BECKMAN COULTER

CE 2797

ACCESS
Immunoassay Systems

Instructions For Use

Access Thyroglobulin

REF 33860

FOR PROFESSIONAL USE ONLY

Rx Only

PRINCIPLE

WARNING

The presence of serum autoantibodies to thyroglobulin (TgAb) can interfere with assays for thyroglobulin (Tg). Therefore, sera which contain TgAb, even at very low levels, should not be tested for Tg.

The concentration of thyroglobulin in a given specimen determined with assays from different manufacturers can vary due to differences in assay methods and reagent specificity. The results reported by the laboratory to the physician must include the identity of the Tg assay used. Values obtained with different assay methods cannot be used interchangeably. If, in the course of monitoring a patient, the assay method used for determining Tg levels serially is changed, additional sequential testing should be carried out to confirm baseline values.

INTENDED USE

The Access Thyroglobulin assay is a paramagnetic particle, chemiluminescent immunoassay for the quantitative determination of thyroglobulin levels in human serum and plasma using the Access Immunoassay Systems. This device is intended to aid in monitoring for the presence of local and metastatic thyroid tissue in patients who have had thyroid gland ablation (using thyroid surgery with or without radioactivity) and who lack serum thyroglobulin antibodies.

SUMMARY AND EXPLANATION

The thyroid is a small endocrine gland located in the base of the neck. It consists of two lateral lobes connected by an isthmus. The gland produces a variety of metabolic hormones in a negative biofeedback loop.

Thyroglobulin (Tg) is a large glycoprotein (MW = 660,000) that is stored in the follicular colloid of the thyroid gland. Thyroglobulin functions as a prohormone in the intrathyroid synthesis of T4 and T3. Lysosomes containing proteases cleave T4 and T3 from Tg, resulting in release of T4 and T3.

Thyroglobulin is present in the serum of normal healthy individuals and can be elevated in numerous disorders which disrupt thyroid tissue. Elevated circulating levels of Tg have been reported in a number of thyroid conditions including Hashimoto's disease, Graves' disease, thyroid adenoma, subacute thyroiditis and thyroid carcinoma.[1]

Thyroid cancer is a relatively common form of cancer. It is not generally highly malignant, and normal life span can be obtained with appropriate follow-up and treatment. Females are affected 2 to 3 times more frequently than males. Thyroglobulin has become a useful tool in the follow-up of patients with differentiated thyroid carcinoma (i.e. papillary-follicular or follicular carcinoma of the thyroid).[1,2,3,4,5] The thyroid is the only source of Tg; therefore, the serum Tg level will drop to a very low or undetectable level after total or near-total thyroidectomy and successful radioiodine ablation of the residual thyroid tissue. A rise in the serum level of Tg points to the recurrence of the disease. Thyroglobulin levels in patients who have undergone only a partial thyroidectomy will retain measurable levels of Tg, depending on how much tissue is remaining after surgery. These patients can be monitored by Tg measurement, but the post-surgical Tg level must be taken into account.

An additional monitoring tool used in conjunction with Tg measurement is imaging, including high-resolution neck ultrasonography, or computed tomography (CT) scanning of neck, chest, abdomen, and brain, in addition to assessment for bone metastases by scintigraphy and CT. Generally, both Tg and imaging techniques can be used to follow newly diagnosed and treated patients. [6,7]

A limiting factor in the use of serum Tg measurements is the presence of Tg autoantibodies found in some patients. These antibodies may interfere with the immunoassay used to measure Tg and can cause false high or false low values. [1,2,3] It is important to determine the levels of Tg autoantibodies in patients requiring serum Tg measurements.[4,8]

METHODOLOGY

The Access Thyroglobulin assay is a simultaneous one-step immunoenzymatic (“sandwich”) assay. A sample is added to a reaction vessel, along with a biotinylated mixture of four monoclonal anti-Tg antibodies, streptavidin coated paramagnetic particles, and monoclonal anti-Tg antibody alkaline phosphatase conjugate. The biotinylated antibodies and the serum or plasma thyroglobulin binds to the solid phase, while the conjugate antibody reacts with a different antigenic site on the thyroglobulin molecule.

After incubation in a reaction vessel, materials bound to the solid phase are held in a magnetic field while unbound materials are washed away. Then, the chemiluminescent substrate is added to the vessel and light generated by the reaction is measured with a luminometer. The light production is directly proportional to the concentration of thyroglobulin in the sample. The amount of analyte in the sample is determined from a stored, multi-point calibration curve.

SPECIMEN

SPECIMEN COLLECTION AND PREPARATION

1. Serum and (heparinized) plasma are the recommended samples.
2. Observe the following recommendations for handling, processing, and storing blood samples:[9]
   - Collect all blood samples observing routine precautions for venipuncture.
   - Allow serum samples to clot completely before centrifugation.
   - Keep tubes stoppered at all times.
   - Physically separate serum or plasma from contact with cells as soon as possible.
   - Store samples tightly stoppered at room temperature (15 to 30°C) for no longer than eight hours.
   - If the assay will not be completed within eight hours, refrigerate the samples at 2 to 8°C.
   - If the assay will not be completed within 48 hours, or for shipment of samples, freeze at -20°C or colder.
   - Thaw samples only once.
3. Use the following guidelines when preparing specimens:
   - Ensure residual fibrin and cellular matter has been removed prior to analysis.
   - Follow blood collection tube manufacturer's recommendations for centrifugation.
4. Each laboratory should determine the acceptability of its own blood collection tubes and serum separation products. Variations in these products may exist between manufacturers and, at times, from lot-to-lot.

REAGENTS

PRODUCT INFORMATION

Access Thyroglobulin Reagent Pack

Ref. No. 33860: 100 determinations, 2 packs, 50 tests/pack

- Provided ready to use.

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

Well	Contents	Ingredients
R1a:	3.25 mL	Dynabeads* paramagnetic particles coated with streptavidin, suspended in a TRIS buffer with protein (bovine), < 0.1% sodium azide, and 0.1% ProClin** 300.
R1b:	3.1 mL	Mouse monoclonal anti-thyroglobulin-alkaline phosphatase (bovine) conjugate in a TRIS buffer with protein (bovine, murine), < 0.1% sodium azide, and 0.1% ProClin 300.
R1c:	3.1 mL	Mouse monoclonal anti-thyroglobulin antibodies coupled to biotin in a HEPES buffer with protein (bovine and mouse), < 0.1% sodium azide, and 0.5% ProClin 300.

*Dynabeads is a registered trademark of Dynal A.S., Oslo, Norway.

**ProClin is a trademark of LANXESS Corp.

WARNING AND PRECAUTIONS

- For *in vitro* diagnostic use.
- Patient samples and blood-derived products may be routinely processed with minimum risk using the procedure described. However, handle these products as potentially infectious according to universal precautions and good clinical laboratory practices, regardless of their origin, treatment, or prior certification. Use an appropriate disinfectant for decontamination. Store and dispose of these materials and their containers in accordance with local regulations and guidelines.
- For hazards presented by the product refer to the following sections: REACTIVE INGREDIENTS and GHS HAZARD CLASSIFICATION.

REACTIVE INGREDIENTS

⚠ CAUTION

Sodium azide preservative may form explosive compounds in metal drain lines. See NIOSH Bulletin: Explosive Azide Hazard (8/16/76).
To avoid the possible build-up of azide compounds, flush wastepipes with water after the disposal of undiluted reagent. Sodium azide disposal must be in accordance with appropriate local regulations.

GHS HAZARD CLASSIFICATION

Thyroglobulin PMP (Compartment R1a)

WARNING

H317 May cause an allergic skin reaction.

	H412	Harmful to aquatic life with long lasting effects.
	P273	Avoid release to the environment.
	P280	Wear protective gloves, protective clothing and eye/face protection.
	P333+P313	If skin irritation or rash occurs: Get medical advice/attention.
	P362+P364	Take off contaminated clothing and wash it before use.
		reaction mass of: 5-chloro-2-methyl-4-isothiazolin -3-one [EC# 247-500-7] and 2-methyl-4-isothiazolin-3-one [EC# 220-239-6](3:1) < 0.05%
Thyroglobulin Conjugate (Compartment R1b)	WARNING	
		
	H317	May cause an allergic skin reaction.
	H412	Harmful to aquatic life with long lasting effects.
	P273	Avoid release to the environment.
	P280	Wear protective gloves, protective clothing and eye/face protection.
	P333+P313	If skin irritation or rash occurs: Get medical advice/attention.
	P362+P364	Take off contaminated clothing and wash it before use.
		reaction mass of: 5-chloro-2-methyl-4-isothiazolin -3-one [EC# 247-500-7] and 2-methyl-4-isothiazolin-3-one [EC# 220-239-6](3:1) < 0.05%
Thyroglobulin Antibody (Compartment R1c)	WARNING	
		
	H316	Causes mild skin irritation.
	H317	May cause an allergic skin reaction.
	H319	Causes serious eye irritation.
	H412	Harmful to aquatic life with long lasting effects.
	P273	Avoid release to the environment.
	P280	Wear protective gloves, protective clothing and eye/face protection.
	P332+P313	If skin irritation occurs: Get medical advice/attention.
	P333+P313	If skin irritation or rash occurs: Get medical advice/attention.
	P337+P313	If eye irritation persists: Get medical advice/attention.
	P362+P364	Take off contaminated clothing and wash it before use.

Ethoxylated lauryl alcohol 1 - < 3%

Ethoxylated alkyl alcohol 0.1 - 0.5%

reaction mass of: 5-chloro-2-methyl-4-isothiazolin -3-one [EC# 247-500-7] and 2-methyl-4-isothiazolin-3-one [EC# 220-239-6](3:1) < 0.05%

SDS	Safety Data Sheet is available at beckmancoulter.com/techdocs

MATERIALS NEEDED BUT NOT SUPPLIED WITH REAGENT KIT

1. Access Thyroglobulin Calibrators
   Provided at zero and approximately 1, 10, 100, 250, and 500 ng/mL.
   Ref. No. 33865
2. Quality control materials: commercial control material
3. Access Thyroglobulin Sample Diluent
   Ref. No. 33866
4. Access Substrate
   Ref. No. 81906
5. Access Wash Buffer II, Ref. No. A16792
   UniCel DxI Wash Buffer II, Ref. No. A16793

EQUIPMENT AND MATERIALS

R1	Access Thyroglobulin Reagent Packs

CALIBRATION

CALIBRATION INFORMATION

An active calibration curve is required for all tests. For the Access Thyroglobulin assay, calibration is required every 56 days. Refer to the appropriate system manuals and/or Help system for information on calibration theory, configuring calibrators, calibrator test request entry, and reviewing calibration data.

QUALITY CONTROL

Quality control materials simulate the characteristics of patient samples and are essential for monitoring the system performance of immunochemical assays. Because samples can be processed at any time in a “random access” format rather than a “batch” format, quality control materials should be included in each 24-hour time period.[10] Include commercially available quality control materials that cover at least two levels of analyte. More frequent use of controls or the use of additional controls is left to the discretion of the user based on good laboratory practices or laboratory accreditation requirements and applicable laws. Follow manufacturer's instructions for reconstitution and storage. Each laboratory should establish mean values and acceptable ranges to assure proper performance. Quality control results that do not fall within acceptable ranges may indicate invalid test results. Examine all test results generated since obtaining the last acceptable quality control test point for this analyte. Refer to the appropriate system manuals and/or Help system for information about reviewing quality control results.

TESTING PROCEDURE(S)

PROCEDURAL COMMENTS

1. Refer to the appropriate system manuals and/or Help system for a specific description of installation, start-up, principles of operation, system performance characteristics, operating instructions, calibration procedures, operational limitations and precautions, hazards, maintenance, and troubleshooting.
2. Mix contents of new (unpunctured) reagent packs by gently inverting pack several times before loading on the instrument. Do not invert open (punctured) packs.
3. Use forty (40) µL of sample for each determination in addition to the sample container and system dead volumes. Refer to the appropriate system manuals and/or Help system for the minimum sample volume required.
4. The system default unit of measure for sample results is ng/mL.

PROCEDURE

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

RESULTS INTERPRETATION

Patient test results are determined automatically by the system software. The amount of analyte in the sample is determined from the measured light production by means of the stored calibration data. Patient test results can be reviewed using the appropriate screen. Refer to the appropriate system manuals and/or Help system for complete instructions on reviewing sample results.

REPORTING RESULTS

EXPECTED RESULTS

1. Each laboratory should establish its own reference ranges to assure proper representation of specific populations.
2. Thyroglobulin concentrations were measured in sera from 152 apparently healthy TgAb negative individuals using the Access Thyroglobulin method. The results ranged from 1.15 to 130.77 ng/mL, with a median of 9.08 ng/mL, and 2.5^{th} and 97.5^{th} percentiles of 1.59 and 50.03 ng/mL.
3. Serum samples from patients with Graves' disease, Hashimoto's disease and other benign conditions were tested in the Access Thyroglobulin assay and gave results ranging from undetectable to 804 ng/mL.
4. In patients who have undergone total or near-total thyroidectomy, with or without ^{131}I radioablation, the Tg concentration should approach zero or the functional sensitivity of the assay.
5. A total of 155 samples were obtained from 127 subjects, originally diagnosed with thyroid cancer (papillary or follicular carcinoma) who had undergone near-total or total thyroidectomy, using surgery (with or without radioactivity). Of these samples, 88 had a clinical diagnosis of cancer recurrence and 67 samples were diagnosed with no recurrence.

Diagnoses	n Samples	n Subjects	Mean Tg (ng/mL)	Standard Deviation	Median Tg (ng/mL)	Range Tg (ng/mL)
Ca Positive Cancer recurrence	88	65	76.2	115.8	35.8	0.58-625.1

Diagnoses	n Samples	n Subjects	Mean Tg (ng/mL)	Standard Deviation	Median Tg (ng/mL)	Range Tg (ng/mL)
Ca Negative No evidence of recurrence	67	62	2.83	4.66	1.88	< 0.1-36.8

6. Any changes in serum Tg concentrations should be interpreted in light of the total clinical presentation of the patient, including clinical history, data from additional testing and other appropriate information. Single measurements of thyroglobulin are of minimal value in assessing disease status. Serial determinations are required, and should be referenced to the post-surgical baseline Tg result.

PROCEDURAL NOTES

LIMITATIONS

1. Samples can be accurately measured within the analytic range of the lower limit of detection and the highest calibrator value (approximately 0.1-500 ng/mL).
   - If a sample contains less than the lower limit of detection for the assay, report the results as less than that value (i.e., < 0.1 ng/mL).
   - If a sample contains more than the stated value of the highest Access Thyroglobulin Calibrator (S5), report the result as greater than that value (i.e., > 500 ng/mL). Alternatively, dilute one volume of sample with 4 or 9 volumes of Access Thyroglobulin Sample Diluent. Refer to the appropriate system manuals and/or Help system for instructions on entering a sample dilution in a test request. The system reports the results adjusted for the dilution.
2. For assays employing antibodies, the possibility exists for interference by heterophile antibodies in the patient sample. Patients who have been regularly exposed to animals or have received immunotherapy or diagnostic procedures utilizing immunoglobulins or immunoglobulin fragments may produce antibodies, e.g. HAMA, that interfere with immunoassays. Additionally, other heterophile antibodies such as human anti-goat antibodies may be present in patient samples.[11,12] Such interfering antibodies may cause erroneous results. Carefully evaluate the results of patients suspected of having these antibodies.
3. The Access Thyroglobulin results should be interpreted in light of the total clinical presentation of the patient, including: symptoms, clinical history, data from additional tests, and other appropriate information.
4. The Access Thyroglobulin assay does not demonstrate any “hook” effect up to 40,000 ng/mL.
5. Samples containing thyroglobulin antibodies (TgAb) cannot be reliably measured. All samples should be screened for Tg antibodies, and samples with detectable levels of Tg antibodies should be interpreted with caution as the true value may be higher than that obtained.[1,2,3,4]
6. This assay is susceptible to interference from high levels of biotin. The recommended daily intake for biotin is 30 µg. High doses of biotin (up to 30 mg per day) may be taken as a dietary supplement aimed at improving hair loss, nail growth, or skin condition.[13]

   Some pharmacokinetic studies have shown that serum concentrations of biotin can reach up to 300 ng/mL when subjects taking supplements containing 20 mg biotin[14] or 1,160 ng/mL for subjects taking doses of biotin up to 300 mg.[13] These studies were performed in apparently healthy subjects and some patients may be taking supplements with biotin at levels > 20 mg per day.

   Clearance rates of biotin may differ between patients tested with this device (e.g., patients with renal impairment), which may lead to higher than expected, or prolonged, concentrations in serum. If medically practicable, patients receiving biotin supplements should discontinue use prior to sample draws to minimize the risk of interference. Specimens with biotin concentrations ≤ 10 ng/mL demonstrated non-significant bias (≤ 10%) in results. Biotin concentrations > 10 ng/mL can lead to significant (> 10%) negative bias in Thyroglobulin results.

PERFORMANCE CHARACTERISTICS

PERFORMANCE CHARACTERISTICS

NOTE: All Specific Performance Characteristics data were generated using TgAb negative samples.

METHODS COMPARISON

A comparison of values using the Access Thyroglobulin assay on the Access Immunoassay System and a commercially available radioimmunoassay kit gave the following statistical data using Deming calculations. The data is presented both across the dynamic range of the assay (0.1-500 ng/mL) and in the clinical relevant range of the assay (0.1-50 ng/mL).

n	Range of Observations (ng/mL)	Intercept (ng/mL)	Slope	Correlation Coefficient (r)
224	0.47-323.0	3.574	0.6691	0.9721
146	0.58-44.8	-0.7800	0.9217	0.9604

DILUTION RECOVERY (LINEARITY)

Three serum samples containing elevated Tg concentrations were diluted with the Access Thyroglobulin Sample Diluent and assayed.

Sample 1	Expected Concentration (ng/mL)	Determined Concentration (ng/mL)	Recovery (%)
Neat	48.11	48.11	100
1:2	24.05	24.66	102.5
1:3	16.04	16.81	104.8
1:5	9.62	10.32	107.3
1:10	4.81	5.46	113.5
		Mean % Recovery	**107.0**

Sample 2	Expected Concentration (ng/mL)	Determined Concentration (ng/mL)	Recovery (%)
Neat	139.47	139.47	100
1:2	69.73	65.96	94.6
1:3	46.49	42.64	91.7
1:5	27.89	25.40	91.0
1:10	13.95	12.61	90.4
		Mean % Recovery	**91.9**

Sample 3	Expected Concentration (ng/mL)	Determined Concentration (ng/mL)	Recovery (%)
Neat	304.63	304.63	100
1:2	152.32	144.66	95.0
1:3	101.55	95.95	94.5
1:5	60.93	58.07	95.3
1:10	30.47	30.06	98.6
		Mean % Recovery	**95.8**

IMPRECISION

This assay exhibits total imprecision of less than 10% at concentrations > 1 ng/mL. One study, using pooled serum controls generating a total of 20 assays, two replicates per assay over 10 days, provided the following data, analyzed via analysis of variance (ANOVA).[10,15]

Patient Sample	Grand Mean (n=40) (ng/mL)	Within Run (%CV)	Between Run (%CV)	Total Imprecision (%CV)
1	3.2	2.2	0.0	2.2
2	4.2	1.4	1.7	2.2
3	21.6	1.4	1.8	2.3
4	130.4	4.4	4.9	6.6
5	344.7	2.0	4.0	4.5

ANALYTICAL SPECIFICITY / INTERFERENCES

Samples containing up to 10 mg/dL (171 µmol/L) bilirubin, lipemic samples containing the equivalent of 1,800 mg/dL (20.32 mmol/L) triolein (triglycerides) and hemolyzed samples containing up to 1 g/dL (10 g/L) hemoglobin do not affect the concentration of thyroglobulin assayed. In addition, samples with 5 g/dL (50 g/L) human serum albumin added to the endogenous albumin in the samples do not affect the concentration of thyroglobulin assayed.

Samples containing up to 50 mg/dL Aspirin, 20 mg/dL Acetaminophen, 40 mg/dL Ibuprofen, and 218.5 µg/dL of Thyroxine do not affect the concentration of thyroglobulin assayed.

Biotin

The following concentrations of biotin were spiked into normal serum samples at high and low Thyroglobulin concentrations and found to give the following percent change in result response.

		Biotin (ng/mL)						
Analyte Range	**Analyte Concentration**	**10**	**25**	**50**	**100**	**300**	**600**	**1,200**
Low	20 - 24 ng/mL	-2%	-7%	-18%	-49%	-79%	-86%	-90%
High	73 - 84 ng/mL	-4%	-9%	-23%	-51%	-80%	-87%	-91%

ANALYTICAL SENSITIVITY

The lowest detectable level of Tg distinguishable from zero (Access Thyroglobulin Calibrator S0) with 95% confidence is 0.1 ng/mL. This value is determined by processing a complete six-point calibration curve, controls and ten replicates of the zero calibrator in multiple assays. The analytical sensitivity value is calculated from the curve at the point that is two standard deviations from the fitted zero calibrator signal.

ADDITIONAL INFORMATION

For a patient/user/third party in the European Union and in countries with identical regulatory regime (Regulation 2017/746/EU on In vitro Diagnostic Medical Devices); if, during the use of this device or as a result of its use, a serious incident has occurred, please report it to the manufacturer and/or its authorized representative and to your national authority.

The Summary of Safety and Performance is available from the EUDAMED database: ec.europa.eu/tools/eudamed

REVISION HISTORY

Revision A

New release of IVDR compliant IFU.

Revision B

Added Translations.

Revision C

Added Translations.

Revision D

Updated ProClin trademark statement.

Revision E

Added Translations.

SYMBOLS KEY

Glossary of Symbols is available at beckmancoulter.com/techdocs (document number C02724).

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