Test Definition: ALPS

ALPS Screen

Overview

Useful For

Diagnosing autoimmune lymphoproliferative syndrome, primarily in patients <45 years of age

Method Name

Flow Cytometry

NY State Available

Yes

Specimen

Specimen Type

Whole Blood EDTA

Shipping Instructions

Specimens are required to be received in the laboratory weekdays and by 4 p.m. on Friday. Draw and package specimen as close to shipping time as possible.

It is recommended that specimens arrive within 24 hours of draw.

Samples arriving on the weekend and observed holidays may be canceled.

Necessary Information

Ordering physician name and phone number are required.

Specimen Required

For serial monitoring, we recommend that specimen draws be performed at the same time of day.

Container/Tube: Lavender top (EDTA)

Specimen Volume: 3 mL

Collection Instructions: Send specimen inoriginal tube. **Do not aliquot.**

Forms

If not ordering electronically, complete, print, and send a Benign Hematology Test Request Form (T755) with the specimen.

Specimen Minimum Volume

0.5 mL

Reject Due To

Gross hemolysis	Reject
Gross lipemia	Reject

Specimen Stability Information

Specimen Type	Temperature	Time	Special Container
Whole Blood EDTA	Ambient	72 hours	PURPLE OR PINK TOP/EDTA

Clinical and Interpretive

Clinical Information

Autoimmune lymphoproliferative syndrome (ALPS) (also known as Canale-Smith syndrome) is a complex clinical disorder of dysregulated lymphocyte homeostasis that is characterized by lymphoproliferative disease, autoimmune cytopenias, splenomegaly, and lymphadenopathy with an increased susceptibility to malignancy.(1) Typically, ALPS is diagnosed by childhood or young adulthood.

Genetic defects in the apoptosis (programmed cell death) pathway have been determined for most cases of ALPS. Apoptosis plays a role in normal immune homeostasis by limiting lymphocyte accumulation and autoimmune reactivity. The interaction of the surface receptor CD95 (FAS) and its ligand (CD95L;FASL) triggers the apoptotic pathway in lymphocytes.

The following molecular ALPS classification has been established:

ALPS Classification	**Molecular/Genetic Defect in Apoptosis**
Type Ia	CD95 (*FAS*) mutations(1)
Type Ib	Heterozygous CD95L (*FASLG*) mutations(1)
Type Ic	Homozygous CD95L (*FASLG*) mutation(2)
Type II	*CASP8* or *CASP10* mutations(1,3)
Type III	Unknown(1,3)

Patients with ALPS have an increase in a normally rare population of T cells (typically <1%) that are alpha beta T-cell receptor (TCR)-positive, as well as negative for both CD4 and CD8 coreceptors (double-negative T cells: DNT).(1) The alpha beta TCR+DNT cells from ALPS patients also express an unusual B-cell-specific CD45R isoform, called B220.(4,5) B220 expression on alpha beta TCR+DNT cells has been demonstrated to be a sensitive and specific marker for ALPS and is associated with *FAS* mutations.(4)

Several other diseases can present with an ALPS-like phenotype, including independent conditions like Evans syndrome (a combination of autoimmune hemolytic anemia and autoimmune thrombocytopenic purpura), Rosai-Dorfman disease (massive painless cervical lymphadenopathy that may be accompanied by leukocytosis, elevated erythrocyte sedimentation rate, and hypergammaglobulinemia), and nodular lymphocyte-predominant Hodgkin disease.(1)

Reference Values

Alpha beta TCR+DNT cells

2-18 years: <2% CD3 T cells

19-70+ years: <3% CD3 T cells

Reference values have not been established for patients that are less than 24 months of age.

Alpha beta TCR+DNT cells

2-18 years: <35 cells/mcL

19-70+ years: <35 cells/mcL

Reference values have not been established for patients that are less than 24 months of age.

Alpha beta TCR+DNT B220+ cells

2-18 years: <0.4% CD3 T cells

19-70+ years: <0.3% CD3 T cells

Reference values have not been established for patients that are less than 24 months of age.

Alpha beta TCR+DNT B220+ cells

2-18 years: <7 cells/mcL

19-70+ years: <6 cells/mcL

Reference values have not been established for patients that are less than 24 months of age.

Interpretation

The presence of increased circulating T cells (CD3+) that are negative for CD4 and CD8 (double-negative T cells: DNT) and positive for the alpha/beta T-cell receptor (TCR) is required for the diagnosis of autoimmune lymphoproliferative syndrome (ALPS).

The laboratory finding of increased alpha beta TCR+DNT cells is consistent with ALPS only with the appropriate clinical picture (nonmalignant lymphadenopathy, splenomegaly, and autoimmune cytopenias). Conversely, there are other immunological disorders, including common variable immunodeficiency (CVID), which have subsets for patients with this clinical picture, but no increase in alpha beta TCR+DNT cells.

If the percent of the absolute count of either the alpha beta TCR+DNT cells or alpha beta TCR+DNT B220+ cells is abnormal, additional testing is indicated. All abnormal alpha beta TCR+DNT cell results should be confirmed (for ALPS) with additional testing for defective in vitro lymphocyte apoptosis, followed by confirmatory genetic testing for *FAS* mutations (call 800-533-1710 for test forwarding information).

Cautions

This test is typically not indicated in older adults. For questions about appropriate test selection, call 800-533-1710.

The sole presence of increased alpha beta TCR+DNT B220+ cells is not sufficient for a diagnosis of autoimmune lymphoproliferative syndrome (ALPS); additional testing is required to confirm a diagnosis of ALPS.

Clinical Reference

1. Worth A, Thrasher AJ, Gaspar HB: Autoimmune lymphoproliferative syndrome: molecular basis of disease and clinical phenotype. Brit J Hematol 2006;133:124-140

2. Del-Rey M, Ruiz-Contreras J, Bosque A, et al: A homozygous *Fas* ligand gene mutation in a patient causes a new type of autoimmune lymphoproliferative syndrome. Blood 2006;108:1306-1312

3. Salmena L, Hakem R: Caspase-8 deficiency in T-cells leads to a lethal lymphinfiltrative immune disorder. J Exp Med 2005;202:727-732

4. Blessing JJH, Brown MR, Dale JK, et al: TCR alpha beta+ CD4-CD8-T-cells in humans with the autoimmune lymphoproliferative syndrome express a novel CD45 isoform that is analogous to urine B220 and represents a marker of altered O-glycan biosynthesis. Clin Immunol 2001;100(3):314-324

5. Bleesing JJH, Janik JE, Fleisher TA: Common expression of an unusual CD45 isoform on T-cells from patients with large granular lymphocyte leukemia and autoimmune lymphoproliferative syndrome. Brit J Hematol 2003;120:93-96

Performance

Method Description

This assay uses a 5-color, single-platform method with a 2-tube panel stained for the following antibodies: CD3, CD4, CD8, CD45, alpha beta TCR, and B220. The sample is stained with the antibody cocktail and incubated in the dark at room temperature for 20 minutes. Following incubation, the samples are treated with BD lysing solution to lyse the RBCs, followed with a wash step using BD FACS wash buffer. The cells are resuspended in 1% paraformaldehyde and analyzed by flow cytometry. The different subsets are expressed as a percent of CD3 T cells, and the absolute counts of all subsets are expressed as cells/mcL.(Unpublished Mayo method; Bleesing JJH, Brown MR, Dale JK, et al: TCR alpha beta + CD4-CD8- T-cells in humans with the autoimmune lymphoproliferative syndrome express a novel CD45 isoform that is analogous to murine B220 and represents a marker of altered O-glycan biosynthesis. Clin Immunol 2001;100[3]:314-324)

PDF Report

No

Day(s) Performed

Monday through Friday

Report Available

3 to 4 days

Specimen Retention Time

4 days

Performing Laboratory Location

Rochester

Fees and Codes

Fees

- Authorized users can sign in to Test Prices for detailed fee information.
- Clients without access to Test Prices can contact Customer Service 24 hours a day, seven days a week.
- Prospective clients should contact their Regional Manager. For assistance, contact Customer Service.

Test Classification

This test was developed using an analyte specific reagent. Its performance characteristics were determined by Mayo Clinic in a manner consistent with CLIA requirements. This test has not been cleared or approved by the US Food and Drug Administration.

CPT Code Information

86356 x2

86359

LOINC® Information

Test ID	Test Order Name	Order LOINC Value
ALPS	ALPS Screen	In Process

Result ID	Test Result Name	Result LOINC Value
23973	%alpha/beta-TCR DNT	34962-1
23974	alpha/beta-TCR DNT	34963-9
28904	% TCR+DNT B220+	88052-6
28905	Absolute TCR+DNT B220+	88053-4
23975	Interpretation	69052-9