LACTOFERRIN SCAN®

An ELISA for the quantitative measurement of fecal lactoferrin
Catalog No. T5009 (96 Tests)
IVD *In Vitro* Diagnostic Medical Device

ESPAÑOL p. 10
Un ensayo ELISA para la medición cuantitativa de la lactoferrina fecal
Nº de catálogo T5009 (96 Pruebas)
IVD Dispositivo médico de diagnóstico *in vitro*

DEUTSCH p. 19
Ein ELISA für die quantitative Messung von Lactoferrin im Stuhl
Katalognummer T5009 (96 Tests)
IVD *In-Vitro*-Diagnostikum

FRANCAISE p. 28
Dosage immunoenzymatique (ELISA) pour la mesure
quantitative de la lactoferrine fécale
Numéro de Catalogue T5009 (96 Analyses)
IVD Dispositif médical de diagnostic *in vitro*

Made in the USA

U. S. Patent # 7,192,724

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LACTOFERRIN SCAN®

INTENDED USE

The LACTOFERRIN SCAN® test is a quantitative ELISA for measuring concentrations of fecal lactoferrin, a marker for fecal leukocytes. An elevated level is an indicator of intestinal inflammation. The test can be used as an *in vitro* diagnostic aid to distinguish patients with active inflammatory bowel disease (IBD) from those with noninflammatory irritable bowel syndrome (IBS).

Caution: U.S. Federal Law restricts this device to sale by or on the order of a physician.

EXPLANATION

Inflammatory bowel disease (IBD) affects an estimated 1 to 2 million people in the United States (1). Ulcerative colitis and Crohn's disease are the primary subgroups of IBD and both involve chronic inflammation of a noninfectious etiology. In cases of chronic intestinal illnesses, infectious diarrhea that may involve intestinal inflammation must be ruled out to confirm a diagnosis of IBD (e.g., those caused by *Shigella*, *Campylobacter*, and *Clostridium difficile*) (9). Although ulcerative colitis and Crohn's disease differ including disease location and complications, both involve disease states that oscillate between flare and remission. During active disease, leukocytes infiltrate the intestinal mucosa and increase the level of fecal lactoferrin (2-10). IBD patients with active disease may present with symptoms similar to another chronic illness, irritable bowel syndrome (IBS), a noninflammatory condition that may affect as many as 20 million Americans, making it difficult to diagnose in the early stages of disease (1). In persons with IBS, the intestine appears normal upon endoscopic examination, leukocytes are not present in the mucosa, and fecal lactoferrin levels are at baseline (6). In suspected cases of ulcerative colitis and Crohn's disease, colonoscopy and barium x-ray examinations are the most commonly used techniques for confirmation of intestinal inflammation and ulceration (2). A non-invasive quantitative test such as the LACTOFERRIN SCAN® test demonstrates active intestinal inflammation and provides physicians an aid for distinguishing IBS from IBD.

PRINCIPLE OF THE TEST

The LACTOFERRIN SCAN® test uses antibodies to human lactoferrin. The microassay wells supplied with the kit contain immobilized polyclonal antibody against lactoferrin. The detecting antibody consists of polyclonal antibody conjugated to horseradish peroxidase. In the assay, standards and serial dilutions of fecal specimens are transferred to the microassay wells. If detectable levels of lactoferrin are present in the specimen, the lactoferrin will bind to the immobilized antibody. After incubation, the wells are washed and the antibody conjugate is added. The conjugate will bind to the lactoferrin bound during the first incubation phase. Any unbound material is removed during a second series of wash steps. Following the addition of *Substrate*, a color is detected due to the enzyme-antibody-antigen complexes that form in the presence of lactoferrin. The absorbance measured is directly proportional to the concentration of lactoferrin present. Lactoferrin standards ranging from 6.25 to 100 ng/mL are used to generate a standard curve. By plotting absorbance values versus lactoferrin concentrations, the lactoferrin concentration in a test sample can be determined.

MATERIALS PROVIDED

DIL | 10X — ***10X Diluent***, 40 mL (10X concentrate of a buffered protein solution containing 0.2% thimerosal). The 1X *Diluent* is also used as the negative control (see TEST PROCEDURE)*

Signal Word: Warning

H373: May cause damage to organs through prolonged or repeated exposure P260, P314, P501

CONJ | ENZ — ***Conjugate***, 7 mL (rabbit polyclonal antibody specific for human lactoferrin conjugated to horseradish peroxidase and in a buffered protein solution containing 0.02% thimerosal)*

SUBS REAG ***Substrate***, 14 mL (solution containing tetramethylbenzidine substrate and peroxide)

LS1 - 5 ***Standards***, 1.5 mL each of LS1 (100 ng/mL), LS2 (50 ng/mL), LS3 (25 ng/mL), LS4 (12.5 ng/mL), and LS5 (6.25 ng/mL) - human lactoferrin standards in a buffered protein solution containing 0.02% thimerosal*

CONTROL + ***Positive Control***, 1.5 mL (10 µg/mL; human lactoferrin in protein buffered solution containing 0.02% thimerosal)*

WASHBUF 20X ***Wash Buffer Concentrate***, 50 mL (20X concentrate containing phosphate-buffered saline, detergent and 0.2% thimerosal)*
Signal Word: Warning
H373: May cause damage to organs through prolonged or repeated exposure P260, P314, P501

H_2SO_4 0.6N ***Stop Solution***, 7 mL (0.6 N sulfuric acid). CAUTION: Avoid contact with skin. Flush with water immediately if contact occurs.
Signal Word: Danger
H314: Causes severe skin burns and eye damage
P260, P264, P280, P301, P330, P331, P303, P361, P353, P363, P304, P340, P310, P321, P305, P351, P338, P501

MA PLT ***Microassay Plate***, 12 strips, 8 wells per strip, coated with purified polyclonal antibody specific for lactoferrin (stored with desiccant)

*contains mercury (Hg)

PRECAUTIONS

1. Rx Only - Prescription Only
2. Reagents from different kits should not be mixed. Do not use the kit past the expiration date.
3. Reagents should be removed from the kit box and allowed to reach room temperature before use.
4. Caps and tips are color coded; do not mix!
5. Gently mix all reagents before dispensing.
6. When handling the microassay wells, avoid scratching the bottom of the wells because this may result in elevated absorbance readings.
7. Hold dropper bottles vertically to ensure proper drop size.
8. Handle specimens and used microassay wells as if capable of transmitting infectious agents. Wear gloves when doing the test.
9. Unused microassay wells must be placed inside the resealable foil pouch with the desiccant to protect them from moisture.
10. Perform the washing procedure as directed to avoid high background reactions.
11. Use fecal specimens within 2 weeks of collection for optimal results. Frozen specimens (-20°C or lower) may lose activity due to freezing and thawing multiple times.
12. Carefully measure fecal specimens to ensure a correct dilution. Difficult to measure specimens should be weighed.
13. Do not freeze the reagents. Store the kit between 2°C and 8°C.
14. The *Substrate* is light sensitive and should be protected from direct sunlight or UV sources.
15. Optimal results are obtained by following the specified test procedure. The concentrations, incubation conditions, and processing specifications have been optimized for sensitivity and specificity. Alterations of the specified procedure and/or test conditions may affect the sensitivity and specificity of the test.
16. The *Positive Control* and *Standards* (LS1-5) contain lactoferrin which is a human derived material. Material has been tested and found negative for antibodies to HIV-1, HIV-2, HCV, and HbsAg. No known test method can offer complete assurance that infectious agents are absent. All human source products should be handled as potentially infectious material. A procedure for handling biohazards is published in the CDC/NIH *Manual of Biosafety in Microbiology & Biomedical Laboratories.*

17. The *10X Diluent* and the *20X Wash Buffer Concentrate* contain 0.2% thimerosal as a preservative. Once diluted to normal use concentration these solutions are classified as non-hazardous. The *Stop Solution* contains 0.6 N sulfuric acid. Flush with water immediately if contact occurs. Take off contaminated clothing and wash it before re-use. Handle reagents according to existing regulations for laboratory safety and good laboratory practice. Safety Data Sheets for this product are available upon request, contact technical support.
18. Follow your national, regional, and local ordinances accordingly for waste disposal regulations. Do not place in trash, dispose of as hazardous waste.

PRELIMINARY PREPARATIONS

1. Remove all reagents from the kit box to warm to room temperature before use.
2. **Prepare 1X *Wash Solution*.** The *Wash Solution* is supplied as a 20X concentrate (a precipitate may be noticed). It should be mixed and diluted to a total volume of 1 liter by adding 50 mL of the concentrate to 950 mL of deionized water. Label the bottle. Store any unused 1X *Wash Solution* between 2°C and 8°C.
3. **Prepare 1X *Diluent*.** The *Diluent* is supplied as a 10X concentrate (a precipitate may be noticed). It should be mixed and diluted to a total volume of 400 mL by adding 40 mL of the concentrate to 360 mL of deionized water. Label the bottle. Store any unused 1X *Diluent* between 2°C and 8°C.
4. ***Microassay Plate* Preparation.** Each Strip contains 8 wells coated with polyclonal antibody specific for lactoferrin. Each specimen or control will require one of these coated wells. Avoid contact with the bottom of the wells because this is the optical window for ELISA readers. Microassay wells not used must be returned to the foil bag and carefully resealed with desiccant.

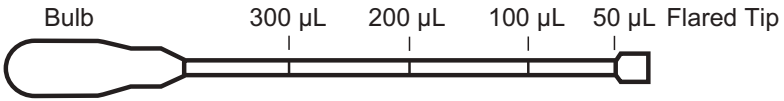
COLLECTION OF SPECIMENS AND PREPARATION OF DILUTIONS

NOTE: Collect fecal specimen into a clean, airtight container with no preservatives. Specimens should be stored between 2°C and 8°C or room temperature for up to 2 weeks from collection then stored frozen at -20°C or lower. Diluted specimens should be stored between 2°C and 8°C for up to 48 hours then discarded. **Mix (vortex) specimens thoroughly prior to performing the assay.** This includes complete mixing of the specimen prior to transfer to *Diluent* as well as complete mixing of the diluted specimen prior to performing the assay.

Prepare Diluted Specimen:

1. Set up three plastic tubes for each test specimen. *Label the tubes #1-#3.* For each specimen, add 450 µL of 1X *Diluent* to each of the three tubes using a pipette. Using a transfer pipette, measure 50 µL of feces (wipe excess specimen from the pipette tip) and add to tube #1. Discard the transfer pipette following the initial specimen dilution. ***For Liquid/Soft Fecal Specimens*** - Using a transfer pipette, carefully add 50 µL (first mark or top of flared tip) of the specimen to tube #1 (1:10 dilution of specimen) and mix well using a vortex mixer. Measure specimen carefully to ensure the correct dilution. ***For Formed/Solid Fecal Specimens*** - Weigh 0.05g or fill the flared tip of the transfer pipette (50 µL; see diagram below) and add to tube #1 (1:10 dilution of specimen) and mix well using a vortex mixer. Measure specimen carefully to ensure the correct dilution.

Transfer Pipette:



2. Transfer 50 µL from tube #1 into tube #2 using a new transfer pipette and vortex (1:100 dilution of specimen).
3. Transfer 50 µL from tube #2 into tube #3 using the same transfer pipette (1:1,000 dilution of specimen).

Prepare *Positive Control*:

4. Set up two plastic tubes for the *Positive Control*. Add 450 µL of 1X *Diluent* to tube #1 and 950 µL to tube #2 using a calibrated pipette.
5. Transfer 50 µL of *Positive Control* to tube #1 (1:10 dilution of *Positive Control*) and mix well using a votex mixer. Transfer 50 µL from tube #1 to tube #2 using a calibrated pipette (1:200 dilution of *Positive Control*).
6. Vortex all tubes for 10 seconds and store between 2° and 8°C until the ELISA is performed. Vortex again before transferring diluted specimens and *Positive Control* to the microassay wells. This ensures thorough mixing of the specimen and controls.

TEST PROCEDURE

Materials provided

2 Plastic adhesive sheets
100 transfer pipettes

Materials and equipment required but not provided

Squirt bottle for 1X *Wash Solution*
Refrigerator for storage
Discard container/absorbent paper
Distilled or deionized water
ELISA reader (450 nm or 450/620 nm)
Vortex mixer
Tubes for dilution of specimen
Bottle for 1X *Diluent*
Incubator set at 37°C ± 2°C

1. Designate and use 2 wells for each Standard, 1 well for the negative control (1X *Diluent*), 1 well for the 1:200 dilution of *Positive Control* and 1 well for specimen dilutions 1:100 and 1:1000. See the table under QUALITY CONTROL for example of well locations.
2. Using a calibrated pipette, add 100 µL of each *Standard* LS1-LS5 to duplicate wells and 100 µL of the 1X *Diluent* and *Positive Control* to designated wells.
3. Add 100 µL from each specimen dilution (1:100 and 1:1000) to separate wells.
4. Cut the adhesive plastic sheet to the size necessary to cover the wells. Cover the wells and incubate them at 37°C ± 2°C for 30 minutes stationary.
5. Shake out the contents of the assay wells into a discard pan.
6. Wash each well 5 times using the 1X *Wash Solution* in a squirt bottle with a fine tipped nozzle, directing the *Wash Solution* to the bottom of the well with force (i.e. fill the wells, then shake the *Wash Solution* out of the wells into a discard pan). Slap the inverted plate on a dry paper towel and repeat **four times** using a dry paper towel each time. If any particulate matter is seen in the wells, continue washing until all the matter is removed.
7. Add 1 drop of *Conjugate* (red cap) to each well. Incubate the wells at 37°C ± 2°C for 30 minutes stationary.
8. Repeat step #6. *Dispose of paper towels and specimen containers properly.*
9. Add 2 drops of *Substrate* (blue cap) to each well. Gently tap the wells to mix the contents. Incubate the wells at room temperature for 15 minutes. Gently tap the wells 1 or 2 times during this incubation period.
10. Add 1 drop of *Stop Solution* (yellow cap) to each well. Gently tap the wells to mix and wait 2 minutes before reading. The addition of the *Stop Solution* converts the blue color to a yellow color which may be quantitated by measuring the optical density at 450 nm or 450/620 nm on a microplate ELISA reader. Wipe the underside of each well with a soft paper towel before measuring the optical density. Read within two to ten minutes after adding *Stop Solution*.
11. Record absorbance values for the *Positive Control* dilution, for the negative control, for each specimen dilution, and for the standards.
12. Average the acceptable readings of duplicate wells before interpreting results.

QUALITY CONTROL

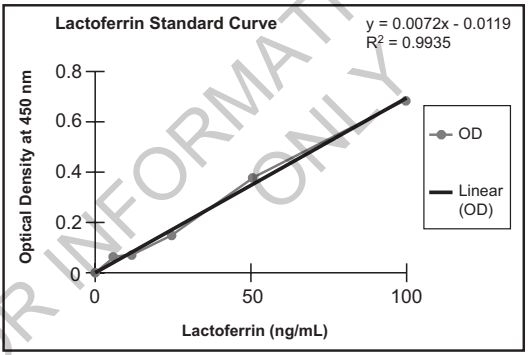
The negative control well containing 1X *Diluent* should have an OD_{450} <0.100 or $OD_{450/620}$ <0.060. The calculated concentration for the *Positive Control* should be in the range of 10 ± 3 µg/mL recovery. Typical layout and values for the standards and samples are shown in the following table and graph. Following the Linear Trend/Regression Type analysis, the R^2 value should be ≥ 0.98. If graph paper is used, points should appear in a straight line.

Typical Layout for Test Samples

LS1 - LS5 - Lactoferrn standards S1 - S18 - Specimens at 1/100 and 1/1000 dilutions

	1	2	3	4	5	6
A	NC	PC(200)	S3(100)	S3(1000)	S11(100)	S11(1000)
B	LS1	LS1	S4(100)	S4(1000)	S12(100)	S12(1000)
C	LS2	LS2	S5(100)	S5(1000)	S13(100)	S13(1000)
D	LS3	LS3	S6(100)	S6(1000)	S14(100)	S14(1000)
E	LS4	LS4	S7(100)	S7(1000)	S15(100)	S15(1000)
F	LS5	LS5	S8(100)	S8(1000)	S16(100)	S16(1000)
G	S1(100)	S1(1000)	S9(100)	S9(1000)	S17(100)	S17(1000)
H	S2(100)	S2(1000)	S10(100)	S10(1000)	S18(100)	S18(1000)

Typical Absorbance Values (OD_{450}) for the Lactoferrin Standard Curve



CALCULATION OF RESULTS

The results in this insert were determined using a Linear Trend/Regression Type analysis. Other data reduction methods may give slightly different results.

1. An appropriate data reduction computer program, using Linear Trend/Regression Type analysis, should be used for optimal estimation of sample values. If a computer program is not available, the data may be plotted using graph paper.
2. Choose the most diluted specimen that gives an OD_{450} or $OD_{450/620}$ value within the standard curve and OD ≥0.100 or 0.060, respectively. If both sample dilutions have absorbance readings greater than the highest concentration of standard, repeat using additional 1:10 dilutions. Conversely, any sample having an absorbance reading less than the lowest concentration of standard should be retested using the 1:10 dilution and if found negative recorded as <1 µg/g wet weight.
3. Plot the average absorbance values of the *Standards* on the y-axis versus the concentration on the x-axis.
4. Perform the Linear Trend/Regression Type analysis and determine if the R^2 value is ≥ 0.98.

5. Instruct the program to produce the equation for the plotted line. The equation should fit the equation of a line which is Y = MX + B, where Y = OD_{450} or $OD_{450/620}$ of the sample, M = Slope, B = Y-intercept and X = Concentration of the unknown sample.
6. Solve the equation for X to determine the concentration of lactoferrin in the specimen.
7. Multiply the value of the unknown sample by the dilution factor.
8. Divide by 1000 to convert ng/mL to µg/mL (approximately µg/g wet weight).

Example Calculation

1. A graph was produced using the data provided in the Quality Control section of this Package Insert.
2. Linear analysis of the graph produced the following equation: y = 0.0072x - 0.0119 and an R^2 value of 0.99.
3. The 1:1000 dilution of specimen #2 was picked for analysis with an absorbance value of 0.450.
4. Solving for X yields: X = 64 ng/mL.
5. Multiply by the dilution factor: 64 x 1000 = 64,000 ng/mL.
6. Convert to µg/g by dividing by 1000: 64,000 / 1000 = 64 µg/ g wet weight.

INTERPRETATION OF VALUES

Lactoferrin Level in feces	Interpretation of results
0 to 7.24 µg/mL (g) feces	Baseline (normal)
≥7.25 µg/mL (g) feces	Elevated

SHELF-LIFE AND STORAGE

The expiration date is given on the outside label of the kit. Expiration dates for each component are listed on the individual labels. The kit containing the reagents with designated shelf-life should be stored between 2° and 8°C and should be returned to the refrigerator as soon as possible after use.

PERFORMANCE CHARACTERISTICS

A multi-center clinical study (3 sites) was done evaluating fecal lactoferrin levels in 180 patients suffering with IBS and IBD (ulcerative colitis disease and Crohn's disease), and compared to 56 healthy persons. Patients were assessed for active disease using the Harvey Bradshaw Activity Index (HBAI) and fecal samples were collected for lactoferrin analysis. Patients with IBS had lactoferrin levels similar to healthy control persons ($p>0.999$). Fecal lactoferrin levels were significantly greater in patients with Crohn's disease and ulcerative colitis, compared to healthy controls ($p<0.05$, $p<0.0006$). A significant number of patients defined as inactive using HBAI had elevated fecal lactoferrin indicating intestinal inflammation. Fecal lactoferrin levels for the study population and statistical analysis of LACTOFERRIN SCAN® test results as compared to the HBAI are shown in Table 1 and Table 2, respectively.

Table 1. Fecal lactoferrin levels of the study population

Study Population N=235	No. of specimens	Fecal lactoferrin (mean µg/mL ± SE)
Inactive UC	41	65.65 ± 24.20
Active UC	31	1814.89 ± 788.25
Inactive CD	26	239.41 ± 82.73
Active CD	51	672.11 ± 241.79
IBS	31	1.27 ± 0.29
Healthy persons	55	1.55 ± 0.41

Table 2. LACTOFERRIN SCAN® test results for distinguishing active inflammatory bowel disease from irritable bowel syndrome/healthy persons

N = 178	Active IBD based on HBAI assessment ≥4	IBD (31)/Healthy Persons (55) based on clinical and self assessment
LACTOFERRIN SCAN® test Elevated	75	3
LACTOFERRIN SCAN® test Baseline	17	83

Sensitivity	81.5%
Specificity	96.5%
Predictive Positive Value	96.2%
Predictive Negative Value	83.0%
Correlation	88.8%

LIMITATIONS OF THE PROCEDURE

1. The LACTOFERRIN SCAN® test is a quantitative test that measures the level of fecal lactoferrin released from leukocytes. The test may not be appropriate in immunocompromised persons. The following patient samples should be excluded from use in the LACTOFERRIN SCAN® test: patients with a history of HIV and/or Hepatitis B and C, patients with a history of infectious diarrhea (within 6 months), and patients having had a colostomy and/or ileostomy within 1 month.
2. Fecal lactoferrin concentrations should not be interpreted as absolute evidence for the presence of a gastrointestinal illness. Prediction of active and inactive disease should be based on a complete clinical evaluation of the patient that may also include multiple fecal lactoferrin level determinations.
3. At this time, the LACTOFERRIN SCAN® test has not been clinically evaluated for use in the detection of leukocytes in other types of clinical specimens. It should be used only for the analysis of fecal specimens.
4. Fecal specimens that have been preserved in 10% Formalin, Merthiolate Formalin, Sodium Acetate Formalin, or Polyvinyl Alcohol cannot be used.
5. Other intestinal ailments, including many gastrointestinal infections and colorectal cancer, often result in elevated levels of lactoferrin in fecal specimens. Therefore, when

evaluating a patient, a clinical assessment must be considered along with LACTOFERRIN SCAN® test results.

6. High levels of fecal lactoferrin may be observed with clinical specimens. Specimens should be serially diluted until the absorbance value falls within the lactoferrin standard curve.
7. Fecal samples from breast fed infants should not be used with this assay.

CROSS-REACTIVITY

Various intestinal organisms were examined for cross-reactivity in the LACTOFERRIN SCAN® test. For the analysis, broth cultures mixed with 1X *Diluent* were evaluated. Broth cultures at log phase containing ≥ 10^8 bacteria per mL were used. Organisms that did not react in the LACTOFERRIN SCAN® test are listed as follows:

Acinetobacter lwoffii
Aeromonas hydrophila
Bacillus cereus
Bacillus subtilis
Bacteroides distasonis
Bacteroides eggerthii
Bacteroides fragilis
Bacteroides ovatus
Bacteroides stercoris
Bacteroides thetaiotaomicron
Bacteroides uniformis
Bacteroides vulgatus
Bifidobacterium adolescentis
Bifidobacterium longum
Campylobacter jejuni
Candida albicans
Candida krusei
Candida tropicalis
Clostridium bifermentans
Clostridium chauvoei
Clostridium difficile
Clostridium haemolyticum
Clostridium histolyticum
Clostridium novyi (types A,B,C)
Clostridium perfringens (types A,B,C,D,E)
Clostridium septicum
Clostridium sporogenes
Clostridium tetani
Enterococcus faecalis
Eubacterium aerofaciens
Escherichia coli
Fusobacterium prausnitzii
Klebsiella pneumoniae
Peptostreptococcus anaerobius
Proteus vulgaris
Pseudomonas aeruginosa
Salmonella choleraesuis
Salmonella enteritidis
Salmonella typhi
Salmonella typhimurium
Shigella dysenteriae
Shigella flexneri
Shigella sonnei
Staphylococcus aureus
Vibrio parahaemolyticus
Yersinia enterocolitica

EFFECT OF FECAL SAMPLE CONSISTENCY

There were no differences observed between fecal specimens having liquid, semi-solid, or solid consistency when compared to the LACTOFERRIN CHEK® test results and/or clinical assessments for disease activity.

REPRODUCIBILITY AND PRECISION

The inter-assay variation was determined by quantitatively analyzing 9 fecal specimens over a 3 day period. The %CV ranged from 12.0% to 47.7%, with a mean value of 33.5% for positive specimens. The intra-assay variation was determined by quantitatively analyzing 9 fecal specimens using 4 replicates in one lot of kits. The %CV ranged from 7.9% to 16.0%, with a mean value of 12.0% for positive specimens.

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Technical Support
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