

QUANTA Lite™ ASCA (*S. cerevisiae*) IgG 708865

For *In Vitro* Diagnostic Use

CLIA Complexity: High

Intended Use

QUANTA Lite™ ASCA (*S. cerevisiae*) IgG is an enzyme-linked immunosorbent assay (ELISA) for the semi-quantitative detection of anti-*Saccharomyces cerevisiae* antibodies (ASCA) of the IgG class in human serum. The presence of ASCA (*S. cerevisiae*) IgG antibodies, used in conjunction with clinical findings and other laboratory tests, may aid in the diagnosis of patients with Crohn's disease.

Summary and Explanation of the test

Inflammatory bowel disease (IBD) is a general term used to describe diseases that cause inflammation of the intestines. Crohn's disease (CD) and ulcerative colitis (UC) are the two major IBDs. In Crohn's disease, inflammation usually occurs in the lower part of the small intestine (distal ileum), but may affect any part of the digestive tract. The inflammation in Crohn's disease extends deep into the affected tissue, in contrast to ulcerative colitis, which causes inflammation and ulcers in the top layers of the lining of the colon and rectum. Inflammation in Crohn's disease is asymmetrical and segmental, with areas of both healthy and diseased tissue, in contrast to ulcerative colitis where inflammation is symmetrical and uninterrupted from the rectum proximally.¹⁻³

Both Crohn's disease and ulcerative colitis are chronic, they affect men and women approximately equally, and they are most common in northern Europe and North America. Approximately 20% of individuals with Crohn's disease have a blood relative with some form of IBD. The age of onset of Crohn's disease is usually around the ages of 15-30 and a second smaller peak of incidence between the ages of 50-70. Over the past decade, several reports have noted an increase in the prevalence of Crohn's disease in various geographic regions.⁴⁻⁷ Although there are many theories concerning the cause of Crohn's disease and ulcerative colitis, none have been proven. Since many of the symptoms of Crohn's disease and ulcerative colitis are similar, diagnosis is often difficult, time consuming, and invasive.¹⁻³ Approximately 10-12% of cases are not initially classifiable and are referred to as "indeterminate colitis." Over time, about half of these patients are eventually classified as CD or UC.⁸⁻¹⁰

Anti-*Saccharomyces cerevisiae* antibodies (ASCA) have been found to be significantly more prevalent in patients with Crohn's disease compared to patients with ulcerative colitis or healthy controls.⁸⁻¹⁴ These antibodies, which can include antibodies of both the IgG and IgA classes, appear to be directed against mannose sequences in the cell wall mannan of *Saccharomyces cerevisiae*.¹⁴⁻¹⁶ The presence of IgG or IgA ASCA have been shown to have a high specificity for Crohn's disease. A recent report found the presence of both IgG and IgA ASCA was 100% specific for Crohn's disease.⁸ Detection of ASCA may be of value in differentiating Crohn's disease from ulcerative colitis in some patients.⁸⁻¹⁰

A subgroup of Crohn's disease patients do not appear to have ASCA antibodies. Whether these individuals form a subgroup of patients with specific clinical characteristics is unknown at present.

Principles of the Procedure

Partially purified and disrupted *S. cerevisiae* antigen is bound to the wells of a polystyrene microwell plate under conditions that will preserve the antigen in its native state. Pre-diluted controls and diluted patient sera are added to separate wells, allowing any ASCA IgG antibodies present to bind to the immobilized antigen. Unbound sample is washed away and an enzyme labeled anti-human IgG conjugate is added to each well. A second incubation allows the enzyme labeled anti-human IgG to bind to any patient antibodies, which have become attached to the microwells. After washing away any unbound enzyme labeled anti-human IgG, the remaining enzyme activity is measured by adding a chromogenic substrate and measuring the intensity of the color that develops. The assay can be evaluated spectrophotometrically by measuring and comparing the color intensity that develops in the patient wells with the color in the control wells.

Reagents

1. Polystyrene microwell ELISA plate coated with a partially purified *S. cerevisiae* antigen (12-1 x 8 wells), with holder in foil package containing desiccants
2. ELISA Negative Control, 1 vial of buffer containing preservative and human serum with no human antibodies to *S. cerevisiae*, prediluted, 1.2mL
3. ASCA IgG ELISA Low Positive, 1 vial of buffer containing preservative and human serum antibodies to *S. cerevisiae*, prediluted, 1.2mL
4. ASCA IgG ELISA High Positive, 1 vial of buffer containing preservative and human serum antibodies to *S. cerevisiae*, prediluted, 1.2mL
5. HRP Sample Diluent, 1 vial – colored pink containing Tris-buffered saline, Tween 20, protein stabilizers and preservative, 50mL
6. HRP Wash Concentrate, 1 vial of 40x concentrate - colored red containing Tris-buffered saline and Tween 20, 25mL. Refer to the Methods Section for dilution instructions.
7. HRP IgG Conjugate, (goat), anti-human IgG, 1 vial – colored blue containing buffer, protein stabilizers and preservative, 10mL
8. TMB Chromogen, 1 vial containing stabilizers, 10mL
9. HRP Stop Solution, 0.344M Sulfuric Acid, 1 vial – colorless, 10mL

Warnings

1. **WARNING:** This product contains a chemical (0.02% chloramphenicol) in the sample diluent, controls, and conjugate known to the State of California to cause cancer.
2. All human source material used in the preparation of controls for this product has been tested and found negative for antibody to HIV, HbsAg, and HCV by FDA cleared methods. No test method however can offer complete assurance that HIV, HBV, HCV or other infectious agents are absent. Therefore, the ASCA IgG ELISA Low Positive, ASCA IgG ELISA High Positive and ELISA Negative Control should be handled in the same manner as potentially infectious material.¹⁷
3. Sodium Azide is used as a preservative. Sodium Azide is a poison and may be toxic if ingested or absorbed through the skin or eyes. Sodium azide may react with lead or copper plumbing to form potentially explosive metal azides. Flush sinks, if used for reagent disposal, with large volumes of water to prevent azide build-up.
4. The HRP conjugate contains a dilute poisonous/corrosive chemical, which may be toxic if ingested in large amounts. To prevent possible chemical burns, avoid contact with skin and eyes.
5. TMB Chromogen contains an irritant, which may be harmful if inhaled, ingested or absorbed through the skin. To prevent injury, avoid inhalation, ingestion or contact with skin and eyes.
6. The HRP Stop Solution consists of a dilute sulfuric acid solution. Avoid exposure to bases, metals, or other compounds, which may react with acids. Sulfuric acid is a poison and corrosive, which may be toxic if ingested. To prevent chemical burns, avoid contact with skin and eyes.
7. Use appropriate personal protective equipment while working with the reagents provided.
8. Spilled reagents should be cleaned up immediately. Observe all federal, state and local environmental regulations when disposing of wastes.

Precautions

1. This product is for *In Vitro* Diagnostic Use.
2. Substitution of components other than those provided in this system may lead to inconsistent results.
3. Incomplete or inefficient washing and insufficient liquid removal from the ELISA well strips will cause poor precision and/or high background.
4. Adaptation of this assay for use with automated sample processors and other liquid handling devices, in whole or in part, may yield differences in test results from those obtained using the manual procedure. It is the responsibility of each laboratory to validate that their automated procedure yields test results within acceptable limits.
5. A variety of factors influence the assay performance. These include the starting temperature of the reagents, the ambient temperature, the accuracy and reproducibility of the pipetting technique, the thoroughness of washing and liquid removal from the wells of the ELISA strips, the photometer used to measure the results, and the length of the incubation times during the assay. Careful attention to consistency is required to obtain accurate and reproducible results.
6. Strict adherence to the protocol is recommended.
7. Incomplete resealing of the zip-lock pouch containing microwell strips and desiccants will result in antigen degradation and poor precision.
8. Unacceptably low absorbencies may be observed following **two** or more uses from a single bottle of HRP conjugate over a period of time. It is important to follow all recommended HRP conjugate handling procedures to prevent this occurrence.
9. Chemical contamination of the HRP conjugate can result from improper cleaning or rinsing of equipment or instruments. Residues from common laboratory chemicals such as formalin, bleach, ethanol or detergent will cause degradation of the HRP conjugate over time. Thoroughly rinse all equipment or instruments after the use of chemical cleaners/disinfectants.

Storage Conditions

1. Store all the kit reagents at 2-8°C. Do not freeze. Reagents are stable until the expiration date when stored and handled as directed.
2. Unused antigen coated microwell strips should be resealed securely in the foil pouch containing desiccants and stored at 2-8°C.
3. Diluted wash buffer is stable for 1 week at 2-8°C.

Specimen Collection

This procedure should be performed with a serum specimen. Addition of azide or other preservatives to the test samples may adversely affect the results. Microbially contaminated, heat-treated, or specimens containing visible particulate should not be used. Grossly hemolyzed or lipemic serum or specimens should be avoided.

Following collection, the serum should be separated from the clot. NCCLS Document H18-A2 recommends the following storage conditions for samples: 1) Store samples at room temperature no longer than 8 hours. 2) If the assay will not be completed within 8 hours, refrigerate the sample at 2-8°C. 3) If the assay will not be completed within 48 hrs, or for shipment of the sample, freeze at -20°C or lower. Frozen specimens must be mixed well after thawing and prior to testing.

Procedure

Materials provided

- 1 ASCA IgG ELISA microwell plate (12-1 x 8 wells), with holder
- 1 1.2mL prediluted ELISA Negative Control

- 1 1.2mL prediluted ASCA IgG ELISA Low Positive
- 1 1.2mL prediluted ASCA IgG ELISA High Positive
- 1 50mL HRP Sample Diluent
- 1 25mL HRP Wash Concentrate, 40x concentrate
- 1 10mL HRP IgG Conjugate, (goat), anti-human IgG
- 1 10mL TMB Chromogen
- 1 10mL HRP Stop Solution, 0.344M Sulfuric Acid

Additional Materials Required But Not Provided

Micropipets to deliver 5, 100, 200-300 and 500µL

Disposable micropipet tips

Test tubes for patient sample dilutions, 4mL volume

Distilled or deionized water

1L container for diluted HRP Wash Concentrate

Microwell plate reader capable of measuring OD at 450nm (and 620nm for dual wavelength readings)

Method

Before you start

1. Bring all reagents and samples to room temperature (20-26°C) and mix well.
2. Dilute the HRP Wash Concentrate 1:40 by adding the contents of the HRP Wash Concentrate bottle to 975mL of distilled or deionized water. If the entire plate will not be run within this period, a smaller quantity can be prepared by adding 2.0mL of the concentrate to 78mL of distilled or deionized water for every 16 wells that will be used. The diluted buffer is stable for 1 week at 2-8°C.
3. Prepare a 1:101 dilution of each patient sample by adding 5µL of sample to 500µL of HRP Sample Diluent. Diluted samples must be used within 8 hours of preparation. **DO NOT DILUTE** the ASCA IgG ELISA Low Positive, ASCA IgG ELISA High Positive and ELISA Negative Control.
4. Determination of the presence or absence of ASCA IgG using arbitrary units requires two wells for each of the three controls and one or two wells for each patient sample. It is recommended that samples be run in duplicate.

Assay procedure

1. **ALL REAGENTS MUST BE BROUGHT TO ROOM TEMPERATURE (20-26°C) PRIOR TO BEGINNING THE ASSAY.** Place the required number of microwells/strips in the holder. **Immediately return unused strips to the pouch containing desiccants and seal securely to minimize exposure to water vapor.**
2. Add 100µL of the **prediluted** ASCA IgG ELISA Low Positive, the ASCA IgG ELISA High Positive, the ELISA Negative Control and the diluted patient samples to the wells. Cover the wells and incubate for 30 minutes at room temperature on a level surface. The incubation time begins after the last sample addition.
3. Wash step: Thoroughly aspirate the contents of each well. Add 200-300µL of the **diluted** HRP Wash buffer to all wells then aspirate. Repeat this sequence twice more for a total of three washes. Invert the plate and tap it on absorbent material to remove any residual fluid after the last wash. It is important to completely empty each well after each washing step. Maintain the same sequence for the aspiration as was used for the sample addition.
4. Add 100µL of the HRP IgG Conjugate to each well. Conjugate should be removed from the bottles using standard aseptic conditions and good laboratory techniques. Remove only the amount of conjugate from the bottle necessary for the assay. **TO AVOID POTENTIAL MICROBIAL AND/OR CHEMICAL CONTAMINATION, NEVER RETURN UNUSED CONJUGATE TO THE BOTTLE.** Incubate the wells for 30 minutes as in step 2.
5. Wash step: Repeat step 3.
6. Add 100µL of TMB Chromogen to each well and incubate **in the dark** for 30 minutes at room temperature.
7. Add 100µL of HRP Stop Solution to each well. Maintain the same sequence and timing of HRP Stop Solution addition as was used for the TMB Chromogen. Gently tap the plate with a finger to thoroughly mix the wells.
8. Read the absorbance (OD) of each well at 450nm within one hour of stopping the reaction. If bichromatic measurements are desired, 620nm can be used as a reference wavelength.

Quality Control

1. The ASCA IgG ELISA Low Positive, the ASCA IgG ELISA High Positive and the ELISA Negative Control should be run with every batch of samples to ensure that all reagents and procedures perform properly.
2. Note that since the ASCA IgG ELISA Low Positive, the ASCA IgG ELISA High Positive and the ELISA Negative Control are prediluted, they do not control for procedural methods associated with dilution of specimens.
3. Additional controls may be tested according to guidelines or requirements of local, state and/or federal regulations or accrediting organizations. Additional suitable control sera may be prepared by aliquoting pooled human serum specimens and storing at $\leq -20^{\circ}\text{C}$.
4. In order for the test results to be considered valid, all of the criteria listed below must be met. If any of these are not met, the test should be considered invalid and the assay repeated.
 - a. The absorbance of the prediluted ASCA IgG ELISA High Positive must be greater than the absorbance of the prediluted ASCA IgG ELISA Low Positive, which must be greater than the

- absorbance of the prediluted ELISA Negative Control.
- b. The prediluted ASCA IgG ELISA High Positive must have an absorbance greater than 1.0 while the prediluted ELISA Negative Control absorbance cannot be over 0.2.
 - c. The ASCA IgG ELISA Low Positive absorbance must be more than twice the ELISA Negative Control or over 0.25.
 - d. The ELISA Negative Control and ASCA IgG ELISA High Positive are intended to monitor for substantial reagent failure. The ASCA IgG ELISA High Positive will not ensure precision at the assay cutoff.
 - e. The user should refer to NCCLS Document C24-A for additional guidance on appropriate QC practices.¹⁸

Calculation of Results

The average OD for each set of duplicates is first determined. The reactivity for each sample can then be calculated by dividing the average OD of the sample by the average OD of the ASCA IgG ELISA Low Positive. The result is multiplied by the number of units assigned to the ASCA IgG ELISA Low Positive found on the label.

$$\text{Sample Value (units)} = \frac{\text{Sample OD}}{\text{ASCA IgG ELISA Low Positive OD}} \times \text{ASCA IgG ELISA Low Positive (units)}$$

Reactivity is related to the quantity of antibody present in a non-linear fashion. While increases and decreases in patient antibody concentrations will be reflected in a corresponding rise or fall in reactivity, the change is not proportional (i.e. a doubling of the antibody concentration will not double the reactivity). If a more accurate quantitation of patient antibody is required, serial dilutions of the patient sample should be run and the last dilution to measure positive in the assay should be reported as the patient's antibody titer.

Interpretation of Results

The ELISA assay is very sensitive to technique and is capable of detecting even small differences in patient populations. The values shown below are suggested values only. Each laboratory should establish its own normal range based upon its own techniques, controls, equipment and patient population according to their own established procedures.

The sample can then be classified as negative (for IgG antibody to *S. cerevisiae*), equivocal, or positive (IgG antibody to *S. cerevisiae* detected) according to the table below:

Negative	Units 0.0 - 20.0
Equivocal	20.1 - 24.9
Positive	≥25

Equivocal specimens should be retested before results are reported.

1. A positive result indicates the presence of ASCA IgG antibodies and suggests the possibility Crohn's disease.
2. A specimen with equivocal levels of ASCA IgG cannot be assessed for antibody status. If the results remain equivocal after repeat testing, the result should be reported as equivocal and/or an additional sample should be taken.
3. A negative result indicates no ASCA IgG antibody or levels below the negative cut-off of the assay.
4. It is suggested that the results reported by the laboratory should include the statement: "The following results were obtained with the INOVA QUANTA Lite™ ASCA (*S. cerevisiae*) IgG ELISA. ASCA IgG values obtained with different manufacturers' assay methods may not be used interchangeably. The magnitude of the reported IgG levels cannot be correlated to an endpoint titer."

Limitations of the Procedure

1. The presence of immune complexes or other immunoglobulin aggregates in the patient sample may cause an increased level of non-specific binding and produce false positives in this assay.
2. A negative ASCA IgG result does not rule out the presence of Crohn's disease.
3. A negative ASCA IgG antibody result does not rule out the presence of ASCA antibodies, because the concentration of antibody may be below the detection limit of the assay.
4. A positive test result only indicates the presence of antibody to *S. cerevisiae* and does not necessarily indicate the presence of Crohn's disease.
5. The assay performance characteristics have not been established for matrices other than serum.
6. The assay performance have not been established for pediatric Crohn's disease or ulcerative colitis patients.
7. Results of this assay should be used in conjunction with clinical findings and other serological tests.

Expected Values

The prevalence of Crohn's disease is estimated from 10 to 198 people/100,000 and appears to be increasing^{4,7}. Crohn's disease is most common in northern Europe and North American populations. It affects men and women approximately equally.

Normal Range

A combined panel of 501 specimens collected from asymptomatic, healthy individuals in California, New York, Austria, Luxembourg and Belgium was tested with the QUANTA Lite™ ASCA IgG ELISA kit. The age of the population ranged from 1 to 75 years old. For the 5 regional populations, the apparent specificity

ranged from 92 to 100% (mean 95.2%). None (0/501) of the specimens were positive for both ASCA IgG and ASCA IgA antibodies. The specificity of the ASCA IgG assay, including all non-Crohn's disease specimens (healthy controls plus disease state sera), was 93.2% (663/711).

Relative Sensitivity and Specificity

Clinically-defined specimens from Crohn's disease, ulcerative colitis, and healthy patients were tested by the QUANTA Lite™ ASCA IgG kit. Of 102 patients which were positive for both ASCA IgG and IgA antibodies, all but 2 were known Crohn's disease patients. None of the normal controls and only 2 of the ulcerative colitis specimens were both ASCA IgG and IgA positive. The age ranges for the Crohn's disease and ulcerative colitis clinical groups was 17-64 and 19-71 years old respectively.

QUANTA Lite™ ASCA ELISA RESULTS

Clinical Group	N=	IgG Pos	IgA Pos	IgG or IgA Pos	IgG and IgA Pos
Crohn's disease	215	74.4% (157/211)	49.0 (103/210)	76.2% (160/210)	47.6% (100/210)
Ulcerative colitis	161	14.2% (22/156)	1.9% (3/158)	14.6% (23/156)	1.3% (2/156)
Healthy controls	148	4.1% (6/145)	1.4% (2/147)	5.6% (8/144)	0% (0/144)

Note: equivocal results excluded from calculations.

Cross-reactivity Study

Sera from 75 patients with autoimmune or infectious disease antibodies and various clinical conditions were tested for cross-reactivity with the QUANTA Lite™ ASCA (*S. cerevisiae*) IgG ELISA. The results summarized below contain combined data from several clinical sites.

Specimen Type	n=	ASCA IgG Positive
Gliadin IgA pos.	12	0
Gliadin IgG pos.	8	2 (25%)
Transglutaminase IgA	7	0
Antinuclear antibody (ANA) pos	8	0
Autoimmune hepatitis (AIH), type1	15	1 (6.6%)
H. pylori positive	10	0
Alcoholic cirrhosis ascites	1	0
Alcoholic hepatitis	2	2 (100%)
Chronic hepatitis C	6	1 (16.7%)
Chronic liver disease	2	0
Granulomatous hepatitis.s/pBCG immuno rx blad.cancer	1	1 (100%)
Hepatitis NOS	1	0
Non-infectious gastroenteritis	1	0
Esophageal varices with bleeding	1	0

Precision and Reproducibility

Intra-assay performance for QUANTA Lite™ ASCA (*S. cerevisiae*) IgG ELISA was evaluated by testing 6 specimens a total of 15 times each.

	Spec.A	Spec.B	Spec.C	Spec.D	Spec.E	Spec.F
Mean (Units)	75.6	13.1	116.6	29.9	10.4	44.8
SD	2.8	0.7	3.0	1.2	0.5	1.7
CV%	3.7	5.2	2.6	4.1	4.5	3.8

Inter-assay variation was assessed by testing, in duplicate, a panel of 8 specimens twice daily for 3 days.

	Spec.1	Spec.2	Spec.3	Spec.4	Spec.5	Spec.6	Spec.7	Spec.8
Mean (Units)	47.7	11.7	123.5	38.8	49.3	117.7	14.9	6.6
SD	1.4	0.4	6.7	1.4	1.2	5.8	0.4	0.3
CV%	3.0	3.5	5.4	3.6	2.4	4.9	2.6	5.0

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