

For *In Vitro* Diagnostic Use

CLIA Complexity: High

Intended Use

The QUANTA Lite™ Celiac DGP Screen is an enzyme-linked immunosorbent assay (ELISA) for the semi-quantitative detection of IgA and IgG antibodies to synthetic, deamidated gliadin-derived peptides in human serum. The presence of these deamidated peptide antibodies can be used in conjunction with clinical findings and other laboratory tests to aid in the diagnosis of both IgA sufficient and IgA deficient celiac disease as well as dermatitis herpetiformis.

Summary and Explanation of the Test

Celiac disease or gluten sensitive enteropathy is a chronic condition whose main features include inflammation and characteristic histologic “flattening” of intestinal mucosa resulting in a malabsorption syndrome. The exact etiology of the disease remains unknown but gliadin, or the alcohol soluble fraction of wheat gluten is clearly the toxic agent.¹

Originally, a series of multiple intestinal biopsies were used to diagnose celiac disease and related disorders. More recently, serological testing has been suggested for screening patients with suspected gluten sensitive enteropathy as well as for monitoring dietary compliance.²⁻⁵ The European Society of Pediatric Gastroenterology and Nutrition (ESPGAN) has recommended use of serological markers such as gliadin as well as reticulin and endomysial antibodies to reduce the number of intestinal biopsies needed to make a diagnosis.⁶

Recent work has revealed that gliadin reactive antibodies from celiac patients bind a very limited number of specific epitopes on the gliadin molecule.^{7,8} These same studies further reveal that selective deamidation of gliadin by the celiac-associated enzyme, tissue transglutaminase, results in enhanced binding by anti-gliadin antibodies. Based on the above observations, assays using deamidated and defined peptides have been shown to have higher diagnostic accuracy for celiac disease when compared to standard anti-gliadin and tTG assays.^{9, 10, 11}

Both gliadin IgA and IgG antibodies are detected in sera of patients with gluten sensitive enteropathy.^{2,3} A sensitive screening strategy for at risk populations includes testing for both IgG and IgA antibodies as a significant proportion of celiac patients are IgA deficient.¹² Gliadin IgA antibodies are of interest for following disease activity over time and for monitoring adherence to a gluten-free diet.⁵

Dermatitis Herpetiformis (DH) is a skin disease that, as with celiac disease, is caused by ingestion of wheat protein. A majority of patients with DH have jejunal villous atrophy identical to that found in celiac disease and strict gluten-free diet improves both gut and skin lesions.^{13, 14} Current serological methods such as the EMA and tTG assays exhibit disappointing performance when testing for DH, with sensitivities ranging from only 60-75%^{15, 16} compared with the 95% and higher sensitivities reported for celiac disease.

The QUANTA Lite™ Celiac DGP Screen is an improved performance test for the simultaneous detection of both IgA and IgG antibodies to a selectively deamidated, synthetic peptide derived from the wheat protein gliadin and as such allows for the detection of celiac disease even with coexistent IgA deficiency.

Principles of the Procedure

Purified synthetic gliadin peptides are 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 gliadin peptide IgA or IgG antibodies present to bind to the immobilized antigen. Unbound sample is washed away and an enzyme labeled anti-human IgA and IgG conjugate is added to each well. A second incubation allows the enzyme labeled anti-human IgA and/or IgG to bind to any patient antibodies, which have become attached to the microwells. After washing away any unbound enzyme labeled anti-human IgA and/or 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 purified gliadin peptides (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 IgA or IgG antibodies to gliadin peptides, prediluted ready to use, 1.2mL
3. Celiac DGP Screen ELISA Low Positive, 1 vial of buffer containing preservative and human serum IgA and IgG antibodies to gliadin peptides, prediluted ready to use, 1.2mL
4. Celiac DGP Screen ELISA High Positive, 1 vial of buffer containing preservative and human serum IgA and IgG antibodies to gliadin peptides, prediluted ready to use, 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 Ig G/A Conjugate, (goat), anti-human IgG and IgA, 1 vial – colorless 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 Celiac DGP Screen ELISA Low Positive, Celiac DGP Screen 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. CLSI (NCCLS) Document H18-A3 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.¹⁸

Procedure

Materials provided

- 1 Celiac DGP Screen ELISA microwell plate (12-1 x 8 wells), with holder
- 1 1.2mL prediluted ELISA Negative Control
- 1 1.2mL prediluted Celiac DGP Screen ELISA Low Positive
- 1 1.2mL prediluted Celiac DGP Screen ELISA High Positive

- 1 50mL HRP Sample Diluent
- 1 25mL HRP Wash Concentrate, 40x concentrate
- 1 10mL HRP Ig G/A Conjugate, (goat), anti-human IgG and IgA
- 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 Celiac DGP Screen ELISA Low Positive, Celiac DGP Screen ELISA High Positive and ELISA Negative Control.
4. Determination of the presence or absence of gliadin IgA and/or 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** Celiac DGP Screen ELISA Low Positive, the Celiac DGP Screen 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 Ig G/A 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 Celiac DGP Screen ELISA Low Positive, the Celiac DGP Screen 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 Celiac DGP Screen ELISA Low Positive, the Celiac DGP Screen 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 Celiac DGP Screen ELISA High Positive must be greater than the absorbance of the prediluted Celiac DGP Screen ELISA Low Positive, which must be greater than the absorbance of the prediluted ELISA Negative Control.
 - b. The prediluted Celiac DGP Screen ELISA High Positive must have an absorbance greater

- c. than 1.0 while the prediluted ELISA Negative Control absorbance cannot be over 0.2.
- d. The Celiac DGP Screen ELISA Low Positive absorbance must be more than twice the ELISA Negative Control or over 0.25.
- e. The ELISA Negative Control and Celiac DGP Screen ELISA High Positive are intended to monitor for substantial reagent failure. The Celiac DGP Screen ELISA High Positive will not ensure precision at the assay cutoff.
- f. The user should refer to CLSI (NCCLS) Document C24-A2 for additional guidance on appropriate QC practices.¹⁹

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 Celiac DGP Screen ELISA Low Positive. The result is multiplied by the number of units assigned to the Celiac DGP Screen ELISA Low Positive found on the label.

$$\text{Sample Value (units)} = \frac{\text{Sample OD}}{\text{Celiac DGP Screen ELISA Low Positive OD}} \times \text{Celiac DGP Screen ELISA Low Positive (units)}$$

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).

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, weak positive, moderate positive to strong positive according to the table below.

	Units
Negative	<20
Weak Positive	20 – 30
Moderate Positive to Strong Positive	>30

1. A positive result indicates the presence of gliadin IgA and/or IgG antibodies and suggests the possibility of certain gluten sensitive enteropathies such as celiac disease and dermatitis herpetiformis.
2. A negative result indicates no gliadin IgA or IgG antibodies or levels below the negative cut-off of the assay.
3. It is suggested that the results reported by the laboratory should include the statement: “The following results were obtained with the INOVA QUANTA Lite™ Celiac DGP Screen. Gliadin IgA and/or IgG values obtained with different manufacturers’ assay methods may not be used interchangeably. The magnitude of the reported antibody levels cannot be correlated to an endpoint titer.”

Limitations of the Procedure

1. A negative result in an untreated patient does not totally rule out gluten-sensitive enteropathy. Negative samples can be retested for other celiac related antibodies such as endomysial (EMA) or tissue transglutaminase (tTG).
2. In treated patients known to express IgA antibodies, gliadin IgA antibody levels represent a better indicator of dietary compliance than gliadin IgG antibody concentrations.⁵
3. False positives (high antibody levels without characteristic histological findings) are possible. Rarely, other gastrointestinal disorders and normal samples can have antibody reacting with the DGP antigen.
4. The association between dermatitis herpetiformis and gluten-sensitive enteropathy is so strong that it has been suggested that both diseases have the same etiology; in these patients, DGP antibody determination is useful to detect asymptomatic celiac disease and to estimate the severity of the gastrointestinal involvement.^{13,14}
5. This test simultaneously detects both IgA and IgG antibodies. If individual determination of specific IgA or IgG antibodies is preferred, INOVA provides separate IgA and IgG ELISA kits (QUANTA Lite™ Gliadin IgA II and QUANTA Lite™ Gliadin IgG II) for this purpose.
6. Results of this assay should be used in conjunction with clinical findings and other serological tests.
7. The assay performance characteristics have not been established for matrices other than serum.

Expected Values

The ability of the QUANTA Lite™ Celiac DGP Screen to detect gliadin IgG and IgA antibodies was evaluated by comparison with QUANTA Lite™ Gliadin IgA II and QUANTA Lite™ Gliadin IgG II ELISAs.

Normal Range

Four hundred and ninety-seven random asymptomatic, healthy individuals residing in the USA were tested for antibodies to DGP. Of these, three hundred of the donors were known to range in age from 14 to 78 and they included an equal number of males and females. Four samples (0.8%) were above the 20-unit cutoff. Two were weak positives with values of 20.1 and 20.2 units and one was a moderate positive with a value of

46.6 units. The fourth positive, at 25.4 units, is believed to be a true celiac due to the fact the sample was also strongly positive for IgA antibodies to tissue transglutaminase (57 units). The mean value of the 497 samples was 3.17 units. The standard deviation of the samples was 3.0 units. The mean value is six standard deviations below the 20-unit cutoff.

Specific Performance Characteristic

Comparison to Predicate Devices

One hundred and one samples from three celiac disease reference labs were tested internally on both the QUANTA Lite™ Celiac DGP Screen, QUANTA Lite™ Gliadin IgA II and QUANTA Lite™ Gliadin IgG II ELISAs. These results, plus the 497 normals are depicted below.

N= 598	Gliadin IgG II and/or Gliadin IgA II		
		Positive	Negative
Celiac DGP Screen	Positive	39	3*
	Negative	11**	545

Positive percent agreement: 39/50 (78.0%)
 Negative percent agreement: 545/548 (99.4%)
 Overall agreement: 548/598 (91.6%)

*Of the 3 samples found to be Celiac DGP Screen positive, yet negative on both the Gliadin II kits, 2 were celiac patients on a gluten free diet with 28.7 and 20.9 units. The third patient was a 1st degree relative of a celiac patient with 20.2 units.

**Of the eleven samples found negative by the Celiac DGP Screen kit yet positive by either Gliadin II kit, 9 were from the normal study. Of the remaining two, both were celiac patients on a gluten free diet. One gave 20.1 units on Gliadin IgG II and the other was 25.3 units on Gliadin IgA II.

Clinical Studies

Samples clinically defined as either celiac patients, celiac patients that are IgA deficient, celiac patients on a gluten-free diet, first degree relatives of a celiac patient, dermatitis herpetiformis patients, IgA deficient controls or non-celiac disease patients were tested in both internal and external clinical studies using the QUANTA Lite™ Celiac DGP Screen. A summary of the clinically defined samples plus 517 of the above mentioned normal range samples is provided below.

Patient Group	#	Positive Celiac DGP Screen	%
Celiacs	85	81	95.3%
Celiac IgA Deficient	50	50	100%
Celiacs on Gluten-Free Diet	33	9	27%
1 st degree relatives	18	2*	11%
Dermatitis Herpetiformis Patients	65	59**	91%
IgA Deficient Controls	36	0	0%
Non-Celiac Disease Patients	81	1	1.2%
Normals	517	4***	0.8%

*One of the relatives was 41.3 units and was both h-tTG and EMA positive. The second was 20.2 units and was both h-tTG and EMA negative.

**In this same group of patients only 54 or 83% were h-tTG positive and 6 of these 65 individuals had no intestinal involvement (Marsh 0 biopsy).

***Of these 4 samples, 1 was 20.1 units and another 20.2 units. The cutoff is 20 units. Another of the 4 was 25.4 units and was also strongly positive for h-tTG and may actually be a celiac.

Celiac DGP Screen ELISA Performance with Celiac Diagnosis:

		Diagnosis		
		Positive	Negative (Disease Controls and Healthy Controls)	Total
QUANTA LITE™ DGP Screen	Positive	131	5	136
	Negative	4	629	633
	Total	135	634	769

Sensitivity: 97% (131/135)
 Specificity: 99.2% (629/634)

Sensitivity – Overall sensitivity for celiac disease is calculated by grouping the results for both the 85 celiacs plus the 50 IgA deficient celiacs. The total number of celiacs is 135 of which 131 or 97% are positive.

Specificity – Specificity can be calculated by grouping the 517 normals (including the h-tTG positive sample) the 81 non-celiac disease controls and the 36 IgA deficient controls. This group totals 634 samples. Of these, only 5 samples were positive for a specificity of 99.2%.

Cross-Reactivity

To assess potential cross reactivity problems with other autoantibodies, a variety of high titer autoantibody positive samples were run on the QUANTA Lite™ Celiac DGP Screen kit. In all, 86 samples were run. Many of the samples were the high positive controls from other INOVA QUANTA Lite™ autoantibody test kits. The

specificities included Centromere (4), Actin (4), Sm (9), SS-A (12), RNP (9), Jo-1 (9), SS-B (8), Scl-70 (8), GBM (4), MPO (6), RF (5), Ribo P (4) and M2 (4). The mean value of these 86 samples was 2.40 units. All of the samples were negative on the QUANTA Lite™ Celiac DGP Screen. The mean value is eight standard deviations below the 20-unit cutoff.

Precision and Reproducibility

Intra-assay performance for QUANTA Lite™ Celiac DGP Screen ELISA was evaluated by testing 13 specimens a total of 5 times each. The results are shown below.

Intra-assay Performance of QUANTA Lite™ Celiac DGP Screen ELISA

	1	2	3	4	5	6	7	8	9	10	11	12	13
Mean units	57.5	51.8	102.0	27.5	121.0	162.0	7.9	4.6	5.3	17.7	25.0	17.4	23.4
SD	0.3	1.4	0.9	0.4	1.3	2.8	0.4	0.2	0.1	0.4	0.7	0.4	0.7
CV %	0.5	2.7	0.9	1.6	1.1	1.7	4.7	4.1	2.6	2.2	2.8	2.2	2.8

Inter-assay variation was assessed by testing, in duplicate, a panel of 8 specimens as well as the kit high positive control (HPC), twice daily (once in the morning and once in the afternoon) for 3 days. A summary of the results of the study is shown below.

Inter-assay Performance of QUANTA Lite™ Celiac DGP Screen ELISA

	HPC	A	B	C	D	E	F	G	H
Mean units	110.4	54.6	48.5	27.5	157.9	9.8	16.4	22.2	18.8
SD	3.4	1.4	1.9	1.0	3.8	0.6	0.1	0.7	0.6
CV%	3.0	2.5	3.8	3.6	2.4	5.8	4.7	3.2	3.4

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