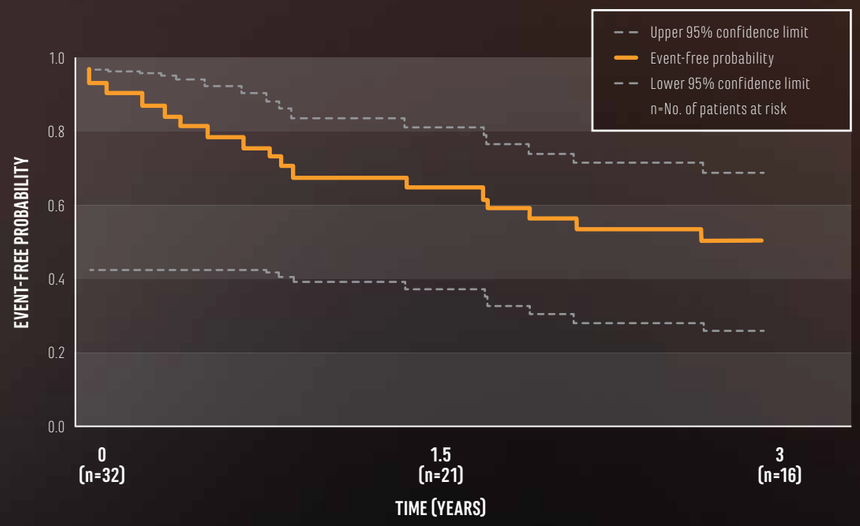
LYSOSOMAL ACID LIPASE DEFICIENCY (LAL-D) LEAVES PATIENTS AT PERSISTENT RISK OF DEVASTATING CONSEQUENCES[1]

LAL-D IS A PROGRESSIVE GENETIC DISEASE ASSOCIATED WITH SIGNIFICANT MORBIDITIES AND PREMATURE MORTALITY[1]

- LAL-D, historically known as Wolman disease and CESD, is a lysosomal storage disorder in which deficient lysosomal acid lipase—a vital enzyme—leads to uncontrolled accumulation of CEs and TGs, and devastating multiorgan damage[2]
  - » **Liver:** hepatomegaly, progressive fibrosis, cirrhosis, and liver failure[2]
  - » **Cardiovascular system:** dyslipidemia leading to accelerated atherosclerosis[2]
  - » **Intestine:** malabsorption in the intestinal villi[1]
  - » **Spleen:** splenomegaly leading to anemia and thrombocytopenia[1,2,4]
- 87% (48/55) of patients showed manifestations in more than one organ; 79% (38/48) of those patients were 19 years of age or younger[1,a]

Nearly 50% of pediatric and adult patients with LAL-D with a clinical biopsy assessment progressed to fibrosis, cirrhosis, or liver transplant within 3 years of first clinical manifestation[5,b]

KAPLAN-MEIER ESTIMATE: 32 PEDIATRIC AND ADULT PATIENTS WITH LAL-D AT RISK FOR FIBROSIS, CIRRHOSIS, OR LIVER TRANSPLANT[5,b]



- In a separate clinical study, 50% (5/10) of patients exhibited worsening of hepatic steatosis after 20 weeks[6,c]

LAL-D LEAVES PATIENTS AT PERSISTENT RISK OF DEVASTATING CONSEQUENCES[1]

[a]Based on an analysis of 55 genotyped patients with LAL-D in a cohort of 135 cases.[1]

[b]Based on modeling, using a subset of 31 patients (≥5 years of age) in an observational study who received a liver biopsy, and 1 additional patient with no biopsy who received a liver transplant. Patients selected by their clinician for liver biopsy are expected to have more evidence of disease progression than patients with LAL-D overall.[5,7]

[c]Based on liver histopathological analyses of hematoxylin and eosin–stained fat in paired morphometric assessments of hepatic steatosis in a subgroup of 10 patients with LAL-D in the placebo arm of 30 patients who underwent biopsy.[5,8]

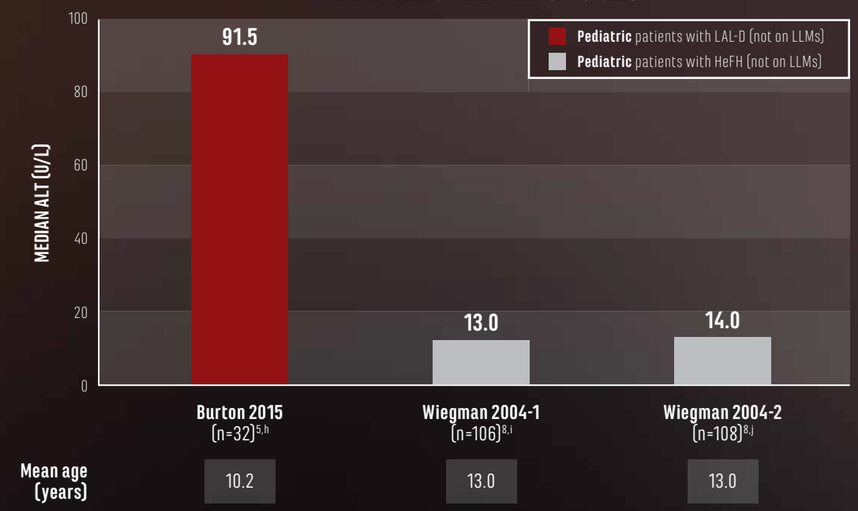
Abbreviations: CE, cholesteryl ester; CESD, cholesteryl ester storage disease; TG, triglyceride.

DYSLIPIDEMIA OFTEN APPEARS AT A YOUNG AGE IN PATIENTS WITH HeFH OR LAL-D, WHICH MAY LEAD TO A HIGH RISK OF CHD[2,8]

- Progression of atherosclerosis can begin to manifest at a young age in patients with HeFH, as also reported for patients with LAL-D[2,8]
  - » Mean LDL-c was 6.1 mmol/L in patients with HeFH (mean age, 12.9 years),[9,d] compared with 5.4 mmol/L in patients with LAL-D (mean age, 16.0 years)[5,e]
- Approximately 67% to 83% of patients with a clinical diagnosis of HeFH have a confirmed mutation[10]; patients have a family history of dyslipidemia and/or premature CHD in first-degree relatives due to the autosomal dominant nature of HeFH[11]
- Patients with HeFH generally have normal ALT levels compared with patients with LAL-D who often have persistently elevated ALT levels from a young age[5,8]

ALT levels reported for patients with LAL-D may be higher than those reported in patients with HeFH[5,8]

MEDIAN ALT LEVELS IN LAL-D[f] AND HeFH[g] STUDIES



NOTE: These studies represent individual publications using different populations of patients. Data are not directly comparable.

HIGH ALT LEVELS MAY HELP DIFFERENTIATE LAL-D FROM HeFH[5,8]

[d]Mean data from a clinical study of pediatric patients with HeFH (n=194).[9]

[e]Mean data from a clinical study of patients with LAL-D (N=66).[5]

[f]In the LAL-D study, an ALT ≥1.5x the ULN according to specified gender-specific normal ranges was one of the eligibility criteria for enrollment; of 64 pediatric patients (≤18 years of age) initially assessed, 2 had ALT levels <ULN.[3,5]

[g]In the HeFH study, a persistent elevation in liver enzymes was one of the exclusion criteria; of 230 potential patients screened, 2 had persistently elevated liver or muscle enzymes.[8]

[h]Interquartile range, 73 to 119.5 U/L.[5]

[i]Interquartile range, 12 to 18 U/L.[8]

[j]Interquartile range, 11 to 18 U/L.[8]

Abbreviations; CHD, coronary heart disease; LDL-c, low-density lipoprotein cholesterol; LLM, lipid-lowering medication; ULN, upper limit of normal.

DIFFERENTIATE LAL-D FROM HeFH

Pediatric patients with no confirmed genetic mutation, or persistently elevated ALT, or no family history of dyslipidemia may not have HeFH[2,3]

Narrowing the diagnosis

CLINICAL FINDINGS DIFFERENTIATE LAL-D FROM HeFH		
	LAL-D[2,3]	**HeFH[8,11]**
ALT	Elevated	Normal[a]
FAMILY HISTORY REQUIRED	No	Yes

The information in this chart is intended as educational information for healthcare professionals. It does not replace a healthcare professional's judgment or clinical diagnosis.

[a]Liver enzymes may be elevated in patients with HeFH taking statins.[11]

Could any of your pediatric patients with suspected HeFH have LAL-D? Test for LAL-D with an enzymatic blood test when you see ***any*** of the following[2,3]:

- ☐ No confirmed mutation
- ☐ Persistently elevated ALT
- ☐ No family history

TEST FOR LAL-D WITH AN ENZYMATIC BLOOD TEST[2,12]

References: 1. Bernstein DL, et al. Cholesteryl ester storage disease: review of the findings in 135 reported patients with an underdiagnosed disease. *J Hepatol*. 2013;58:1230-43. doi:10.1016/j.jhep.2013.02.014. **2.** Reiner Ž, et al. Lysosomal acid lipase deficiency—an under-recognized cause of dyslipidaemia and liver dysfunction. *Atherosclerosis*. 2014;235:21-30. doi:10.1016/j.atherosclerosis.2014.04.003. **3.** Burton BK, et al. *N Engl J Med*. 2015;373:1010-20. doi:10.1056/NEJMoa1501365. **4.** Hoffman EP, et al. Lysosomal acid lipase deficiency. In: Pagon RA, et al, eds. *GeneReviews*. Seattle, WA: University of Washington; 2015. http://www.ncbi.nlm.nih.gov/books/NBK305870/. Accessed October 9, 2015. **5.** Data on file, Alexion Pharmaceuticals. **6.** Abel F, et al. Poster presented at: the International Liver Congress 2016. April 13-17, 2016; Barcelona, Spain. **7.** Burton BK, et al. Clinical features of lysosomal acid lipase deficiency. *J Pediatr Gastroenterol Nutr*. 2015;61:619-25. doi:10.1097/MPG.0000000000000935. **8.** Wiegman A, et al. Efficacy and safety of statin therapy in children with familial hypercholesterolemia: a randomized controlled trial. *JAMA*. 2004;292:331-7. doi:10.1001/jama.292.3.331. **9.** Kusters DM, et al. Ten-year follow-up after initiation of statin therapy in children with familial hypercholesterolemia [letter]. *JAMA*. 2014;312:1055-7. **10.** De Castro-Orós I, et al. The genetic basis of familial hypercholesterolemia: inheritance, linkage, and mutations. *Appl Clin Genet*. 2010;3:53-64. **11.** Goldman AC, et al. Familial hypercholesterolemia: screening, diagnosis and management of pediatric and adult patients. *J Clin Lipid*. 2011;5:S1-S8. doi:10.1016/j.jacl.2011.04.003. **12.** Hamilton J, et al. A new method for the measurement of lysosomal acid lipase in dried blood spots using the inhibitor Lalistat 2. *Clin Chim Acta*. 2012;413:1207-10. doi:10.1016/j.cca.2012.03.019.

ALEXION®