



## Test Definition: EBLPD

Epstein Barr Virus (EBV) Susceptibility and Lymphoproliferative Disorders Gene Panel, Varies

### Overview

#### Useful For

Providing a comprehensive genetic evaluation for patients with a personal or family history suggestive of Epstein-Barr virus (EBV) susceptibility or a heritable predisposition to lymphoproliferative disease

Establishing a diagnosis of a hereditary form of EBV susceptibility or a related disorder, allowing for appropriate management and surveillance for disease features based on the gene or variant involved

Identifying variants within genes known to be associated with heritable EBV susceptibility and/or lymphoproliferative disease, allowing for predictive testing of at-risk family members

This test is **not useful for** diagnosing acute/recent EBV infection.

#### Reflex Tests

Test Id	Reporting Name	Available Separately	Always Performed
CULAF	Amniotic Fluid Culture/Genetic Test	Yes	No
_STR1	Comp Analysis using STR (Bill only)	No, (Bill only)	No
_STR2	Add'l comp analysis w/STR (Bill Only)	No, (Bill only)	No
CULFB	Fibroblast Culture for Genetic Test	Yes	No
MATCC	Maternal Cell Contamination, B	Yes	No

#### Genetics Test Information

This test utilizes next-generation sequencing to detect single nucleotide and copy number variants in 25 genes associated with Epstein-Barr virus (EBV) susceptibility and lymphoproliferative disorders: *ATM*, *CARD11*, *CARMIL2*, *CD27*, *CD70*, *CORO1A*, *CTLA4*, *CTPS1*, *DEF6*, *GATA2*, *ITK*, *LRBA*, *MAGT1*, *PIK3CD*, *PRF1*, *PRKCD*, *RASGRP1*, *SH2D1A*, *STK4*, *STX11*, *STXBP2*, *TET2*, *TNFRSF9*, *UNC13D*, and *XIAP*. See [Targeted Genes and Methodology Details for Epstein Barr Virus \(EBV\) Susceptibility and Lymphoproliferative Disorders Gene Panel](#) and Method Description for additional details.

Identification of a disease-causing variant may assist with diagnosis, prognosis, clinical management, recurrence risk assessment, familial screening, and genetic counseling for EBV susceptibility and a heritable predisposition to lymphoproliferative disorders.

#### Testing Algorithm

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**Skin biopsy:**

For skin biopsy or cultured fibroblast specimens, fibroblast culture will be performed at an additional charge. If viable cells are not obtained, the client will be notified.

**Cord blood:**

For cord blood specimens that have an accompanying maternal blood specimen, maternal cell contamination studies will be performed at an additional charge.

**Special Instructions**

- [Informed Consent for Genetic Testing](#)
- [Informed Consent for Genetic Testing \(Spanish\)](#)
- [Targeted Genes and Methodology Details for Epstein Barr Virus \(EBV\) Susceptibility and Lymphoproliferative Disorders Gene Panel](#)
- [Viral Susceptibility, Lymphoproliferation, and Hemophagocytic Lymphohistiocytosis Patient Information](#)

**Method Name**

Sequence Capture Next-Generation Sequencing (NGS) followed by Polymerase Chain Reaction (PCR) and Sanger Sequencing as needed

**NY State Available**

Yes

**Specimen****Specimen Type**

Varies

**Ordering Guidance**

For inborn errors of immunity causing susceptibility to viruses other than the Epstein-Barr virus (EBV), see VIRID / Viral Susceptibility, Defects in Intrinsic and Innate Immunity, Gene Panel, Varies.

For the diagnosis of acute/recent EBV infection see either MONOS / Infectious Mononucleosis, Rapid Test, Serum; or EBVAB / Epstein-Barr Virus Antibody Profile, Serum.

Patients who have had a previous bone marrow transplant from an allogenic donor should not have testing performed on blood, bone marrow, or saliva because any results generated will reflect the genome of the donor rather than the recipient. Testing on patients who have an active hematologic malignancy or hematologic disorder with clonal proliferation may identify both somatic mutations and germline variants, which may result in test failure or necessitate follow-up testing to determine whether the detected variant is germline or somatic. For these patients, testing a skin biopsy or cultured fibroblasts is recommended. For instructions for testing patients who have received a bone marrow transplant or have an active hematologic disorder, call 800-533-1710. For more information see Cautions.

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Customization of this panel and single gene analysis for any gene present on this panel are available. For more information see CGPH / Custom Gene Panel, Hereditary, Next-Generation Sequencing, Varies. To modify this panel via CGPH, use the Inborn Errors of Immunity/Bone Marrow Failure/Telomeropathy/Pulmonary Fibrosis/Very Early Onset IBD/Pancreatitis disease state for step 1 on the [Custom Gene Ordering Tool](#).

Targeted testing for familial variants (also called site-specific or known variants testing) is available for the genes on this panel. See FMTT / Familial Variant, Targeted Testing, Varies. To obtain more information about this testing option, call 800-533-1710.

### Additional Testing Requirements

**For cord blood specimens:** Maternal cell contamination (MCC) studies are available. **Order MATCC / Maternal Cell Contamination, Molecular Analysis, Varies on both the cord blood and maternal specimens under separate order numbers.** Cord blood testing will proceed without MCC studies, but results may be compromised if MCC is present.

### Specimen Required

**Patient Preparation:** A previous hematopoietic stem cell transplant from an allogenic donor will interfere with testing. For information about testing patients who have received a hematopoietic stem cell transplant, call 800-533-1710.

### Submit only 1 of the following specimens:

**Specimen Type:** Whole blood

**Container/Tube:** Lavender top (EDTA) or yellow top (ACD)

**Specimen Volume:** 3 mL

#### Collection Instructions:

1. Invert several times to mix blood.
2. Send whole blood specimen in original tube. **Do not aliquot.**
3. Whole blood collected postnatal from an umbilical cord is also acceptable. See Additional Information

**Specimen Stability Information:** Ambient (preferred) 4 days/Refrigerated

#### Additional Information:

1. Specimens are preferred to be received within 4 days of collection. Extraction will be attempted for specimens received after 4 days, and DNA yield will be evaluated to determine if testing may proceed.
2. To ensure minimum volume and concentration of DNA are met, the requested volume must be submitted. Testing may be canceled if DNA requirements are inadequate.
3. For postnatal umbilical cord whole blood specimens, maternal cell contamination studies are recommended to ensure test results reflect that of the patient tested. A maternal blood specimen is required to complete maternal cell contamination studies. Order MATCC / Maternal Cell Contamination, Molecular Analysis, Varies on both the cord blood and maternal blood specimens under separate order numbers.

**Specimen Type:** Skin biopsy

**Supplies:** Fibroblast Biopsy Transport Media (T115)

**Container/Tube:** Sterile container with any standard cell culture media (eg, minimal essential media, RPMI 1640). The solution should be supplemented with 1% penicillin and streptomycin.

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**Specimen Volume:** 4-mm Punch

**Specimen Stability Information:** Ambient (preferred) <24 hours/Refrigerated <24 hours

**Additional Information:**

1. Specimens are preferred to be received within 24 hours of collection. Culture and extraction will be attempted for specimens received after 24 hours and will be evaluated to determine if testing may proceed.
2. A separate culture charge will be assessed under CULFB / Fibroblast Culture for Biochemical or Molecular Testing. An additional 3 to 4 weeks are required to culture fibroblasts before genetic testing can occur.

**Specimen Type:** Cultured fibroblasts

**Container/Tube:** T-25 flask

**Specimen Volume:** 2 Flasks

**Collection Instructions:** Submit confluent cultured fibroblast cells from a skin biopsy from another laboratory. Cultured cells from a prenatal specimen will not be accepted.

**Specimen Stability Information:** Ambient (preferred)/Refrigerated (<24 hours)

**Additional Information:**

1. Specimens are preferred to be received within 24 hours of collection. Culture and extraction will be attempted for specimens received after 24 hours and will be evaluated to determine if testing may proceed.
2. A separate culture charge will be assessed under CULFB / Fibroblast Culture for Biochemical or Molecular Testing. An additional 3 to 4 weeks are required to culture fibroblasts before genetic testing can occur.

**Specimen Type:** Extracted DNA

**Container/Tube:**

**Preferred:** Screw Cap Micro Tube, 2 mL with skirted conical base

**Acceptable:** Matrix tube, 1 mL

**Collection Instructions:**

1. The preferred volume is at least 100 µL at a concentration of 75 ng/µL.
2. Include concentration and volume on tube.

**Specimen Stability Information:** Frozen (preferred) 1 year/Ambient/Refrigerated

**Additional Information:** DNA must be extracted in a CLIA-certified laboratory, or equivalent, and must be extracted from a specimen type listed as acceptable for this test (including applicable anticoagulants). Our laboratory has experience with Chemagic, Puregene, Autopure, MagnaPure, and EZ1 extraction platforms and cannot guarantee that all extraction methods are compatible with this test. If testing fails, one repeat will be attempted, and if unsuccessful, the test will be reported as failed and a charge will be applied. If applicable, specific gene regions that were unable to be interrogated due to DNA quality will be noted in the report.

**Specimen Type:** Blood spot

**Supplies:** Card-Blood Spot Collection (Filter Paper) (T493)

**Container/Tube:**

**Preferred:** Collection card (Whatman Protein Saver 903 Paper)

**Acceptable:** PerkinElmer 226 filter paper or blood spot collection card

**Specimen Volume:** 2 to 5 Blood spots

**Collection Instructions:**

1. An alternative blood collection option for a patient older than 1 year is a fingerstick. For detailed instructions, see

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**[How to Collect a Dried Blood Spot Sample.](#)**

2. Let blood dry on the filter paper at ambient temperature in a horizontal position for a minimum of 3 hours.
3. Do not expose specimen to heat or direct sunlight.
4. Do not stack wet specimens.
5. Keep specimen dry

**Specimen Stability Information:** Ambient (preferred)/Refrigerated

**Additional Information:**

1. Blood spot specimens are acceptable but not recommended. Multiple extractions will be required to obtain sufficient yield for supplemental analysis, and there is significant risk for test failure due to insufficient DNA.
2. Due to lower concentration of DNA yielded from blood spot, some aspects of the test may not perform as well as DNA extracted from a whole blood sample. When applicable, specific gene regions that were unable to be interrogated will be noted in the report. Alternatively, additional specimen may be required to complete testing.
3. For collection instructions, see [Blood Spot Collection Instructions](#)
4. For collection instructions in Spanish, see [Blood Spot Collection Card-Spanish Instructions](#) (T777)
5. For collection instructions in Chinese, see [Blood Spot Collection Card-Chinese Instructions](#) (T800)

**Specimen Type:** Saliva

**Patient Preparation:** Patient should not eat, drink, smoke, or chew gum 30 minutes prior to collection.

**Supplies:**

DNA Saliva Kit High Yield (T1007)

Saliva Swab Collection Kit (T786)

**Container/Tube:**

**Preferred:** High-yield DNA saliva kit

**Acceptable:** Saliva swab

**Specimen Volume:** 1 Tube if using T1007 or 2 swabs if using T786

**Collection Instructions:** Collect and send specimen per kit instructions.

**Specimen Stability Information:** Ambient (preferred) 30 days/Refrigerated 30 days

**Additional Information:** Saliva specimens are acceptable but not recommended. Due to lower quantity/quality of DNA yielded from saliva, some aspects of the test may not perform as well as DNA extracted from a whole blood sample. When applicable, specific gene regions that were unable to be interrogated will be noted in the report. Alternatively, additional specimen may be required to complete testing.

**Forms**

1. **New York Clients-Informed consent is required.** Document on the request form or electronic order that a copy is on file. The following documents are available:

-[Informed Consent for Genetic Testing](#) (T576)

-[Informed Consent for Genetic Testing \(Spanish\)](#) (T826)

2. [Viral Susceptibility, Lymphoproliferation, and Hemophagocytic Lymphohistiocytosis Patient Information](#)

**Specimen Minimum Volume**

See Specimen Required

**Reject Due To**

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All specimens will be evaluated at Mayo Clinic Laboratories for test suitability.

**Specimen Stability Information**

Specimen Type	Temperature	Time	Special Container
Varies	Varies		

**Clinical & Interpretive****Clinical Information**

Epstein-Barr virus (EBV) is a ubiquitous virus, and over 90% of adults have been infected by, and now carry, the virus. While infection is often asymptomatic in children, it may cause infectious mononucleosis in older children and adults. Additionally, EBV has been associated with multiple cancer types. The majority of healthy individuals control EBV in a latent state through the action of natural killer (NK) cells and T cells. Individuals with inborn errors of immunity may experience severe and fatal consequences of EBV infection, including severe infectious mononucleosis, lymphoproliferation, hemophagocytic lymphohistiocytosis (HLH), and lymphoma.

The inborn errors of immunity that contribute to susceptibility to EBV infection can follow several mechanisms. In one group, genetic variants may result in EBV-induced HLH and a lack of NK and CD8+ T-cell cytotoxicity due to issues with the cytotoxic granules. Another group is characterized by impaired activation and expansion of T cells that specifically target EBV and may be due to genetic variants in genes involved in T-cell receptor signaling, DNA metabolism and synthesis, or the costimulatory receptors of the tumor necrosis factor-receptor superfamily. In general, disease-causing variants in *SH2D1A*, *CD27*, *CD70*, and *TNFRSF9* may result in a more selective predisposition to EBV infection, while other defects may result in broader viral susceptibility.

**Reference Values**

An interpretive report will be provided.

**Interpretation**

All detected variants are evaluated according to American College of Medical Genetics and Genomics recommendations.(1) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

**Cautions**

Clinical Correlations:

Test results should be interpreted in the context of clinical findings, family history, and other laboratory data.

Misinterpretation of results may occur if the information provided is inaccurate or incomplete.

If testing was performed because of a clinically significant family history, it is often useful to first test an affected family member. Detection of a reportable variant in an affected family member would allow for more informative testing of at-risk individuals.

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To discuss the availability of additional testing options or for assistance in the interpretation of these results, contact Mayo Clinic Laboratories genetic counselors at 800-533-1710.

**Technical Limitations:**

Next-generation sequencing may not detect all types of genomic variants. In rare cases, false-negative or false-positive results may occur. The depth of coverage may be variable for some target regions; assay performance below the minimum acceptable criteria or for failed regions will be noted. Given these limitations, negative results do not rule out the diagnosis of a genetic disorder. If a specific clinical disorder is suspected, evaluation by alternative methods can be considered.

There may be regions of genes that cannot be effectively evaluated by sequencing or deletion and duplication analysis as a result of technical limitations of the assay, including regions of homology, high guanine-cytosine (GC) content, and repetitive sequences. Confirmation of select reportable variants will be performed by alternate methodologies based on internal laboratory criteria.

This test is validated to detect 95% of deletions up to 75 base pairs (bp) and insertions up to 47 bp. Deletions-insertions (delins) of 40 or more bp, including mobile element insertions, may be less reliably detected than smaller delins.

**Deletion/Duplication Analysis:**

This analysis targets single and multi-exon deletions/duplications; however, in some instances, single exon resolution cannot be achieved due to isolated reduction in sequence coverage or inherent genomic complexity. Balanced structural rearrangements (such as translocations and inversions) may not be detected.

Deletion/duplication events that extend past the genes included on the panel may occur. In these instances, genes included in the ordered test are provided on the report and interpreted, and genomic breakpoints are reported if they are confirmed. However, copy number variants for genes not listed in the Method Description are typically not reported or interpreted for haploinsufficiency/triplosensitivity. CMCB / Chromosomal Microarray, Congenital, Blood; WESPR / Panel to Whole Exome Sequencing Reflex Test, Varies; or WGSDX / Whole Genome Sequencing for Hereditary Disorders, Varies is recommended for a full interpretation of deletions/duplications predicted to extend past the genes included on the panel.

This test is not designed to detect low levels of mosaicism or to differentiate between somatic and germline variants. If there is a possibility that any detected variant is somatic, additional testing may be necessary to clarify the significance of results.

Genes may be added or removed based on updated clinical relevance. For the most up to date list of genes included in this test and detailed information regarding gene-specific performance and technical limitations, see Method Description or contact a laboratory genetic counselor.

If the patient has had an allogeneic hematopoietic stem cell transplant or a recent non-leukoreduced blood transfusion, results may be inaccurate due to the presence of donor DNA. Call Mayo Clinic Laboratories for instructions for testing patients who have received a bone marrow transplant.

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**Reclassification of Variants:**

Currently, it is not standard practice for the laboratory to systematically review previously classified variants on a regular basis. The laboratory encourages healthcare professionals to contact the laboratory at any time to learn how the classification of a particular variant may have changed over time. Due to broadening genetic knowledge, it is possible that the laboratory may discover new information of relevance to the patient. Should that occur, the laboratory may issue an amended report.

**Variant Evaluation:**

Evaluation and categorization of variants are performed using published American College of Medical Genetics and Genomics and the Association for Molecular Pathology recommendations as a guideline.<sup>(1)</sup> Other gene-specific guidelines may also be considered. Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance. Variants classified as benign or likely benign are not reported.

Multiple in silico evaluation tools may be used to assist in the interpretation of these results. The accuracy of predictions made by in silico evaluation tools is highly dependent upon the data available for a given gene, and periodic updates to these tools may cause predictions to change over time. Results from in silico evaluation tools should be interpreted with caution and professional clinical judgment.

Rarely, incidental or secondary findings may implicate another predisposition or presence of active disease. These findings will be carefully reviewed to determine whether they will be reported.

**Clinical Reference**

1. Richards S, Aziz N, Bale S, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. *Genet Med* 2015;17(5):405-424.
2. Tangye SG. Genetic susceptibility to EBV infection: insights from inborn errors of immunity. *Hum Genet.* 2020;139(6-7):885-901
3. Fournier B and Latour S. Immunity to EBV as revealed by immunodeficiencies. *Curr Opin Immunol.* 2021;72:107-115
4. Ravell JC, Chauvin SD, He T, Lenardo M. An update on XMEN disease. *J Clin Immunol.* 2020;40(5):671-681
5. Tangye SG, Al-Herz W, Bousfiha A, et al. Human inborn errors of immunity: 2022 update on the classification from the International Union of Immunological Societies Expert Committee. *J Clin Immunol.* 2022;42(7):1473-1507. doi:10.1007/s10875-022-01289-3

**Performance****Method Description**

Next-generation sequencing (NGS) and/or Sanger sequencing are performed to test for the presence of variants in coding regions and intron/exon boundaries of the genes analyzed, as well as some other regions that have known disease-causing variants. The human genome reference GRCh37/hg19 build was used for sequence read alignment. At least 99% of the bases are covered at a read depth over 30X. Sensitivity is estimated at above 99% for single nucleotide

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variants, above 94% for deletions/insertions (delins) less than 40 base pairs (bp), and above 95% for deletions up to 75 bp and insertions up to 47 bp. NGS and/or a polymerase chain reaction (PCR)-based quantitative method is performed to test for the presence of deletions and duplications in the genes analyzed. A supplemental PCR-based method is used to detect an inversion in *UNC13D*. Confirmation of select reportable variants may be performed by alternate methodologies based on internal laboratory criteria.

There may be regions of genes that cannot be effectively evaluated by sequencing or deletion and duplication analysis as a result of technical limitations of the assay, including regions of homology, high guanine-cytosine (GC) content, and repetitive sequences. Refer to the [Targeted Genes and Methodology Details for Epstein Barr Virus \(EBV\) Susceptibility and Lymphoproliferative Disorders Gene Panel](#) for details regarding the targeted genes analyzed for each test and specific gene regions not routinely covered. (Unpublished Mayo method)

Genes analyzed: *ATM*, *CARD11*, *CARMIL2*, *CD27*, *CD70*, *CORO1A*, *CTLA4*, *CTPS1*, *DEF6*, *GATA2*, *ITK*, *LRBA*, *MAGT1*, *PIK3CD*, *PRF1*, *PRKCD*, *RASGRP1*, *SH2D1A*, *STK4*, *STX11*, *STXBP2*, *TET2*, *TNFRSF9*, *UNC13D*, and *XIAP*

**PDF Report**

Supplemental

**Day(s) Performed**

Varies

**Report Available**

28 to 42 days

**Specimen Retention Time**

Whole blood: 28 days (if available); Saliva: 30 days (if available); Extracted DNA: 3 months; Blood spots: 1 year (if available)

**Performing Laboratory Location**

Mayo Clinic Laboratories - Rochester Main Campus

**Fees & 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 account representative. For assistance, contact [Customer Service](#).

**Test Classification**

This test was developed and its performance characteristics determined by Mayo Clinic in a manner consistent with CLIA requirements. It has not been cleared or approved by the US Food and Drug Administration.

## Test Definition: EBLPD

Epstein Barr Virus (EBV) Susceptibility and  
Lymphoproliferative Disorders Gene Panel,  
Varies

### CPT Code Information

81443  
88233-Tissue culture, skin, solid tissue biopsy (if appropriate)  
88240-Cryopreservation (if appropriate)

### LOINC® Information

Test ID	Test Order Name	Order LOINC® Value
EBLPD	EBV/Lymphoproliferation GenePanel	103739-9

Result ID	Test Result Name	Result LOINC® Value
619789	Test Description	62364-5
619790	Specimen	31208-2
619791	Source	31208-2
619792	Result Summary	50397-9
619793	Result	82939-0
619794	Interpretation	69047-9
619795	Additional Results	82939-0
619796	Resources	99622-3
619797	Additional Information	48767-8
619798	Method	85069-3
619799	Genes Analyzed	82939-0
619800	Disclaimer	62364-5
619801	Released By	18771-6