EB VCA IgG EIA ID: Black

Enzyme Immunoassay (EIA) for the Detection of EB VCA IgG Antibodies in Human Serum.

For *In Vitro* Diagnostic Use Only 25184 • 96 Tests

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1 - INTENDED USE

For the qualitative and semi-quantitative detection of human IgG antibodies to Epstein-Barr (EB) viral capsid antigen (VCA) in human serum by enzyme immunoassay. The test may be used in conjunction with other serologicals, as an aid in the diagnosis of infectious mononucleosis. These reagents have not received FDA clearance for use in testing blood or plasma donors.

2 - SUMMARY AND EXPLANATION OF THE TEST

Epstein-Barr virus (EBV) is the etiological agent of infectious mononucleosis (IM).[1] The designation of infectious mononucleosis classically refers to an Epstein-Barr virus-induced illness in young adults characterized by reactive blood smears, exudative pharyngitis, prominent cervical lymphadenopathy, and serologically detectable heterophile antibodies. These clinical manifestations can also be caused by a number of other pathogenic agents including cytomegalovirus, *Toxoplasma gondii*, rubella virus, hepatitis virus, human immunodeficiency virus (HIV), and uncommonly by drugs such as Halothane, Hydantoin, Dapasone, and Azulfidine.[2,3,4]

Diagnosis of acute EBV IM is generally confirmed by a positive heterophile antibody test. The severity of the disease, however, is not indicated by the relative titer of heterophile antibodies.[5] In addition, difficulties in diagnosis arise when the heterophile antibody test is negative, or when the clinical manifestations are atypical or unusually severe.

Heterophile-negative IM occurs in 10 to 20 percent of adults, and in an even greater percentage of children.[6,7] IM diagnosis in these individuals may be confirmed by the detection and identification of antibodies to specific EB antigens which include: viral capsid antigen (VCA), early antigens, diffuse and restricted (EA-D and EA-R), and Epstein-Barr nuclear antigen (EBNA).

IgG antibodies to VCA may be present early during EBV infection, but they persist indefinitely after the occurrence of clinical disease and may merely indicate EBV infection at some time in the past. IgM antibodies to VCA, on the other hand, are present in the circulation 1 to 6 weeks after the onset of EBV illness and usually disappear in 3 to 6 months. Thus the presence of VCA IgM usually suffices for the diagnosis of acute IM. Further verification may be obtained by testing for the presence of antibodies directed against the other EBV-specific antigens, early antigen and EBNA. Heterophile antibody negative sera demonstrating VCA IgM and transient levels of antibody to early antigen are considered diagnostic for acute IM. In contrast,

antibodies to EBNA appear late during IM infections, and IgG antibodies to EBNA may persist for years, even for life, and are indicative of the convalescent phase of IM infection.

The EB VCA IgG EIA test is an ELISA test which utilizes a microwell format. Test results are obtained after one and one-half hours incubation time. They are objective and normalized as Index values, permitting uniformity of reporting.

3 - PRINCIPLE OF THE TEST

Diluted samples are incubated in VCA antigen-coated wells. VCA IgG antibodies (if present) are immobilized in the wells. Residual sample is eliminated by washing and draining, and conjugate (enzyme labeled antibodies to human IgG) is added and incubated. If IgG antibodies to VCA are present, the conjugate will be immobilized in the wells. Residual conjugate is eliminated by washing and draining, and the substrate is added and incubated. In the presence of the enzyme, the substrate is converted to a yellow end product which is read photometrically.

4 - REAGENTS

EB VCA IgG EIA Product Description
Catalog No. 25184 (96 Tests)

Component	Contents	Preparation
Coated Wells 12 eight-well strips	• Coated inactivated Epstein-Barr VCA antigen • Black wells	Use as supplied. Return unused strips to pouch and reseal. Do not remove desiccant.*
Well support 1 Frame	• Plate frame	Use as supplied.
Diluent** 1 bottle (25 mL)	• Phosphate-buffered saline with a protein stabilizer • Pink Color	Use as supplied.
Calibrator 1** 1 vial (0.5 mL)	• Human serum, strongly reactive for VCA IgG antibodies • Index value shown on vial label	Dilute in Diluent as described.
Calibrator 2** 1 vial (0.5 mL)	• Human serum, moderately reactive for VCA IgG antibodies • Index value shown on vial label	Dilute in Diluent as described.
Positive Control** 1 vial (0.5 mL)	• Human serum, reactive for VCA IgG antibodies • Index value shown on vial label	Dilute in Diluent as described.
Negative Control** 1 vial (0.5 mL)	• Human serum, non-reactive for VCA IgG antibodies	Dilute in Diluent as described.
Conjugate** 2 bottles (12 mL)	• Goat anti-human IgG labeled with alkaline phosphatase (calf) • Green Color	Use as supplied.
Substrate*** 1 bottle (12 mL)	• p-Nitrophenyl phosphate	Use as supplied.
Wash Concentrate** 1 bottle (30 mL)	• Tris-buffered saline • Tween 20™ • pH 8.0	Dilute in 1 liter of distilled or deionized water.
Stop Reagent 1 bottle (12 mL)	• Trisodium phosphate 0.5 M	Use as supplied.

* The color of the desiccant does not affect the performance of the kit.
** Contains 0.1% sodium azide.
*** The substrate may develop a slight yellow color during storage. One hundred microliters of substrate should yield an absorbance value less than 0.35, when read in a microwell against air or water.

Store these reagents at 2-8°C up to the expiration date indicated on the bottle labels. Do not allow them to contact the skin or eyes. If contact occurs, wash with copious amounts of water. Do not remove desiccant.

5 - OTHER MATERIALS REQUIRED

1. Microplate washer
2. Pipettors for dispensing 4, 100, and 200 µL
3. Timer
4. 1 or 2 liter container for Wash Solution
5. Distilled or deionized water
6. Dilution tubes or microwells
7. Microwell reader capable of reading absorbance at 405 nm.

6 - PRECAUTIONS FOR USERS

For *In Vitro* Diagnostic Use

1. Test samples, Calibrator(s), Controls, and the materials that contact them should be handled as potential biohazards. The calibrators and controls have been tested and found to be non-reactive for HIV, hepatitis B surface antigen, and HCV antibodies by licensed tests. However, no method can offer complete assurance that HIV, hepatitis B virus, HCV, or other infectious agents are absent. Handle reagents and patient samples as if capable of transmitting infectious disease following recommended *Universal Precautions* for bloodborne pathogens as defined by OSHA[9], Biosafety Level 2 guidelines from the current CDC/NIH *Biosafety in Microbiological and Biomedical Laboratories*[10], WHO *Laboratory Biosafety Manual*[11], and/or local, regional, and national regulations.
2. The concentrations of anti-EB VCA IgG in a given specimen determined with assays from different manufacturers can vary due to differences in assay methods and reagent specificity.
3. Avoid contact with open skin.
4. Never pipet by mouth.
5. Certain test reagents contain dilute **sodium azide**, which may be harmful if enough is ingested (more than supplied in kit). Azides are reported to react with lead and copper in plumbing to form compounds that may detonate on percussion. If disposing of solutions containing sodium azide down drains, flush with large volumes of water to minimize the build-up of metal-azide compounds. Dispose of contents and container in accordance with local, regional, national, and international regulations.
6. For more hazard information, refer to the product Safety Data Sheet (SDS), which is available at www.bio-rad.com and upon request.

7. Any lot number of the following reagents may be used with this assay provided they have the correct catalog number and are not used beyond their labeled expiration date:
    - Diluent - Catalog # 25189
    - Substrate - Catalog # 25192
    - Wash Concentrate - Catalog # 25190
    - Stop Reagent - Catalog # 25191

    Do not mix any other reagents from different lots.
8. Do not use reagents beyond their stated expiration date.
9. Incubation times recommended in the Test Procedure section should be adhered to.
10. Unused Coated Wells should be kept in their resealable bag with desiccant and stored in the refrigerator.
11. This product should be used by qualified personnel.
12. There are no health hazards associated with the intact desiccant packet. Do not cut, split, or otherwise compromise it as dusts that may be generated could pose a health hazard. If the desiccant has been compromised, do not remove it from the plate pouch.

7 - SPECIMEN COLLECTION, PREPARATION, AND STORAGE

Sera should be separated from clotted blood. If specimens are not tested within 8 hours, they should be stored at 2 to 8°C for up to 48 hours. Beyond 48 hours, specimens should be stored at -20°C or below. Multiple freeze-thaw cycles should be avoided. Samples containing visible particulate matter should be clarified by centrifugation; and hemolyzed, icteric, or grossly contaminated samples should not be used. Samples should not be heat-inactivated before testing.

8 - TEST PROCEDURE

Materials Provided

See REAGENTS section on page 5.

EIA Procedure

1. Allow all reagents and patient samples to reach room temperature before use. Return them promptly to refrigerator after use.
2. Prepare working wash solution by adding entire bottle of Wash Concentrate (30 mL) to 1 liter of water. Once diluted,

the wash solution can be stored at room temperature for up to two months, or at 4°C until the expiration date printed on the Wash Concentrate bottle.

3. Prepare 1:51 dilutions of test samples, Calibrator(s), Positive and Negative Controls, in the test set Diluent. For example: add 4 µL of sample to 200 µL of Diluent in a dilution well or tube, and mix well.

   Note: For qualitative assays, a single Calibrator (Calibrator 2) may be used; for semi-quantitative assays, it is necessary to use Calibrator 1 and Calibrator 2 to prepare a calibration curve. The blank serves as the zero calibrator.

4. Place appropriate number of Coated Wells in the Well Support.

   Note: For combination testing (multiple assays per plate), the strips should be assembled on a white background with good lighting. Be sure to note the placement of each strip and the corresponding color.

5. Transfer 100 µL of each diluted Calibrator, Control, and patient sample to the wells.

   Note: Include one well which contains 100 µL of Diluent only. This will serve as the reagent blank and will ultimately be used to zero the photometer before reading the test results.

6. Incubate the wells at room temperature (20 to 25°C) for 30 ± 5 minutes.
7. Wash wells four times, with at least 250 µL of wash solution per well. Do not allow the wells to soak between washes. Aspirate thoroughly after the last wash.
8. Place 2 drops (or 100 µL) of Conjugate into each well.
9. Incubate the wells at room temperature (20 to 25°C) for 30 ± 5 minutes.
10. Wash wells four times with at least 250 µL of wash solution per well. Do not allow the wells to soak between washes. Aspirate thoroughly after the last wash.
11. Place 2 drops (or 100 µL) of Substrate into each well.
12. Incubate at room temperature (20 to 25°C) for 30 ± 5 minutes.
13. Place 2 drops (or 100 µL) of Stop Reagent into each well. Tap the plate gently, or use other means to assure complete mixing.
14. Read and record the absorbance of the contents of each well at 405 nm against the reagent blank.

Note: Adjust the photometer to zero absorbance at 405 nm against the reagent blank. Readings should be made within 2 hours after the reactions have been stopped.

9 - QUALITY CONTROL

Test Validation Criteria

1. The Calibrator(s), Positive and Negative Controls must be included in each test run.
2. The absorbance value of Calibrator 1 must be ≥ 0.400 when read against the reagent blank.
3. The absorbance value of Calibrator 2 must be ≥ 0.200 when read against the reagent blank.
4. The absorbance value of the reagent blank should be < 0.350.
5. The Negative Control must have an Index value < 0.9.
6. The Positive Control must have an Index value equal to or greater than 1.1 when using a single Calibrator (Calibrator 2). When using the calibration curve, the Positive control must have an Index value within the range printed on the label. Users may supply an alternative Positive Control if they wish.
7. The Negative and Positive Controls are intended to monitor for substantial reagent failure. The Positive Control will not ensure precision at the assay cutoff. Additional controls may be tested according to guidelines or requirements of local, state, and/or federal regulations or accrediting organizations. For guidance on appropriate quality control practices, please refer to NCCLS document C24-A, *Internal Quality Control Testing: Principles and Definitions*.
8. If any of these criteria are not met, the test is invalid and should be repeated. If the test is invalid, patient results can not be reported.

10-INTERPRETATION OF RESULTS

Calculation of Results

Qualitative results may be calculated using a single calibrator. For semi-quantitative results, use a calibration curve consisting of two or more calibrators.

Single Calibrator (Calibrator 2)
Determine the Index value for each test sample (or Control) using the following formula:

$$\frac{\text{Calibrator 2 Index}}{\text{Calibrator 2 Absorbance}} \times \text{Test Sample Absorbance} = \text{Test Sample Index}$$

If the Calibrator is run in duplicate, use the average absorbance value to calculate results.

Calibration Curve
Alternatively, test results may be calculated from a three-point curve comprised of: Calibrator 1 (high-point), Calibrator 2 (mid-point) and the reagent blank (zero/origin), using a point-to-point curve fit.

Interpretation of Results

Index Value	Interpretation
< 0.9	Negative for anti-EB VCA IgG antibody
≥ 0.9 and < 1.1	Equivocal*
≥ 1.1	Positive for anti-EB VCA IgG antibody

* Index values which fall between 0.9 and 1.1 indicate an equivocal result. Subsequent samples should be drawn at least fourteen days later and tested simultaneously with the initial sample. If the subsequent sample is positive, seroconversion has occurred, which may be indicative of recent infection. If the subsequent sample remains equivocal, antibody status is undetermined and the sample is deemed equivocal. Other clinical and serological evidence should be sought in these cases.

The EB VCA IgG EIA cutoff values were based on statistical analyses of the results of tests of 25 serum specimens that were negative for anti-VCA IgG antibodies when tested by another commercial VCA IgG test. The cutoff values were challenged in tests of positive and negative specimens (see Performance Characteristics).

Specimens that yield absorbance values above the range of the test set calibrator(s) may be pre-diluted in the test set Diluent and reassayed. The resulting Index value must be multiplied by the dilution factor. Example: If the specimen has been pre-diluted 1:5 before testing, the resulting Index value should be multiplied by 5.

Semi-quantitative interpretation: Dose response experiments have been performed at Laboratory B (Miami, FL) by assaying serial dilutions of positive specimens. Typical results of these experiments are shown in Figure 1. An analysis of these experiments was performed to establish the criteria for recognizing significant changes in antibody levels. To determine significant differences between EB VCA IgG EIA Index values, calculate the ratio of the Index values by dividing the larger Index

value by the smaller one. If the ratio is ≤ 2.00, the difference is not significant. If the ratio is between 2.01 and 3.87, the difference is equivocal. If the ratio is ≥ 3.88, the difference is significant.

Values obtained with different manufacturers' assay methods may not be used interchangeably. The magnitude of the reported IgG level cannot be correlated to an endpoint titer. The magnitude of the assay result above the cutoff is not an indicator of the total antibody present.

Specimens collected too early during the course of the disease may not contain anti-EB VCA IgG antibody.

11-LIMITATIONS

The results obtained with the EB VCA IgG EIA test serve only as an aid to diagnosis and should not be interpreted as diagnostic in themselves. Test results should be evaluated in relation to patient symptoms, clinical history, and other laboratory findings.

The timing of the appearance of IgG antibodies to VCA is subject to variations among individuals and serological assays.

Some sera, drawn very early at the onset of symptoms, may not contain detectable levels of VCA antibody and may require the drawing of another test specimen 1-2 weeks later.

The assay's performance characteristics with immunosuppressed individuals have not been established.

The prevalence of IgG antibodies to VCA will affect the assay's predictive value.

This assay is not intended for viral isolation and/or identification.

The assay's performance characteristics have not been established for testing newborn specimens, or cord blood, or matrices other than human serum.

Dose response experiments have demonstrated that specimens yielding EB VCA IgG EIA Index values up to 89.2 do not exhibit a high-dose hook effect.

The assay's performance characteristics were not established for visual result determination.

12-EXPECTED VALUES

Nearly all individuals have been infected with EBV by the time they reach adulthood.[8] Characteristically, IgG antibodies to VCA

appear relatively early during IM infections and persist for years, even for life.

Serum samples obtained randomly from 57 normal South Florida blood donors were assayed by the EB VCA IgG EIA test. All 57 samples tested positive for IgG antibodies to VCA. The samples yielded Index values between 1.1 and 20.8, with a mean Index value of 13.8.

Table 1: Results of EB VCA IgG EIA tests of 57 archival specimens (frozen), from normal South Florida blood donors. The assays were performed at Laboratory B (Miami, FL).

Index Value Ranges	Number of Specimens	Percentage of Specimens
< 1.1	0	0
≥ 1.1 to < 5	6	10.5
≥ 5 to < 15	20	35.1
≥ 15	31	54.4

13-PERFORMANCE CHARACTERISTICS

Comparative Testing

The results of EB VCA IgG EIA tests correlate well with other commercial serological tests. Serum specimens obtained from normal South Florida blood donors, from patients whose sera were submitted to clinical laboratories in South Florida for diagnostic testing, and from serum brokers were assayed by the EB VCA IgG EIA test and other commercial serological assays. The assays were performed at an independent laboratory (Lab A, Miami, FL) and at Laboratory B (Miami, FL). Forty-eight percent of the serum specimens tested at Laboratory A were from female donors ranging in age from 1 to 89 years (mean = 24 years). Fifty-two percent were from male donors between 1 and 75 years of age (mean = 28 years). The results obtained in these studies are shown below in Tables 2 and 3, respectively.

Table 2: Results of tests of 90 archival patient specimens tested at Laboratory A (Miami, FL) using the EB VCA IgG EIA test and another commercial test.

Comparative Test #1	EB VCA IgG EIA		
	Positive	Equivocal	Negative
Positive	74	2	0
Equivocal	0	0	0
Negative	7	4	3

	%	95 % C.I.**
Relative sensitivity*	100	96.0 to 100
Relative specificity*	30	1.6 to 58.4
Overall Agreement*	91.7	85.8 to 97.6

* Excluding equivocal results

** Calculated by the Exact Method[12]

Table 3: Results of tests of 157 archival patient specimens tested at Laboratory B (Miami, FL) using the EB VCA IgG EIA test and another commercial test.

Comparative Test #2	EB VCA IgG EIA		
	Positive	Equivocal	Negative
Positive	130	2	11
Equivocal	2	1	0
Negative	1	1	9

	%	95 % C.I.**
Relative sensitivity*	92.2	87.8 to 96.6
Relative specificity*	90.0	1.4 to 100
Overall Agreement*	92.1	87.7 to 96.4

* Excluding equivocal results

** Calculated by the Exact Method[12]

Please be advised that "relative" sensitivity and specificity refers to the comparison of this assay's results to that of a similar assay. There was not an attempt to correlate the assay's results to disease presence or absence. No judgment can be made on the comparison assay's accuracy to predict disease.

Sensitivity and specificity relative to serological profile

One hundred and fifty-seven archival serum specimens (see Table 3) were tested at Laboratory B using the EB VCA IgG EIA test and other commercially available EIA tests for detecting VCA IgG, VCA IgM, and EBNA IgG. One hundred and thirty-seven of these sera were able to be characterized as acute (VCA IgM antibody present and EBNA IgG antibody absent), seropositive (VCA IgG and EBNA IgG antibodies present and VCA IgM antibodies absent), or seronegative (no serological evidence of EBV IgM, EBV IgG, or EBNA IgG antibodies) on the basis of their serological profile. The sensitivity, specificity, and agreement of the EB VCA IgG EIA assay were determined based on these characterizations. It was assumed that the VCA IgG

response should be negative for seronegative samples and positive for the acute and convalescent samples. The results have been summarized below in Table 4.

Table 4: Results of tests performed at Laboratory B, with 137 selected serum specimens, using the EB VCA IgG EIA test, and other commercially available tests for VCA IgG, VCA IgM, and EBNA IgG antibodies.

EB VCA IgG EIA	Serum Characterization		
	Acute VCA IgM Positive EBNA IgG Negative	Seropositive VCA IgM Negative VCA IgG Positive EBNA IgG Positive	Seronegative VCA IgM Negative VCA IgG Negative EBNA IgG Negative
Positive	21	100	0
Negative	3	2	9
Equivocal	1	0	1
Total	25	102	10

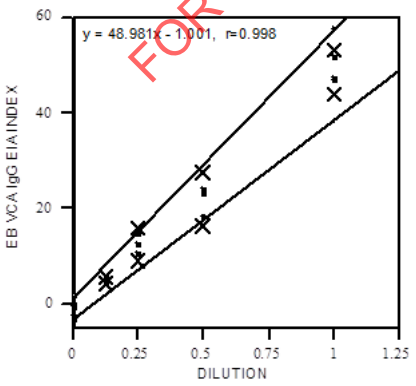
	Samples*	%	95% C.I.**
Relative specificity (Acute)	21/24	87.5	74.3 to 100
Relative sensitivity (Seropositive)	100/102	98.0	95.3 to 100
Relative specificity (Seronegative)	9/9	100	92.0 to 100***
Relative agreement	130/135	96.3	93.1 to 99.5

* Equivocal results were not included in the calculations, nor were they retested.
** 95 % confidence intervals (CI) were calculated using the normal method.
*** The seronegative 95% confidence interval was calculated assuming 0.1 false positive.

Titration curve

Several strongly positive serum specimens were serially diluted (two-fold) in triplicate in the test kit Diluent and assayed by the EB VCA IgG EIA test. Typical results are shown in Figure 1.

Figure 1: Titration curve for a strongly positive specimen.



The triplicate data for each dilution are shown as points, the 95% confidence limits for each set of triplicate data are indicated by (x's), and the 95% confidence limits for the slopes and

y-intercepts are represented by straight lines. The formula for the linear regression for the triplicate data is also shown in Figure 1.

Cross-reactivity study

The EB VCA IgG EIA test does not cross-react with antibodies directed against other Epstein-Barr virus antigens, other herpes viruses, and other unrelated viruses. Of ten specimens that were unreactive in the EB VCA IgG EIA test, 2 were positive for VCA IgM antibody, 3 for EB NA antibody, 2 for herpes simplex virus antibody, 3 for cytomegalovirus antibody, 3 for varicella zoster virus antibody, 4 for rubella antibody, and 2 for measles antibody.

Precision

Eight serum specimens (2 negative and 6 positive) and the EB VCA IgG EIA Positive and Negative Controls were assayed in triplicate on three separate occasions.

The precision experiments were performed manually at an independent laboratory (Lab A) and at Laboratory B. These results are shown below in Tables 5 and 6, respectively.

Table 5: Results intra-assay and inter-assay precision tests performed at Lab A. Values were calculated from EB VCA IgG EIA Index values.

	INTRA-ASSAY			INTER-ASSAY		
SAMPLE	MEAN INDEX	S.D	C.V. %	MEAN INDEX	S.D	C.V. %
Pos. Control	4.5	0.115	2.6	4.2	0.316	7.6
Neg. Control	0.8	0.058	NA	0.8	0.000	NA
1	0.3	0.000	NA	0.3	0.067	NA
2	0.3	0.058	NA	0.3	0.000	NA
3	7.1	0.874	12.2	6.8	0.719	10.6
4	5.4	0.115	2.2	5.4	0.497	9.2
5	3.0	0.115	3.9	2.9	0.141	4.9
6	3.6	0.306	8.4	3.6	0.265	7.4
7	4.2	0.350	8.3	4.3	0.330	7.8
8	4.0	0.250	6.3	3.7	0.360	9.8

Table 6: Results intra-assay and inter-assay precision tests performed at Lab B. Values were calculated from EB VCA IgG EIA Index values.

	INTRA-ASSAY			INTER-ASSAY		
SAMPLE	**MEAN INDEX**	**S.D**	**C.V. %**	**MEAN INDEX**	**S.D**	**C.V. %**
Pos. Control	2.5	0.231	9.1	2.4	0.207	8.5
Neg. Control	0.3	0.058	NA	0.2	0.000	NA
1	0.3	0.000	NA	0.3	0.053	NA
2	0.2	0.000	NA	0.2	0.033	NA
3	6.7	0.321	4.8	6.4	0.381	6.0
4	6.9	0.400	5.8	6.5	0.451	6.9
5	3.3	0.577	17.3	2.9	0.468	16.3
6	4.4	0.361	8.2	4.0	0.438	10.9
7	6.6	0.400	6.2	5.8	0.620	10.7
8	4.4	0.100	2.3	4.1	0.490	12.0

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Revised: February 2015
Part # 503934C