Access
Immunoassay Systems

TOTAL IgE
REF 35000

Intended Use

The Access Total IgE assay is a paramagnetic particle, chemiluminescent immunoassay for the quantitative determination of total E (IgE) levels in human serum and plasma (heparin, EDTA) using the Access Immunoassay Systems.

Summary and Explanation

Immunoglobulin E (IgE) was first isolated and defined as a new immunoglobulin class by Ishizaka, et al. and Johansson and Bennich in the 1960's.[1,2] IgE has a molecular weight of approximately 188,000 daltons, making it slightly larger than the monomers of the other immunoglobulins. The epsilon (ε) heavy chain contains five domains (VH, Cε1, Cε2, Cε3, and Cε4) with the IgE receptor binding region believed to be located near the Cε2–Cε3 region. High affinity IgE specific receptors are found on the surface membranes of mast cells and basophils. Once IgE has been bound by these receptors, it plays a key role in the generation of immediate hypersensitivity reactions.

The World Health Organization (WHO) has recognized IgE as a unique immunoglobulin and has established calibration standards for it.[3,4] One international unit (IU) of IgE has been defined as equal to 2.4 ng.

The levels of circulating IgE in serum are extremely low compared to the other immunoglobulins. Levels at birth are almost non-detectable, but increase with age to approximately 20 IU/mL (48 µg/L) in normal adults.[5] IgE has been linked to atopic disease and there is a strong correlation between increased total serum IgE levels and allergy.[6] The determination of total IgE levels has been found to be useful in the assessment of atopic diseases such as allergic rhinitis, extrinsic asthma, urticaria, and atopic eczema.[7,8] Several investigators have also shown that increased IgE levels in cord blood and infants may have a predictive value for the early onset of allergic disease.[9,10,11,12] Patients with pulmonary aspergillosis, parasitic infestations, and some immunodeficiencies have also been found to have increased amounts of IgE.[13,14,15]

Total IgE levels may vary due to a variety of different factors, including genetic disposition and allergen exposure. Low levels of circulating IgE do not necessarily indicate the absence of allergic disease as certain individuals may have low total IgE levels but have a high concentration of allergen-specific IgE.

The Access Total IgE assay is based on the two-site immunoradiometric assay (IRMA) described by Addison, et al., but utilizes an enzyme-labeled antibody in place of the radio-labeled tracer.[16]

Principles of the Procedure

The Access Total IgE assay is a sequential two-step immunoenzymatic ("sandwich") assay. A sample is added to a reaction vessel along with paramagnetic particles coated with goat anti-mouse: mouse anti-IgE complexes. The IgE in the sample binds to the mouse anti-IgE on the particles. After incubation in a reaction vessel, materials bound to the solid phase are held in a magnetic field while unbound materials are washed away. Equine anti-IgE conjugated to alkaline phosphatase is then added and binds to the previously bound IgE on the particles. A second separation and wash step removes unbound conjugate. Then, the chemiluminescent substrate Lumi-Phos* 530 is added to the vessel and light generated by the reaction is measured with a luminometer. The light production is directly proportional to the concentration of IgE in the sample. The amount of analyte in the sample is determined from a stored, multi-point calibration curve.

Product Information

Access Total IgE Reagent Pack

Cat. No. 35000: 100 determinations, 2 packs, 50 tests/pack

- Provided ready to use.
- Store upright and refrigerate at 2 to 10°C.
- Refrigerate at 2 to 10°C for a minimum of two hours before use on the instrument.
- Stable until the expiration date stated on the label when stored at 2 to 10°C.
- Stable at 2 to 10°C for 28 days after initial use.
- Signs of possible deterioration are a broken elastomeric layer on the pack or control values out of range.
- If the reagent pack is damaged (i.e., broken elastomer), discard the pack.
- All antisera are polyclonal unless otherwise indicated.

R1a:	Paramagnetic particles coated with goat anti-mouse IgG: mouse monoclonal anti-IgE complexes suspended in TRIS buffered saline, with surfactant, BSA matrix, protein (goat), < 0.1% sodium azide, and 0.1% ProClin** 300.
R1b:	Equine anti-IgE-alkaline phosphatase (bovine) conjugate in TRIS buffered saline, with surfactant, BSA matrix, protein (equine), < 0.1% sodium azide, and 0.1% ProClin 300.

Warnings and Precautions

- For *in vitro* diagnostic use.
- Patient samples and blood-derived products may be routinely processed with minimum risk using the procedure described. However, handle these products as potentially infectious according to universal precautions and good clinical laboratory practices, regardless of their origin, treatment, or prior certification. Use an appropriate disinfectant for decontamination. Store and dispose of these materials and their containers in accordance with local regulations and guidelines.
- Sodium azide may react with lead and copper plumbing to form highly explosive metal azides. On disposal of liquids, flush with a large volume of water to prevent azide build-up.[17]
- Xi. Irritant: 0.1% ProClin 300.

R 43: May cause sensitization by skin contact.

S 28-37: After contact with skin, wash immediately with plenty of soap and water. Wear suitable gloves.

- The Material Safety Data Sheet (MSDS) is available upon request.

Specimen Collection and Preparation

1. Serum and plasma (heparin, EDTA) are the recommended samples.
2. Observe the following recommendations for handling, processing, and storing blood samples:[18]
   - Collect all blood samples observing routine precautions for venipuncture.
   - Allow serum samples to clot completely before centrifugation.
   - Keep tubes stoppered at all times.
   - Within two hours after centrifugation, transfer at least 500 µL of cell-free sample to a storage tube. Tightly stopper the tube immediately.
   - Store samples tightly stoppered at room temperature (15 to 30°C) for no longer than eight hours.
   - If the assay will not be completed within eight hours, refrigerate the samples at 2 to 8°C.
   - If the assay will not be completed within 48 hours, or for shipment of samples, freeze at -20°C or colder.
   - Thaw samples only once.

3. Use the following guidelines when preparing specimens:
   - Ensure residual fibrin and cellular matter has been removed prior to analysis.
   - Follow blood collection tube manufacturer's recommendations for centrifugation.
4. Each laboratory should determine the acceptability of its own blood collection tubes and serum separation products. Variations in these products may exist between manufacturers and, at times, from lot-to-lot.
5. Do not use heat-inactivated samples for this assay.

Materials Provided

R1 Access Total IgE Reagent Packs

Materials Required But Not Provided

1. Access Total IgE Calibrators
   Provided at zero and approximately 3, 15, 60, 240, 1000 and 3000 IU/mL (7, 36, 144, 576, 2400 and 7200 µg/L).
   Cat. No. 35005
2. Quality Control (QC) materials: commercial control material.
3. Access Substrate
   Cat. No. 81906
4. **Access, Access 2, SYNCHRON LXi:**
   Access Wash Buffer II, Cat. No. A16792
   UniCel DxI:
   UniCel DxI Wash Buffer II, Cat. No. A16793
5. Access Total IgE Calibrator S0
   Cat. No. 35006

Procedural Comments

1. Refer to the appropriate system manuals and/or Help system for a specific description of installation, start-up, principles of operation, system performance characteristics, operating instructions, calibration procedures, operational limitations and precautions, hazards, maintenance, and troubleshooting.
2. Mix contents of new (unpunctured) reagent packs by gently inverting pack several times before loading on the instrument. Do not invert open (punctured) packs.
3. Use ten (10) µL of sample for each determination in addition to the sample container and system dead volumes. Refer to the appropriate system manuals and/or Help system for the minimum sample volume required.
4. The system default unit of measure for sample results is IU/mL. To change sample reporting units to the International System of Units (SI units), µg/L, refer to the appropriate system manuals and/or Help system. To manually convert concentrations to the International System, multiply IU/mL by multiplication factor 2.4.

Procedure

Refer to the appropriate system manuals and/or Help system for information on managing samples, configuring tests, requesting tests, and reviewing test results.

Calibration Details

An active calibration curve is required for all tests. For the Access Total IgE assay, calibration is required every 28 days. Refer to the appropriate system manuals and/or Help system for information on calibration theory, configuring calibrators, calibrator test request entry, and reviewing calibration data.

Quality Control

Quality control materials simulate the characteristics of patient samples and are essential for monitoring the system performance of immunochemical assays. Because samples can be processed at any time in a "random access" format rather than a "batch" format, quality control materials should be included in each 24-hour time period.[19] Include commercially available quality control materials that cover at least two levels of analyte. More frequent use of controls

or the use of additional controls is left to the discretion of the user based on good laboratory practices or laboratory accreditation requirements and applicable laws. Follow manufacturer's instructions for reconstitution and storage. Each laboratory should establish mean values and acceptable ranges to assure proper performance. Quality control results that do not fall within acceptable ranges may indicate invalid test results. Examine all test results generated since obtaining the last acceptable quality control test point for this analyte. Refer to the appropriate system manuals and/or Help system for information about reviewing quality control results.

Results

Patient test results are determined automatically by the system software using a weighted four parameter logistic curve (4PLC) math model. The amount of analyte in the sample is determined from the measured light production by means of the stored calibration data. Patient test results can be reviewed using the appropriate screen. Refer to the appropriate system manuals and/or Help system for complete instructions on reviewing sample results.

Limitations of the Procedure

1. Samples can be accurately measured within the analytic range of the lower limit of detection and the highest calibrator value (approximately 0.25–3000 IU/mL [0.6–7200 µg/L]).
   - If a sample contains less than the lower limit of detection for the assay, report the results as less than that value (i.e., < 0.25 IU/mL [< 0.6 µg/L]).
   - If a sample contains more than the stated value of the highest Access Total IgE Calibrator (S6), report the result as greater than that value (i.e., > 3000 IU/mL [> 7200 µg/L]). Alternatively, dilute one volume of sample with nine volumes of Access Total IgE Calibrator S0 (zero), which is also available as Access Total IgE Calibrator S0 Cat. No. 35006. Refer to the appropriate system manuals and/or Help system for instructions on entering a sample dilution in a test request. The system reports the results adjusted for the dilution.
2. For assays employing antibodies, the possibility exists for interference by heterophile antibodies in the patient sample. Patients who have been regularly exposed to animals or have received immunotherapy or diagnostic procedures utilizing immunoglobulins or immunoglobulin fragments may produce antibodies, e.g. HAMA, that interfere with immunoassays. Additionally, other heterophile antibodies such as human anti-goat antibodies may be present in patient samples.[20,21]
   Such interfering antibodies may cause erroneous results. Carefully evaluate the results of patients suspected of having these antibodies.
3. The Access Total IgE results should be interpreted in light of the total clinical presentation of the patient, including: symptoms, clinical history, data from additional tests and other appropriate information.

Expected Values

1. Each laboratory should establish its own reference ranges to assure proper representation of specific populations.
2. Total IgE concentrations were measured in serum samples from 134 adult subjects (over 21 years of age) having no known history of allergy, using the Access Total IgE assay. The results were as follows.

n	Geometric Mean* (IU/mL)	2 SD Range* (IU/mL)	Arithmetic Mean (IU/mL)	95% Range** (IU/mL)
134	17.48	1.27–241.3	35.0	1.31–165.3

n	Geometric Mean* (µg/L)	2 SD Range* (µg/L)	Arithmetic Mean (µg/L)	95% Range** (µg/L)
134	42	3–579	84	3–397

* Logarithmic transformations

** Non-parametric estimate of 95% confidence interval

Specific Performance Characteristics

Methods Comparison

A comparison of 105 values using the Access Total IgE assay on the Access Immunoassay system and a commercially available enzyme immunoassay kit gave the following statistical data:

n	Range of Observations (IU/mL)	Intercept (IU/mL)	Slope	Correlation Coefficient (r)
105	1.42–2439.0	9.23	0.97	0.995

A comparison of 47 values obtained by assaying clinical samples of serum and plasma (heparin) using the Access Total IgE assay kit on the Access Immunoassay system gave the following statistical data:

n	Range of Observations (IU/mL)	Intercept (IU/mL)	Slope	Correlation Coefficient (r)
47	2.17–365.52	1.048	0.99	0.998

A comparison of 46 values obtained by assaying clinical samples of serum and plasma (EDTA) using the Access Total IgE assay kit on the Access Immunoassay system gave the following statistical data:

n	Range of Observations (IU/mL)	Intercept (IU/mL)	Slope	Correlation Coefficient (r)
46	2.17–365.52	-0.012	0.985	0.998

Dilution Recovery (Linearity)

Multiple gravimetric dilutions of two samples containing various IgE levels with Access Total IgE Calibrator S0 (zero) resulted in the following data:

Sample 1	Expected Concentration (IU/mL)	Determined Concentration (IU/mL)	Recovery (%)
Neat	N/A	2383.0	N/A
1/1.26	1891.3	1800.4	95.2
1/1.66	1435.5	1472.3	102.6
1/2.50	953.2	952.9	100.0
1/4.98	478.5	507.2	106.0
1/19.57	121.8	133.5	109.6
		Mean % Recovery	**102.7**

Sample 2	Expected Concentration (IU/mL)	Determined Concentration (IU/mL)	Recovery (%)
Neat	N/A	1417.9	N/A
1/1.25	1134.3	1089.0	96.0
1/1.68	844.0	847.0	100.4
1/2.54	558.2	540.0	96.7
1/4.98	284.7	284.7	100.0
1/19.96	71.0	74.1	104.4
		Mean % Recovery	**99.5**

Spiking Recovery

Addition of five different levels of IgE to two patient samples with low total IgE resulted in the following data:

Sample 1	Expected Concentration (IU/mL)	Determined Concentration (IU/mL)	Recovery (%)
Neat	N/A	9.5	N/A
Level 1	54.2	54.6	100.7
Level 2	187.6	195.4	104.2
Level 3	480.5	467.9	97.4
Level 4	1078.2	1159.0	107.5
Level 5	1694.3	1744.8	103.0
		Mean % Recovery	**102.6**

Sample 2	Expected Concentration (IU/mL)	Determined Concentration (IU/mL)	Recovery (%)
Neat	N/A	11.5	N/A
Level 1	91.2	95.1	104.3
Level 2	328.0	319.6	97.4
Level 3	638.3	585.8	91.8
Level 4	1240.9	1233.0	99.4
Level 5	1820.9	1945.0	106.8
		Mean % Recovery	**99.9**

Imprecision

This assay exhibits total imprecision of less than 10% across the assay range. One study, using commercially available human serum based control material generating two assays per day, two replicates per assay, for 10 days, provides the following data, analyzed via analysis of variance. (ANOVA).[22,23]

Sample	Grand Mean (n=40) (IU/mL)	Within Run (%CV)	Total Imprecision (%CV)
Low	21.2	3.3	3.6
Medium	57.8	3.7	4.5
High	229.0	4.2	4.7

Analytical Specificity/Interferences

Samples containing up to 10 mg/dL (171 µmol/L) bilirubin, lipemic samples containing the equivalent of 1800 mg/dL (20.32 mmol/L) triolein, and hemolyzed samples containing up to 1000 mg/dL (10 g/L) hemoglobin do not affect the concentration of IgE assayed.

In addition, samples ranging from 5–9 g/dL (50–90 g/L) albumin do not affect the concentration of IgE assayed.

Cross-reactivity was evaluated by testing neat IgA, IgG, IgM, and IgD myeloma sera in the Access Total IgE assay. When available, both kappa and lambda light chain myelomas were utilized. IgE concentration and percent cross-reactivity columns describe data obtained from the samples with the maximum concentration of myeloma protein tested.

Immunoglobulin Class	Number of Samples Tested	Maximum Concentration of Myeloma Protein Tested (mg/dL)	IgE Concentration (IU/mL)	Cross-reactivity (%)
IgA	2	4750	1.13	5.8×10^{-6}
IgG	3	6747	0.22	8.0×10^{-7}
IgM	2	2432	6.48	6.5×10^{-5}
IgD	1	1020	3.08	7.3×10^{-5}

Analytical Sensitivity

The lowest detectable level of IgE distinguishable from zero (Access Total IgE Calibrator S0) with 95% confidence is 0.25 IU/mL (0.6 µg/L). This value is determined by processing a complete seven point calibration curve, controls, and ten replicates of the zero calibrator in multiple assays. The analytical sensitivity value is interpolated from the curve at the point that is two standard deviations from the mean measured zero calibrator signal.

Access
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TOTAL IgE CALIBRATORS
REF 35005

Intended Use

The Access Total IgE Calibrators are intended to calibrate the Access Total IgE assay for the quantitative determination of total IgE levels in human serum and plasma (heparin, EDTA) using the Access Immunoassay Systems.

Summary and Explanation

Quantitative assay calibration is the process by which samples with known analyte concentrations (i.e., assay calibrators) are tested like patient samples to measure the response. The mathematical relationship between the measured responses and the known analyte concentrations establishes the calibration curve. This mathematical relationship, or calibration curve, is used to convert RLU (Relative Light Unit) measurements of patient samples to specific quantitative analyte concentrations.

Traceability

The measurand (analyte) in the Access Total IgE Calibrators is traceable to the WHO 2nd International Reference Preparation for Immunoglobulin E (IgE) 75/502.[4] Traceability process is based on EN ISO 17511.

The assigned values were established using representative samples from this lot of calibrator and are specific to the assay methodologies of the Access reagents. Values assigned by other methodologies may be different. Such differences, if present, may be caused by inter-method bias.

Product Information

Access Total IgE Calibrators

Cat. No. 35005: S0, 6.0 mL/vial; S1–S6, 4.0 mL/vial

- Provided ready to use.
- Store upright and refrigerate at 2 to 10°C.
- Mix contents by gently inverting before use. Avoid bubble formation.
- Stable until the expiration date stated on the label when stored at 2 to 10°C.
- Signs of possible deterioration are control values out of range.
- Refer to calibration card for exact concentrations.

S0:	Equine serum with < 0.1% sodium azide, and 0.5% ProClin** 300. Contains 0.0 IU/mL (µg/L) IgE.
S1, S2, S3, S4, S5, S6:	Human IgE in equine serum at levels of approximately 3, 15, 60, 240, 1000 and 3000 IU/mL (7, 36, 144, 576, 2400 and 7200 µg/L), respectively, with < 0.1% sodium azide, and 0.5% ProClin 300.
Calibration Card:	1

Warnings and Precautions

- For *in vitro* diagnostic use.
- Human source material used in the preparation of the reagent has been tested and found negative or non-reactive for Hepatitis B, Hepatitis C (HCV), and Human Immunodeficiency Virus (HIV-1 and HIV-2). Because no known test method can offer complete assurance that infectious agents are absent, handle reagents and patient samples as if capable of transmitting infectious disease.[24]
- Sodium azide may react with lead and copper plumbing to form highly explosive metal azides. On disposal of liquids, flush with a large volume of water to prevent azide build-up.[17]
- Xi. Irritant: 0.5% ProClin 300.

R 43: May cause sensitization by skin contact.

S 28–37: After contact with skin, wash immediately with plenty of soap and water. Wear suitable gloves.

- The Material Safety Data Sheet (MSDS) is available upon request.

Procedure

Refer to the appropriate system manuals and/or Help system for information on calibration theory, configuring calibrators, calibrator test request entry, and reviewing calibration data.

Calibration Details

The Access Total IgE Calibrators are provided at seven levels - zero and approximately 3, 15, 60, 240, 1000 and 3000 IU/mL. The calibrators are prepared gravimetrically from human IgE and normal equine serum. Assay calibration data are valid up to 28 days.

Calibrators run in duplicate.

Limitations of the Procedure

If there is evidence of microbial contamination or excessive turbidity in a reagent, discard the vial.

Access
Immunoassay Systems

TOTAL IgE CALIBRATOR S0
REF 35006

Intended Use

The Access Total IgE Calibrator S0 is intended for use with the Access Total IgE assay to dilute patient samples containing analyte concentrations greater than the analyte specific S6 calibrator.

Summary and Explanation

The analyte level in patient samples may exceed the level of the specific S6 calibrator. If a quantitative value is required, it will be necessary to dilute the samples in order to determine the analyte concentration.

Product Information

Access Total IgE Calibrator S0

Cat. No. 35006: 6.0 mL/vial

- Provided ready to use.
- Store upright and refrigerate at 2 to 10°C.
- Mix contents by gently inverting before use. Avoid bubble formation.
- Stable until the expiration date stated on the label when stored at 2 to 10°C.

S0:	Equine serum with < 0.1% sodium azide, and 0.5% ProClin** 300. Contains 0.0 IU/mL (µg/L) IgE.

Warnings and Precautions

- For *in vitro* diagnostic use.
- Human source material used in the preparation of the reagent has been tested and found negative or non-reactive for Hepatitis B, Hepatitis C (HCV), and Human Immunodeficiency Virus (HIV-1 and HIV-2). Because no known test method can offer complete assurance that infectious agents are absent, handle reagents and patient samples as if capable of transmitting infectious disease.[24]
- Sodium azide may react with lead and copper plumbing to form highly explosive metal azides. On disposal of liquids, flush with a large volume of water to prevent azide build-up.[17]
- Xi. Irritant: 0.5% ProClin 300.

R 43: May cause sensitization by skin contact.

S 28-37: After contact with skin, wash immediately with plenty of soap and water. Wear suitable gloves.

- The Material Safety Data Sheet (MSDS) is available upon request.

Procedure

Samples can be accurately measured within the analytic range of the lower limit of detection and the highest calibrator value of the specific assay. If a sample contains more analyte than the stated value of the S6 calibrator, dilute the sample following dilution instructions in the labeling under "Limitations of the Procedure" in the reagent pack section. Refer to the appropriate system manuals and/or Help system for instructions on how to enter a sample dilution in a test request.

Limitations of the Procedure

If there is evidence of microbial contamination or excessive turbidity in the reagent, discard the vial.

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