BECKMAN COULTER

CE 2797

ACCESS
Immunoassay Systems

Access Free T4

Instructions For Use

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REF C76421

FOR PROFESSIONAL USE ONLY

For *in vitro* diagnostic use

Rx Only

For use on Access 2, DxC 500i, UniCel DxC 600i, UniCel DxI 600, UniCel DxI 800, UniCel DxC 880i, UniCel DxC 860i, UniCel DxC 680i, and UniCel DxC 660i systems

PRINCIPLE

INTENDED USE

The Access Free T4 assay is a paramagnetic particle, chemiluminescent immunoassay for the quantitative determination of free thyroxine levels in human serum and plasma (heparin) for the diagnosis and treatment of thyroid diseases using the Access Immunoassay Systems.

SUMMARY AND EXPLANATION

The clinical importance of free T4 determination is as an aid in the diagnosis of thyroid disorders.[1,2,3,4]

The hypothalamic-pituitary-thyroid axis controls thyroid hormone synthesis, release, and action. Thyrotropin-releasing hormone (TRH) secreted from the hypothalamus stimulates the synthesis and release of thyrotropin or thyroid-stimulating hormone (TSH). TSH, in turn, stimulates the synthesis, storage, secretion, and metabolism of thyroxine (T4) and triiodothyronine (T3). Both free and bound forms of T4 and T3 are present in the blood. More than 99% of the T4 and T3 circulate in the blood bound to carrier proteins, leaving less than 1% unbound. It is this level of unbound or free hormone that correlates with the functional thyroid state in most individuals.[5,6]

Free T4 and free T3 regulate normal growth and development by maintaining body temperature and stimulating calorigenesis. In addition, free T4 and free T3 affect all aspects of carbohydrate metabolism as well as certain areas of lipid and vitamin metabolism.

Elevated free T4 levels support the clinical findings of a diagnosis of hyperthyroidism while low free T4 levels coupled with appropriate clinical findings, can establish a diagnosis of hypothyroidism. Measurement of free T4 levels along with other thyroid tests and clinical findings can establish subclinical hyperthyroid and hypothyroid diagnoses.[3,4,7]

Equilibrium dialysis RIA is considered the reference method for measuring free T4 because it allows for the separation of free T4 from protein bound T4 before direct measurement of the free T4.[6] However, this method is cumbersome, technically demanding, and not suited to routine clinical laboratory use. More recently, radioimmunoassays and enzyme immunoassays have been developed for measuring free T4. These assays employ various combinations of analog or non-analog tracers and one-step or two-step incubation procedures.

METHODOLOGY

Assay type: two-step, competitive

The Access Free T4 assay is a two-step enzyme immunoassay. Biotinylated monoclonal anti-Thyroxine (T4) antibody pre-coupled to streptavidin particles, sample, and buffered protein solution are added to the reaction vessel. During this

first incubation the anti-T4 antibody binds to the free T4 in the sample. After incubation in a reaction vessel, materials bound to the solid phase are held in a magnetic field while unbound materials are washed away. Next, buffered protein solution and triiodothyronine (T3)-alkaline phosphatase conjugate are added to the reaction vessel. The T3-alkaline phosphatase conjugate binds to the vacant anti-T4 antibody binding sites.

After incubation, 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 inversely proportional to the concentration of analyte in the sample. Analyte concentration is automatically determined from a stored calibration.

SPECIMEN

SPECIMEN COLLECTION AND PREPARATION

1. Serum and plasma (lithium heparin) are the recommended sample types.
   - The Access Free T4 Assay has not been validated for dry blood spot samples.
2. Observe the following recommendations for handling, processing, and storing blood samples:[8,9]
   - Collect all blood samples observing routine precautions for venipuncture.
   - Allow serum samples to clot completely before centrifugation in a vertical, closure up position.
     - Nonanticoagulated tubes containing gel or a clot activator should be stored in an upright position as soon as the mixing is complete.
     - Precentrifugation serum/cells contact time is according to tube manufacturer's recommendations. Clotting may be slowed at cooler temperatures or if patient is on anticoagulant therapy.
   - 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 for up to 48 hours.
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.
5. Thaw samples only once.
6. Avoid assaying lipemic or hemolyzed samples.

REAGENTS

CONTENTS

Access Free T4 Reagent Pack
Ref. No. C76421: 100 determinations, 2 packs, 50 tests/pack

The same reagent formulation is used on all Access Immunoassay Systems.

Well	Contents	Ingredients
R1a:	3.37 mL	Dynabeads* paramagnetic particles coated with streptavidin and mouse monoclonal anti-Thyroxine (T4) coupled to biotin in a TRIS buffer with protein (avian), surfactant, 0.125% NaN_3, and 0.125% ProClin** 300.
R1b:	13.25 mL	TRIS buffered saline with protein (avian), surfactant, < 0.1% NaN_3, and 0.1% ProClin 300.
R1c:	3.1 mL	TRIS buffered saline with protein (avian), surfactant, 0.125% NaN_3, and 0.125% ProClin 300.
R1d:	3.1 mL	Triiodothyronine-alkaline phosphatase (bovine) conjugate in a TRIS buffer with protein (avian), surfactant, < 0.1% NaN_3, and 0.1% ProClin 300.
R1e:	3.1 mL	TRIS buffer with protein (avian and murine), surfactant, 0.125% NaN_3, and 0.125% 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.
- 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,[10] 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

FT4 PMP Plus (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. Sodium Azide < 0.18% 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%
FT4 Buffer 1 (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%
FT4 Buffer 2 Plus (Compartment R1c)	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. Sodium Azide < 0.18% 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%
FT4 Conjugate (Compartment R1d)	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%
FT4 BT-Mc FT4 BOS Plus (Compartment R1e)	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.
		Sodium Azide < 0.18%
		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 Free T4 Calibrators
   Provided at zero and approximately 0.5, 1.0, 2.0, 3.0, and 6.0 ng/dL (6.4, 12.9, 25.7, 38.6, and 77.2 pmol/L).
   Ref. No. 33885
2. Quality Control (QC) materials: commercial control material.
3. Access Substrate
   Ref. No. 81906
4. Access Wash Buffer II, Ref. No. A16792
   UniCel DxI Wash Buffer II, Ref. No. A16793

REAGENT PREPARATION

Provided ready to use.

REAGENT STORAGE AND STABILITY

Stability	
Unopened at 2 to 10°C	Up to stated expiration date
After opening at 2 to 10°C	28 days

- Store upright.
- Refrigerate at 2 to 10°C for a minimum of two hours before use on the instrument.
- Signs of possible deterioration are a broken elastomeric layer on the pack or quality control values out of range.
- If the reagent pack is damaged (e.g., broken elastomer), discard the pack.

CALIBRATION

An active calibration curve is required for all tests. Calibration is required every 28 days. See calibrator Instructions for Use (IFU) for additional calibration information. Refer to the appropriate system manuals and/or Help system for information on calibration method, configuring calibrators, calibrator test request entry, and reviewing calibration data.

QUALITY CONTROL

Quality control materials are essential for monitoring the system performance. Quality controls with varying concentration ranges should be run individually at least once every 24 hours when the assay is being performed.[11] Quality control ranges should be determined by each laboratory's individual requirements. Follow applicable regulations and guidelines for quality control.

TESTING PROCEDURE(S)

PROCEDURE

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. Refer to the appropriate system manuals and/or Help system for information on managing samples, configuring tests, requesting tests, and reviewing test results.
3. Mix contents of new (unpunctured) reagent packs by gently inverting pack several times before loading on the instrument. Do not invert open (punctured) packs.
4. Use 30 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.
5. The system default unit of measure for sample results is ng/dL. To change sample reporting units to the International System of Units (SI units), pmol/L, refer to the appropriate system manuals and/or Help system. To manually convert concentrations to the International System, multiply ng/dL by multiplication factor 12.87.

LIMITATIONS

1. 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.[12,13] Such interfering antibodies may cause erroneous results. Carefully evaluate the results of patients suspected of having these antibodies.

2. Other potential interferences could be present in the sample and may cause erroneous results in immunoassays. Some examples that are documented in literature include rheumatoid factor, fibrin, endogenous alkaline phosphatase, exogenous alkaline phosphatase (e.g. asfotase alfa, Strensiq) and proteins capable of binding to alkaline phosphatase. Carefully evaluate results if the sample is suspected of having these types of interferences.[14,15]
3. The Free T4 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. Do not dilute samples as this could lead to incorrect results.

RESULTS INTERPRETATION

Test results are determined automatically by the system software. 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

MEASURING INTERVAL

Approximately 0.40 – 6.0 ng/dL (5.15 – 77.2 pmol/L)

Samples can be accurately measured within the analytic range of the lower limit of quantitation (LoQ) and the highest calibrator value (approximately 0.40-6.0 ng/dL [5.15-77.2 pmol/L]).

1. If a sample contains less than the lower limit of quantitation for the assay, report the results as less than that value (i.e., < 0.40 ng/dL [< 5.15 pmol/L]).
2. If a sample contains more than the stated value of the highest Access Free T4 Calibrator (S5), report the result as greater than that value (i.e., > 6.0 ng/dL [> 77.2 pmol/L]).

SAMPLES CANNOT BE DILUTED FOR FREE T4 DETERMINATIONS.

EXPECTED VALUES

1. Each laboratory should validate or establish its own reference intervals to assure proper representation of specific populations.
2. Sera samples were obtained from a minimum of 150 males and 150 females ranging in age from 18-60 years old. The samples were collected from the east, west and central United States. Following the guidance of both the National Academy of Clinical Biochemists (NACB) Laboratory Support for the Diagnosis and Monitoring of Thyroid Disease[16] and the American Association of Clinical Endocrinologists,[17,18,19] the following screening criteria was utilized: TSH value 0.3-3.0 µIU/mL, no known personal or family history of thyroid disease or autoimmune disease and the absence of thyroid medication. After completing the Access TSH screen, 32 samples were excluded due to TSH values outside of the 0.3-3.0 µIU/mL range.

n	95% Reference Limit (ng/dL)	95% CI for Lower Limit (ng/dL)	95% CI for Upper Limit (ng/dL)
316	0.61-1.12	0.54-0.67	1.07-1.24

n	95% Reference Limit (pmol/L)	95% CI for Lower Limit (pmol/L)	95% CI for Upper Limit (pmol/L)
316	7.86-14.41	7.00-8.57	13.73-15.96

3. Sera samples were obtained from a minimum of 120 women in the first, second and third trimester of pregnancy.

Sample Type	n	95% Reference Limit (ng/dL)	90% CI for Lower Limit (ng/dL)	90% CI Upper Limit (ng/dL)
1st Trimester	131	0.52-1.10	0.47-0.57	1.08-1.27
2nd Trimester	120	0.45-0.99	0.40-0.48	0.80-1.08
3rd Trimester	121	0.48-0.95	0.45-0.51	0.83-1.23

Sample Type	n	95% Reference Limit (pmol/L)	90% CI for Lower Limit (pmol/L)	90% CI Upper Limit (pmol/L)
1st Trimester	131	6.67-14.12	6.00-7.31	13.86-16.28
2nd Trimester	120	5.79-12.70	5.19-6.14	10.24-13.86
3rd Trimester	121	6.11-12.20	5.77-6.62	10.68-15.79

4. Samples containing thyroxine autoantibodies can be assayed in two step procedures such as the Access Free T4 assay without significant interference.[6]

PERFORMANCE CHARACTERISTICS

ASSAY CRITERIA AND REPRESENTATIVE DATA

Representative data is provided for illustration only. Performance obtained in individual laboratories may vary.

METHODS COMPARISON

A study based on CLSI EP09c, 3rd Edition[20] using Passing-Bablok regression compared the Access 2 Immunoassay System and a commercially available immunoassay system.

N	Concentration Range* (ng/dL)	Slope	Slope 95% CI	Intercept	Intercept 95% CI	Correlation Coefficient R
163	0.27 to 5.32	1.02	1.00 to 1.04	-0.04	-0.06 to -0.02	0.98

*Values are commercially available immunoassay system values

LINEARITY

A study based on CLSI EP06-Ed2[21] performed on the Access 2 Immunoassay System determined the assay demonstrated linearity across the measuring interval.

IMPRECISION

This assay was designed to have within-laboratory imprecision listed below:

- ≤ 0.06 ng/dL SD at concentrations < 0.61 ng/dL
- ≤ 10% CV at concentrations ≥ 0.61 ng/dL

A study based on CLSI EP05-A3[22] performed on the Access 2 Immunoassay System tested multiple samples in duplicate in 2 runs per day for a minimum of 20 days.

Concentration (ng/dL)			Within-Run (Repeatability)		Between-Run		Between-Day		Within-Laboratory	
Sample	**N**	**Mean**	**SD**	**%CV**	**SD**	**%CV**	**SD**	**%CV**	**SD**	**%CV**
Sample 1	80	0.42	0.03	7.4	0.02	5.1	0.02	4.3	0.04	10.0
Sample 2	80	0.86	0.03	3.1	0.01	1.4	0.01	1.0	0.03	3.5
Sample 3	80	1.7	0.05	2.9	0.02	1.0	0.03	1.8	0.06	3.5
Sample 4	80	2.4	0.07	2.9	0.03	1.2	0.08	3.4	0.11	4.6
Sample 5	80	4.2	0.10	2.3	0.04	1.0	0.14	3.4	0.17	4.2

ANALYTICAL SPECIFICITY / INTERFERENCES

Serum samples that contain Free T4 concentrations of approximately 0.8 and 1.5 ng/dL were spiked with multiple concentrations of the substances listed in the following table. The spiked samples were run on a single Access 2 Immunoassay System. The values were calculated based upon CLSI EP07-A3.[23] The interference was determined by testing controls (with no interfering substance added) and matched test samples (with interfering substance added). None of the compounds tested were found to cause significant interference, as defined by a shift in dose that is greater than 10% using the highest test concentrations provided in the following table.

Substance	Highest Concentration Added
Albumin	10.0 g/dL
Aspirin	60 mg/dL
Bilirubin (unconjugated)	10 mg/dL
Biotin	3,510 ng/mL
Hemoglobin	1 g/dL
Lipemia (triolein)	1,800 mg/dL
Methimazole	0.4 mg/dL
Phenylbutazone	7.5 mg/dL
Phenytoin	5.0 mg/dL
Prealbumin (TBPA)	600 µg/mL
Sodium Salicylate	50 mg/dL
Thiouracil	5.0 mg/dL
Thyroxine Binding Globulin	16 mg/dL

A study evaluated the potential for cross-reactivity of the antibody used in the Free T4 assay with substances that are similar in structure to T4. Serum samples that contain Free T4 concentrations of 0.8 and 1.5 ng/dL were spiked with the substances listed in the following table. The spiked samples were run on an Access 2 Immunoassay System. The values were calculated based upon CLSI EP07-A3[23] guidelines. Cross-reactivity was observed when the listed substances were tested at the indicated concentrations.

Substance	Analyte Added (ng/dL)	Cross-reactivity (%)
D-T4	10,000	≤ 100
L-T3	500,000	≤ 2

Substance	Analyte Added (ng/dL)	Cross-reactivity (%)
R-T3	100,000	≤ 25
Tetraiodothyroacetic Acid	25,000	≤ 10
D-T3	500,000	≤ 1.0
3,3' L-T2	5,000,000	≤ 0.1
3,5 L-T2	5,000,000	≤ 0.1
3',5' L-T2	5,000,000	≤ 0.1
L-Tyrosine	5,000,000	≤ 0.01
d-Tyrosine	5,000,000	≤ 0.01
Monoiodotyrosine	5,000,000	≤ 0.01
Diiodotyrosine	5,000,000	≤ 0.01

DETECTION CAPABILITY

Limit of Blank (LoB), Limit of Detection (LoD), and Limit of Quantitation (LoQ) studies were conducted on Access 2 Immunoassay Systems following CLSI guideline EP17-A2.[24] The LoB study included multiple reagent lots and 3 instruments over a minimum of 3 days. The LoD and LoQ studies included multiple reagent lots and 3 instruments over a minimum of 5 days.

	ng/dL	pmol/L
Limit of Blank (LoB)	0.25	3.22
Limit of Detection (LoD)	0.40	5.15
Limit of Quantitation (LoQ) ≤ 20% within-lab CV	0.40	5.15

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.

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May be covered by one or more pat. -see www.beckmancoulter.com/patents.

REVISION HISTORY

Revision A

Initial release.

Revision B

Updated ProClin trademark statement.

Revision C

Updated "For Use" section.

SYMBOLS KEY

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

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EC REP Beckman Coulter Ireland Inc., Lismeehan, O'Callaghan's Mills, Co. Clare, Ireland +(353) (0) 65 683 1100

Beckman Coulter, Inc., 250 S. Kraemer Blvd., Brea, CA 92821 U.S.A.
+(1) 800-854-3633
www.beckmancoulter.com