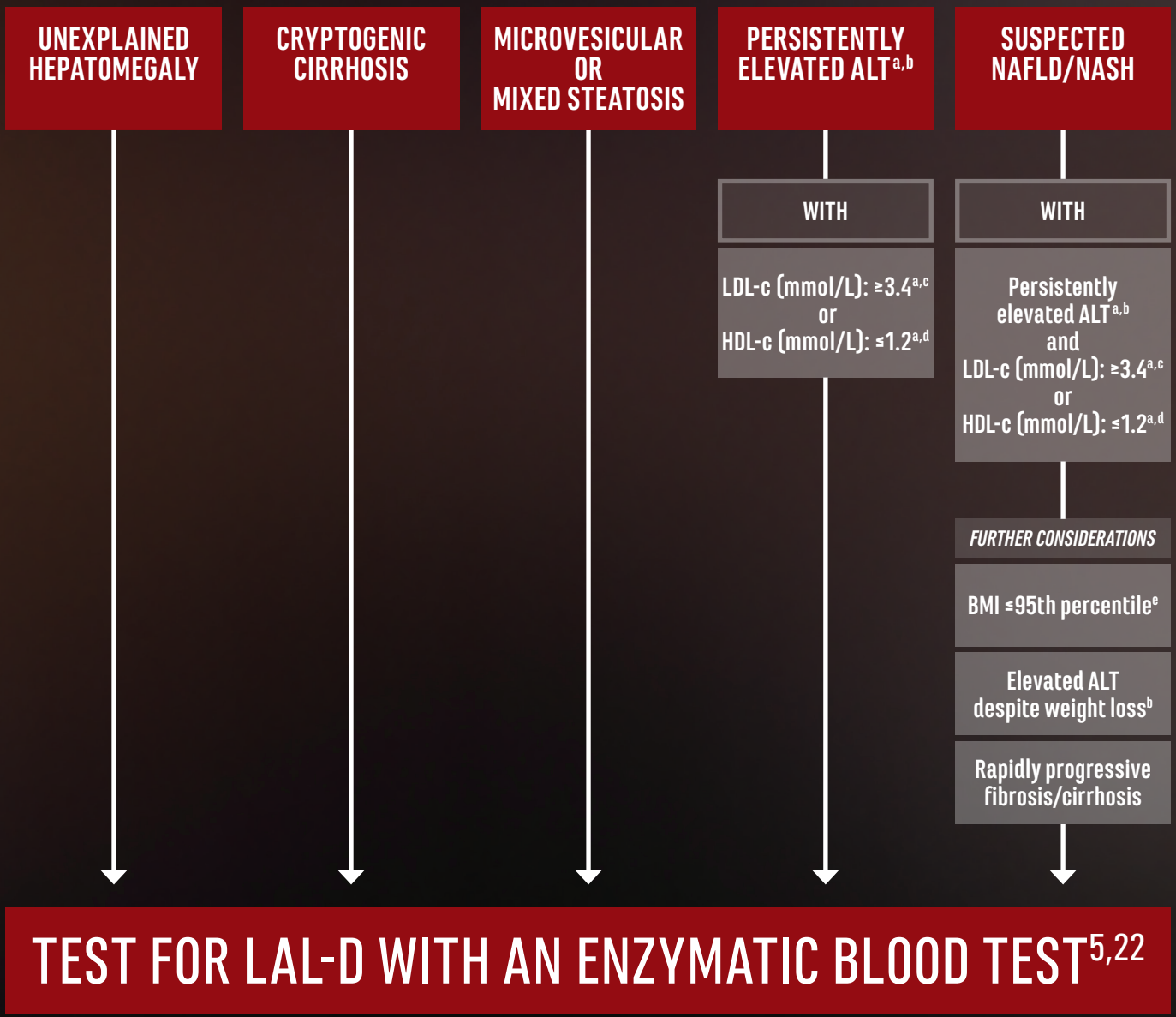
SUSPECT LAL-D IN PEDIATRIC PATIENTS WHO HAVE LIVER ABNORMALITIES [1,3,5,6,9,23]

Are patients with LAL-D hiding in your practice?



[a]At baseline, patients in a clinical trial evaluating a potential treatment for LAL-D had a mean LDL-c of 5.4 mmol/L and a mean HDL-c of 0.8 mmol/L; 73% (48/66) of patients had ALT ≥1.5x ULN and <3x ULN, and 27% (18/66) of patients had ALT ≥3x ULN. An ALT ≥1.5x ULN according to specified gender-specific normal ranges was one of the eligibility criteria for enrollment.[3,6]

[b]Above age- and gender-specific ULN.[5]

[c]In adult patients (mmol/L): LDL-c ≥4.1 (≥3.4 in patients on LLMs).[5,6,23]

[d]In adult patients (mmol/L): HDL-c ≤1.0 (males)/≤1.3 (females).[5,6,23]

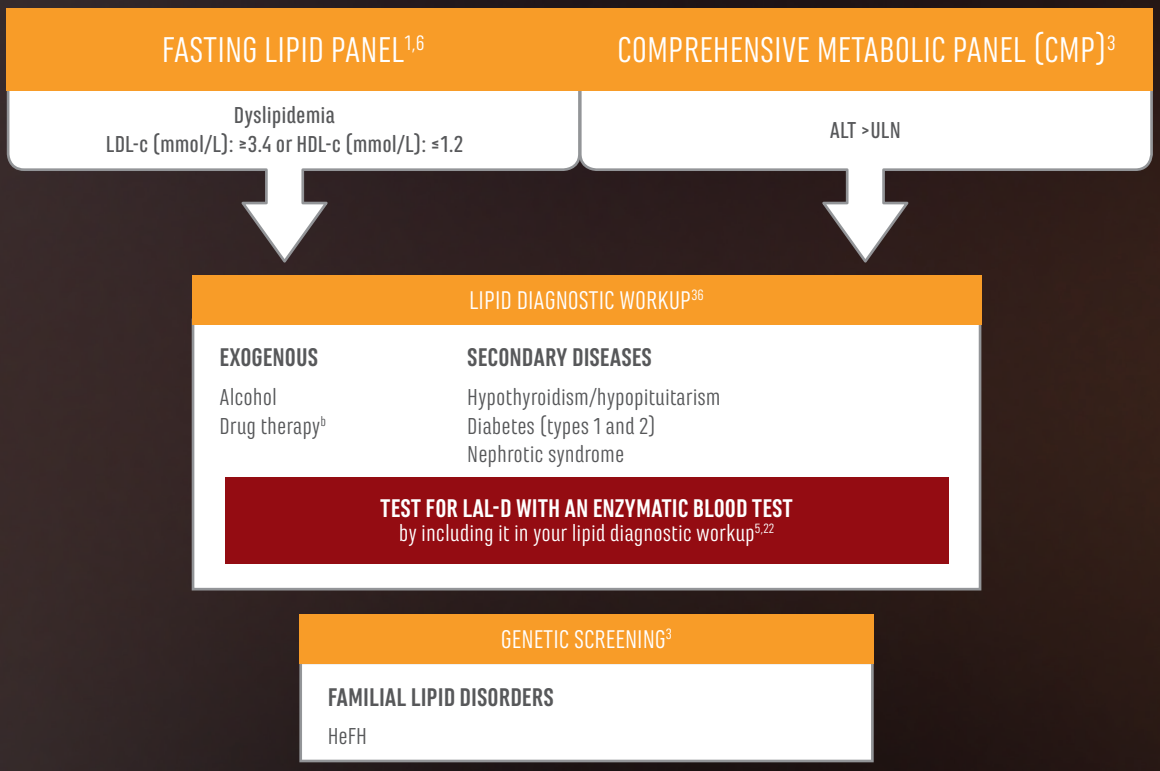
[e]BMI ≤95th percentile for age and gender.[3,5]

Abbreviations: BMI, body mass index; LLM, lipid-lowering medication; ULN, upper limit of normal.

ALEXION

INCLUDE LAL-D EARLY IN YOUR DYSLIPIDEMIA WORKUP[5,22,a]

When evaluating pediatric patients for secondary causes of dyslipidemia, **test for LAL-D prior to genetic screening**[5,22]



[a] LAL-D is historically known as Wolman disease or CESD.[5]

[b] Drug therapies such as corticosteroids, isotretinoin, beta-blockers, oral contraceptives, chemotherapeutic agents, antiretroviral agents.[36]

- Pediatric NHLBI guidelines for cardiovascular health recommend universal lipid screening for children 9 to 11 and 18 to 21 years of age[36]
  - » Additionally, pediatric APS guidelines for diagnosis and treatment of hyperlipidemia recommend cholesterol testing for every child or adolescent[3,37]

TEST FOR LAL-D WITH AN ENZYMATIC BLOOD TEST PRIOR TO GENETIC SCREENING WHEN EVALUATING A PATIENT WITH DYSLIPIDEMIA[5,22]

Abbreviations: APS, Arbeitsgemeinschaft für Pädiatrische Stoffwechselstörungen; CESD, cholesteryl ester storage disease; NHLBI, National Heart, Lung, and Blood Institute.
The information in these pages is intended as educational information for healthcare professionals. It does not replace a healthcare professional's judgment or clinical diagnosis.

References: 1. Burton BK, et al. *N Engl J Med*. 2015;373:1010-20. doi:10.1056/NEJMoa1501365. 2. Data on file, Alexion Pharmaceuticals. 3. Reiner Ž, et al. *Atherosclerosis*. 2014;235:21-30. doi:10.1016/j.atherosclerosis.2014.04.003. 4. Daniels SR, et al. *Pediatrics*. 2008;122:198-208. doi:10.1542/peds.2008-1349. 5. Bernstein DL, et al. *J Hepatol*. 2013;58:1230-43. doi:10.1016/j.jhep.2013.02.014. 6. Grundy SM, et al. *Circulation*. 2004;109:433-8. doi:10.1161/01.CIR.0000111245.75752.C6. 7. Hamilton J, et al. *Clin Chim Acta*. 2012;413:1207-10. doi:10.1016/j.cca.2012.03.019. 8. National Heart, Lung, and Blood Institute. https://www.nhlbi.nih.gov/files/docs/peds_guidelines_sum.pdf. Published October 2012. Accessed August 23, 2016. 9. Chourdakis M, et al. http://www.awmf.org/uploads/tx_szleitlinien/027-068l_s2k_Hyperlipid%C3%A4mien_Kinder_Jugendliche_2016-02.pdf. Published 2015. Accessed August 23, 2016.

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COULD IT BE LAL-D? THESE SIGNS AND LAB VALUES SHOULD RAISE SUSPICION FOR LAL-D[1,3,5,6,23,38]

Patients who have LAL-D may present with ***any*** of the following:

- ☑ LDL-c (mmol/L): ≥3.4[c,d] or HDL-c (mmol/L): ≤1.2[c,e] with[1,6]
  - Persistently elevated ALT[5,6,c,f]
- ☑ Suspected FCH with any of the following[5]:
  - Persistently elevated ALT[5,6,c,f]
  - No family history[5]
- ☑ Suspected HeFH with any of the following[5]:
  - No confirmed mutation[5]
  - Persistently elevated ALT[5,6,c,f]
  - No family history[5]
- ☑ Suspected metabolic syndrome with any of the following[5,38]:
  - Persistently elevated ALT[5,6,c,f] and
    - LDL-c (mmol/L): ≥3.4[1,6,c,d] or
    - HDL-c (mmol/L): ≤1.2[1,6,c,e]
  - BMI ≤95th percentile[3,5,g]
  - Normal fasting glucose/blood pressure[3]

TEST FOR LAL-D IF YOU RECOGNIZE ANY OF THESE SIGNS OR LAB VALUES IN YOUR PATIENTS[1,3,5,6,22,23,38]

[c] At baseline, patients in a clinical trial evaluating a potential treatment for LAL-D had a mean LDL-c of 5.4 mmol/L and a mean HDL-c of 0.8 mmol/L; 73% (48/66) of patients had ALT ≥1.5x ULN and <3x ULN, and 27% (18/66) of patients had ALT ≥3x ULN. An ALT ≥1.5x ULN according to specified gender-specific normal ranges was one of the eligibility criteria for enrollment.[3,6]

[d] In adult patients (mmol/L): LDL-c ≥4.1 (≥3.4 in patients on LLMs).[5,6,23]

[e] In adult patients (mmol/L): HDL-c ≤1.0 (males)/≤1.3 (females).[5,6,23]

[f] Above age- and gender-specific ULN.[5]

[g] BMI ≥95th percentile for age and gender.[3,5]

ALEXION

AN ENZYMATIC DBS TEST CAN HELP DIAGNOSE LAL-D[5,22]

The DBS test is highly accurate and easy to prepare, transport, and interpret for testing in high-risk populations[22,44]

PREPARATION	STORAGE	TRANSPORT
		
A blood sample is spotted onto the DBS card; once completely dry, LAL activity is measured using a specific LAL inhibitor[22]	**DBS can be stored at room temperature** for short periods or at -20°C for longer periods[22]	DBS can be easily **shipped via regular mail**[44]

INTERPRETATION OF LAL ENZYME DBS RESULTS[3]

RESULTS	CLINICAL INTERPRETATIONS
Affected	**LAL-D confirmed** by reduced LAL activity
Indeterminate[a]	**Repeat** with fresh sample
Not affected	**Rules out** LAL-D

[a]LAL above cutoff for affected, but below the normal reference range.[3]

- Measurement of LAL activity in leukocyte and fibroblast samples can also be used to test for LAL-D[1]
- Testing for LAL-D may be simplified through the use of an EMR system
  - » If the LAL-D DBS test is available through your EMR system, create a preference list that includes LAL-D among the tests that you typically order for a liver or lipid diagnostic workup
- Family screening of identified patients is also critical[1]

TEST FOR LAL-D WITH AN ENZYMATIC DBS TEST[5,22]

Abbreviations: DBS, dried blood spot; EMR, electronic medical record.

References: 1. Burton BK, et al. *N Engl J Med*. 2015;373:1010-20. doi:10.1056/NEJMoa1501365. 2. Bernstein DL, et al. *J Hepatol*. 2013;58:1230-43. doi:10.1016/j.jhep.2013.02.014. 3. Reiner Ž, et al. *Atherosclerosis*. 2014;235:21-30. doi:10.1016/j.atherosclerosis.2014.04.003. 4. Grundy SM, et al. *Circulation*. 2004;109:433-8. doi:10.1161/01.CIR.0000111245.75752.C6. 5. Data on file, Alexion Pharmaceuticals. 6. Daniels SR, et al. *Pediatrics*. 2008;122:198-208. doi:10.1542/peds.2008-1349. 7. Hamilton J, et al. *Clin Chim Acta*. 2012;413:1207-10. doi:10.1016/j.cca.2012.03.019. 8. Grüner N, et al. *J Vis Exp*. 2015;97:e52619. doi:10.3791/52619.

ALEXION