FEMTOLAB H. PYLORI CNX
INSTRUCTIONS FOR USE

1. INTENDED USE

The FemtoLab H. pylori Cnx enzyme immunoassay (EIA) is an *in vitro* qualitative procedure for the detection of *Helicobacter pylori* antigens in human stool. Test results are intended to aid in the diagnosis of *Helicobacter pylori* infection and to monitor response post-therapy in adult patients and children.

2. EXPLANATION OF THE TEST

In 1984 Marshall and Warren described the presence of a Campylobacter-like organism in the antrum and corpus of patients with histological evidence of gastritis and peptic ulcers (1). Nowadays *H. pylori* is well recognized as a major cause of gastrointestinal diseases (2).

Infection by *H. pylori* leads to inflammation, which has a strong correlation with chronic gastritis, ulcers of the stomach and the duodenum, and gastric carcinoma (3, 4). Patients with successful eradication therapy show evidence for this cause and effect relationship - often gastritis and ulcers are cured.

These bacteria have adapted to live in the acidic environment of the stomach. The enzyme urease cleaves urea into ammonia and carbon dioxide, thus neutralizing the acid and enabling *H. pylori* to survive the bactericidal conditions of the stomach. The production of catalase and superoxide dismutase protects the bacteria from neutrophilic attack in the stomach mucosa (3).

Many *H. pylori* infected patients develop gastritis, and about 10% of them ulcers. 90% of patients suffering from ulcers of the duodenum or the stomach are *H. pylori* positive, regardless of age. The reasons for these phenomena as well as the way of infection are subject to worldwide research (5).

There are two general methods of diagnosing *H. pylori* infection:

1. direct detection of the organism and
2. indirect determination by the detection of antibodies developed by the patient against *H. pylori* (1, 6, 7).

Direct, but invasive methods to detect *H. pylori* infection are the rapid urease test, histology or the culture of the organism from the biopsy material (8). Culturing of *H. pylori* from biopsy material is difficult and time consuming. The technical difficulties can lead to false negative results and therefore to a reduced sensitivity. In addition, *H. pylori* tends to colonize the mucosa in patches and can therefore be missed during endoscopy (9).

Another direct way of diagnosing *H. pylori* is the use of an urea breath test, which detects carbon dioxide produced by the urease activity. Although highly sensitive and specific, it requires specialized instrumentation as well as the ingestion of isotope-labeled urea by the patient (8, 10).

A commonly used method is the serological detection of antibodies specific for *H. pylori*. This is an indirect approach detecting *H. pylori* specific antibodies developed by the patient (10). Sensitivity and specificity vary greatly among those tests. Furthermore, eradication control with serological methods is insufficient, because the significant decrease of antibody level takes several months.

FemtoLab H. pylori Cnx is a sandwich-type enzyme immunoassay (EIA) in a microplate format for the direct, noninvasive detection of *H. pylori* antigens in human stool specimens. It is based on monoclonal antibodies which ensures lot to lot reproducibility of test kits. Due to the direct detection of antigens this test can be used for the initial diagnosis of *H. pylori* infection as well as for monitoring eradication success four to six weeks after completion of eradication therapy and also for the diagnosis of reinfection.

3. BIOLOGICAL PRINCIPLE OF THE TEST

FemtoLab H. pylori Cnx from Connex GmbH, Martinsried, is a sandwich-type enzyme immunoassay using dual amplification technology for the determination of *H. pylori* antigens in stool specimens.

The wells of the microplate are coated with monoclonal antibodies specific for *H. pylori* antigens.

Supernatant of a fecal suspension as well as horseradish peroxidase (HRP) labeled monoclonal antibodies (Antibody Conjugate) are added to the wells in one step. During incubation, *H. pylori* antigens present in a sample bind to the antibodies on the microplate and to the HRP labeled antibodies thus forming a 'sandwich complex'.

The wells are washed in order to remove unbound Antibody Conjugate. A colorless single-component enzyme substrate (Tetramethylbenzidine - TMB) is added. Bound HRP oxidizes TMB to a blue colored product. By adding the Stop Solution the color changes to yellow. The intensity of the color is determined spectrophotometrically.

4. MATERIALS PROVIDED

The contents of one package are sufficient for 96 determinations. Each test kit contains:

Contents		
Antibody coated Microplate 12 strips of 8 breakaway wells coated with monoclonal antibodies specific for *H. pylori* antigens in a resealable foil bag containing a desiccant		96 wells
Microplate strip sealer		1pc.
Wooden stick applicators		100 pcs.
Sample Diluent 75 mM phosphate buffered solution, pH 7.4 with antimicrobial agents	*ready to use*	55 ml
Buffered Wash Solution (10x) 250 mM phosphate buffered solution, pH 7.4 with detergent and antimicrobial agents	*10 x concentrated*	100 ml
Positive Control inactivated fractionated *H. pylori* lysate in 75 mM phosphate buffered, red colored solution, pH 7.4, with antimicrobial agents	*ready to use*	2 ml
Negative Control 75 mM phosphate buffered, blue colored solution, pH 7.4 with antimicrobial agents	*ready to use*	2 ml
Antibody Conjugate monoclonal antibodies specific for *H. pylori* antigens conjugated to horseradish peroxidase in a 75 mM phosphate buffered, green colored solution, pH 7.4, with antimicrobial agents	*ready to use*	7 ml
TMB/Substrate Solution aqueous solution of TMB and hydrogen peroxide	*ready to use*	12 ml
Stop Solution 1 M sulfuric acid	*ready to use*	12 ml

5. MATERIALS NOT PROVIDED

- Distilled or deionized water
- **EIA microplate washer** or multichannel pipette, squirt bottle
- **EIA microplate reader** for detection of absorbance at 450 / 620 to 650 nm or 450 nm
- Centrifuge (minimum 5000 rpm)
- Microplate shaker
- Vortex mixer
- Graduated cylinder for preparing the wash buffer
- Precision pipettes and disposable tips to deliver 50, 100 or 500 µl
- Test tubes
- Absorbent paper

6. PRECAUTIONS

6.1. Safety precautions

1. All reagents in this test kit may be used for *in vitro* diagnostics only.
2. The test should be used by experienced laboratory personnel only. The test protocol must be followed strictly. Please refer to guidelines for safety regulations in medical laboratories.
3. Patient samples are to be considered potentially infectious and precautions according to safety regulations for handling infectious materials must be taken. Kit reagents and controls should be handled under the same safety precautions.
4. Samples of high risk patients must be marked and treated accordingly, e.g. processed in a laminar flow hood.
5. **Caution:** The Stop Solution contains 1 M sulfuric acid (H_2SO_4). Avoid contact with skin and eyes. Rinse immediately with plenty of water if any contact occurs.
6. Reagents of this kit contain antimicrobial agents and the Substrate Solution contains Tetramethylbenzidine. Avoid contact with skin and eyes. Rinse immediately with plenty of water if any contact occurs.

6.2. Technical precautions

1. All reagents have to be stored at 2 to 8°C and must not be used after the expiration date printed on the labels. Do not freeze any kit components. An exchange of individual reagents between kits of different lot numbers is not possible.
2. Strips and solutions should not be used if the pouch is damaged or liquids have leaked, respectively.
3. Allow all reagents and the microplate to reach room temperature and mix the reagents gently before use. Ensure that the microplate pouch with the remaining strips and the desiccant is well sealed to avoid moisture and stored at 2 to 8°C after use.
4. All reagents are provided ready to use except for the 10x Buffered Wash Solution.
5. Include the Positive and Negative Control in every test run to monitor for reagent stability and correct performance of the assay procedure.
6. Strictly observe the indicated incubation times and temperature.
7. Ensure that no cross-contamination occurs between wells. It is essential that the Antibody Conjugate does not contaminate reagents and equipment.
8. Microbial contamination has to be avoided. When pipetting Antibody Conjugate or Substrate Solution, aliquots for the required number of wells should be taken to avoid multiple entry of pipette tips into reagent bottles. Never pour unused reagents back into the original bottles.
9. Do not allow microwells to dry between incubation steps.
10. Strictly follow the described wash procedure. Insufficient washing may cause elevated background signal.
11. Avoid direct sunlight during all incubation steps. The colorless Substrate Solution has to be protected from exposure to direct light to avoid coloration by autooxidation. If the Substrate Solution has turned blue, the reagent has to be discarded.
12. Replace color-coded caps on correct vials to avoid cross-contamination.
13. Do not reuse microwells.

7. SHELF LIFE AND STORAGE OF THE TEST KIT

The expiration date of the kit is stated on the outer box label. Store all components at 2 to 8°C. Do not freeze any kit components. Unused microplate strips should be stored in the resealable foil pouch containing the desiccant.

8. SPECIMEN COLLECTION AND STORAGE

The test can be performed on either fresh or frozen stool samples. Fresh samples may be transported without cooling for two days. Upon arrival in the laboratory the samples should be stored at -20°C or below.

If the test is performed within three days after arrival, the samples may be stored at 2 to 8°C without interference with the assay performance. Repeated freezing and thawing of samples should be avoided.

Stool in transport media or preservatives is inappropriate for testing.

Sampling of stool may be facilitated for the patient by using the ©Med Auxil - Stool Catcher. Orders may be placed at Med Auxil, Verlag fuer Praxishilfen, Northeimer Str. 4, D - 37581 Bad Gandersheim, Germany; Fax +4953823707.

9. TEST PROCEDURE

Please refer to sections **6.1. Safety precautions** and **6.2. Technical precautions** before performing the test.

9.1. Preparation of reagents

Before use, allow all reagents to reach room temperature and mix gently. Return reagents to 2 to 8°C after use.

1 part of the concentrated **Buffered Wash Solution (10x)** (vial with brown cap) is diluted with **9 parts of distilled or deionized water**. For example: 7 ml Buffered Wash Solution (10x) diluted with 63 ml distilled or deionized water is sufficient to wash one strip. The diluted Washing Buffer has a shelf life of 3 months if stored in a closed bottle at 2 to 8°C. The concentrated Buffered Wash Solution may show a slight precipitate. Bring to room temperature and mix gently to dissolve the precipitate before use.

9.2. Preparation of specimen

Pipette **500 µl of the Sample Diluent** (clear cap) into a properly marked tube. Mix the stool sample. Using a wooden stick applicator add a pea-sized **stool sample** (approx. **0.1 g**) to the Sample Diluent. Homogenize for 15 seconds on a vortex mixer. Use a new wooden stick applicator for each sample. Centrifuge the suspension for 5 minutes at ≥ 5000 rpm. Stool suspension may be stored for 24 h at 2 to 8°C but not frozen.

9.3 Incubation of stool supernatant with Antibody Conjugate

Remove the required number of wells for samples and controls from the pouch and place into the microwell holder. Take the strips out of the foil bag only after the strips have reached room temperature to avoid moisture. The foil bag should be opened with a pair of scissors without detaching the fastener. Unused wells must be returned to the foil bag containing the desiccant, closed tightly and stored at 2 to 8°C.

Pipette 50 µl of the stool supernatant, 50 µl of the Positive Control (red cap) and **50 µl of the Negative Control** (clear cap) into separate wells.

Add 50 µl of the ready to use **Antibody Conjugate** (green cap) directly to each well. Incubate at 18 to 27°C on a mechanical shaker for **60 ± 5 minutes**. Covering the microplate with the included microplate strip sealer cut to size is recommended.

9.4. Washing

Washing may be performed using a microplate washer or manually using a multichannel pipette or a squirt bottle. Carefully remove the plate sealer and dispose the plate contents into a biohazard waste container. Wash the plate **5 times** with **250-300 µl Washing Buffer** per well.

If using a microplate washer, be sure that the liquid is completely aspirated after each washing step. After the final washing step, the inverted microplate should be firmly tapped on absorbent paper.

If washing is performed by hand ensure that each well is filled with wash buffer and the liquid is completely removed after every washing cycle by tapping the inverted plate onto absorbent paper. Using a fume hood is recommended. Microwells must not dry out between steps.

9.5. Color reaction

Add **100 µl of the Substrate Solution** (blue cap) into each well and incubate at room temperature, preferably in the dark. After **10 minutes**, stop the reaction by adding **100 µl Stop Solution** (yellow cap).

9.6. Measurement

Spectrophotometric determination is performed using an EIA microplate reader at a wavelength of 450 nm and a reference wavelength between 620 and 650 nm when available. Ensure that the reader is blanked to air and the bottom of the wells are clean before reading. The measurement should be made within 15 minutes after stopping the reaction.

9.7. Disposal

Any liquid that has been brought into contact with potentially infectious material has to be discarded in a container with a disinfectant. Contaminated materials must only be disposed of after autoclaving. Disposal has to be performed in accordance to local legislation.

10. QUALITY CONTROL

Positive and Negative Control have to be included in every test run to ensure reagent stability and correct performance of the assay procedure. The following quality criteria have to be met, otherwise the assay has to be repeated:

Positive Control	**$OD_{450 / 620 \text{ to } 650 \text{ nm}}$ > 1.00 (OD_{450nm} > 1.04)**
Negative Control	**$OD_{450 / 620 \text{ to } 650 \text{ nm}}$ < 0.10 (OD_{450nm} < 0.14)**

Controls are intended to monitor for substantial reagent failure. The Positive Control will not ensure precision at the cut-off.

Kit components should be examined visually for signs of contamination, deterioration or leakage. Substrate Solution must not be used if turned blue.

If the Negative Control yields absorbance values > 0.10 (> 0.14 respectively) this may indicate insufficient washing. It is recommended to wash the strips more intensively when repeating the test.

Any well, positive by a spectrophotometer but without visible color, should be cleaned on the underside of the well and re-read. If OD-values below zero are observed, the wavelengths used should be verified, the reader re-blanked to air and the measurement repeated.

11. INTERPRETATION OF RESULTS

Test results are interpreted as follows:

Dual wavelength (450 / 620 to 650 nm)

Specimens with absorbance values ≥ 0.150 are positive.

Specimens with absorbance values < 0.150 are negative.

Single wavelength (450 nm)

If it is not possible to use a reference wavelength between 620 and 650 nm on the microplate reader, the cut off is as follows:

Specimens with absorbance values ≥ 0.190 are positive.

Specimens with absorbance values < 0.190 are negative.

A positive test result indicates the presence of *H. pylori* antigens. A negative result indicates the absence of *H. pylori* antigens or a concentration of antigens below the detection limit.

When using single wavelength measurement the microplate reader data should be verified visually for consistent results.

Extremely strong positive samples may show a precipitate within a few minutes after adding the Stop Solution. These samples are to be considered positive.

12. LIMITATIONS OF THE PROCEDURE

FemtoLab H. pylori Cnx is a qualitative test and no quantitative interpretation should be made. Test results should be interpreted by the clinician in conjunction with clinical findings and/or other diagnostic procedures.

Antimicrobials, proton pump inhibitors and bismuth preparations are known to suppress growth of *H. pylori*. Stool sampling must be performed not earlier than 2 weeks after termination of ingestion of proton pump inhibitors and bismuth preparations and 4 weeks after termination of ingestion of antibiotics, respectively.

FemtoLab H. pylori Cnx reflects the actual *H. pylori* status. However, differential diagnosis with invasive endoscopic methods might be indicated in order to examine the presence of any other complicating conditions, e.g. ulcer, autoimmune gastritis and malignancies.

A test result within 0.020 absorbance units around the cut-off value should be interpreted with caution.

13. EXPECTED VALUES

Epidemiological studies have shown that the infection by *H. pylori* is very common throughout the world. In Europe and North America 25-50% of the population carries *H. pylori*. Even higher prevalence rates of 70-90% have been reported for Asia, Africa and South America (1, 11).

The frequency of *H. pylori* infection has been shown to correlate with age, ethnic background, socioeconomic class and the general health environment. E.g. the prevalence of infection in the United States increases with age at approximately 1% per year (12).

Expected values depend on geographic location and type of population studied. The rate of positive test results may vary due to the type of test employed and the method of specimen collection and handling.

14. SPECIFIC PERFORMANCE CHARACTERISTICS

14.1. Clinical studies

Study 1: Primary diagnosis in adult patients

The FemtoLab H. pylori Cnx test was evaluated on 356 patients (201 female, 155 male, age range 18 - 82 years) from 10 centers in Germany undergoing endoscopy because of abdominal pain and dyspepsia. Stool testing was performed in independent laboratories in a blinded fashion.

The patients had a variety of gastric pathologies noted, including: mild gastritis (n=61), chemical toxic gastritis (n=98), *H. pylori* associated gastritis (n=144), antral erosions (n=11), atrophic gastritis (n=2), gastric ulcer (n=5), duodenal ulcer (n=3), adenocarcinoma (n=2), submucous tumor (n=1) Schatzki's Ring (n=1), Crohn gastritis (n=1), asymptomatic (n=27).

FemtoLab H. pylori Cnx test results were compared to the diagnosis of *H. pylori* infection as judged by histology.

FemtoLab H. pylori Cnx showed a sensitivity of 95.3% and a specificity of 97.1%. Confidence intervals (CI) were calculated using the exact binomial method. Results are shown in table 1.

Table 1: Primary diagnosis in adult patients using FemtoLab H. pylori Cnx and the reference test histology

FemtoLab H. pylori Cnx	histology +	histology -
+	141	6
-	7	202

sensitivity	95.3%
± 95% CI	90.5-98.1%
specificity	97.1%
± 95% CI	93.8-98.9%

Study 2: Primary diagnosis in pediatric patients

The FemtoLab H. pylori Cnx assay was tested in a study performed with fecal samples from children undergoing endoscopy because of abdominal pain and/or other intestinal disorders. 239 children (124 male, 115 female, age range 6 months to 18 years) from three pediatric gastroenterology centers in Europe were included.

As reference tests histology and culture were used. The patient was defined *H. pylori* positive if histology and/or culture were positive and *H. pylori* negative if both tests were negative.

FemtoLab H. pylori Cnx showed a sensitivity of 98.6% and a specificity of 99.4%. Confidence intervals (CI) were calculated using the exact binomial method.

Table 2: Primary diagnosis in pediatric patients using FemtoLab H. pylori Cnx and the reference tests histology/culture

FemtoLab H. pylori Cnx	histology culture +	histology culture -
+	70	1
-	1	167

sensitivity	98.6%
± 95% CI	92.4 - 100%
specificity	99.4%
± 95% CI	96.7 - 100%

Study 3: Control of eradication therapy

40 *H. pylori* infected children (age 3 to 15 years) with recurrent abdominal pain were recruited in two pediatric gastroenterology centers (13). *H. pylori* infection was shown by urea breath test and serology. All 40 stool samples were identified positive by FemtoLab H. pylori Cnx (sensitivity =100%; 95% CI = 91.2 - 100%).

Eradication was performed by triple therapy for seven days. Eradication control was performed by urea breath test four weeks after therapy.

FemtoLab H. pylori Cnx showed a sensitivity of 100% and a specificity of 96.9%. Confidence intervals (CI) were calculated using the exact binomial method. Results are shown in table 3.

Table 3: Control of eradication therapy using FemtoLab H. pylori Cnx and urea breath test four weeks after completion of eradication therapy

FemtoLab H. pylori Cnx	urea breath test +	urea breath test -
+	8	1
-	0	31

sensitivity	100%
± 95% CI	63.1 - 100%
specificity	96.9%
± 95% CI	83.8 - 99.9%

14.2. Limit of detection

FemtoLab H. pylori Cnx detects 5 femtomol antigens per gram stool.

14.3. Reproducibility

Intra-assay and inter-assay variations were determined by testing weak positive (n=2), medium positive (n=2) and strong positive (n=2) as well as negative samples (n=2). Reproducibility testing was performed in three independent laboratories in Europe. Each sample was tested in 10 wells at each site. Intra-assay and inter-assay coefficients of variations (CV) were calculated and are presented below. Ranges for OD-values and intra- and inter-assay variances are given for the different stool samples tested.

Table 4: Intra- and inter-assay variation of FemtoLab H. pylori Cnx

	negative	weak positive	medium positive	strong positive
$OD_{450/630\ nm}$	0.02 - 0.03	0.49 - 0.90	1.31 - 2.66	3.00 - 3.77
Intra-assay CV	6.6 - 17.4%	2.7 - 10.1%	2.1 - 4.0%	1.1 - 6.1%
Inter-assay CV	6.0 - 27.1%	27.3 - 31.3%	29.0 - 30.2%	7.5 - 7.8%

14.4. CROSSREACTIVITY

FemtoLab H. pylori Cnx stool assay is highly specific for antigens from *H. pylori*. No crossreactivity was observed when testing the microorganisms listed below. In contrast *H. pylori* gave a positive test result.

Acinetobacter lwoffii [1]
Aeromonas hydrophila anaerogenes [1]
Aeromonas hydrophila hydrophila [1]
Bacteroides thetaiotaomicron [2]
Bacteroides vulgatus [2]
Campylobacter fetus [1, 2]
Campylobacter jejuni [2]
Citrobacter freundii [1, 2]
Enterobacter cloacae [1]
Enterococcus faecalis [1, 2]
Enterococcus faecium [1]
Escherichia coli [1, 2]
Escherichia hermannii [1]
Eubacterium aerofaciens [2]
Klebsiella pneumoniae [2]
Lactoccocus lactis [1]
Listeria innocua [1]
Peptostreptococcus productus [2]
Proteus mirabilis [1, 2]
Proteus vulgaris [1,2]
Providencia stuartii [1]
Pseudomonas aeruginosa [1]
Pseudomonas fluorescens [1]
Pseudomonas putida [1]
Salmonella agona [1]
Salmonella choleraesuis [1]
Salmonella infantis [1]
Salmonella ohio [1]
Salmonella typhimurium [1]
Serratia proteamaculans [1]
Shigella flexneri [1]
Shigella sonnei [1]
Staphylococcus aureus [1]
Streptococcus agalactiae [1]
Streptococcus dysgalactiae [1]
Yersinia enterocolitica [2]

[1] For each strain a concentration of ≥ 1×10^8 organisms/ml sample buffer was tested.

[2] Negative stool was spiked with 100 µg lysate protein/ml and tested by FemtoLab H. pylori Cnx.

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