Whole PTH™ (1-84) Specific

Immunoradiometric (IRMA) Assay
(Coated Bead-Technology)
For the quantitative determination of human whole PTH
****For In Vitro Diagnostic Use Only**

CE

Scantibodies
(Part Number: 3KG056)

Store at 2 - 8° C

INTENDED USE

This kit has been designed for the quantitative determination of human whole parathyroid hormone (PTH) without cross-reaction to PTH (7-84) fragment in blood samples.[32,33,34,35]

PHYSIOLOGY

The Whole PTH™ peptide (1-84) is secreted by parathyroid glands under the regulation of the extra-cellular concentration of ionized calcium, vitamin D and magnesium. PTH acts with respect to calcium on the kidney and the skeleton[4,5]. PTH binds to receptors, which stimulate adenylate-cyclase to produce cyclic adenosine monophosphate (cAMP) from adenosine triphosphate (ATP)[10,13]. The biological activity of PTH resides in the first 3 amino acids of the N-terminal portion of the molecule. PTH is metabolized either intra glandular or in the peripheral organs into fragments. Circulatory PTH are immunologically heterogenous [7,6,12,13,18,19]. A recent study of circulation immunoreactive PTH showed that significant amounts of a large carboxyl-terminal PTH fragment, PTH (7-84), presented in blood samples from uremic patients[31]. Biologically inactive fragments with molecular weights of 4000 - 7000 Daltons circulate with a half-life of 30 minutes in healthy persons [4,5].

cAMP or other PTH dependent processed metabolites (e.g. hypophosphatemia) stimulate the renal hydroxylation of 25-(OH) vitamin D to 1,25-$(OH)_2$ vitamin D. This vitamin D metabolite stimulates calcium absorption by the small intestine. Severe vitamin D deficiency results in an enhanced secretion of PTH compared to the secretion of calcium. Hypomagnesemia in the primary stage stimulates hypocalcemia. Severe hypomagnesemia results in the reduced secretion of PTH.

Primary and secondary hyperparathyroidism, kidney insufficiency, malabsorption-syndrome and pseudo-hypoparathyroidism result in elevated concentrations of PTH[14,15,16]. Decreased concentrations of PTH coincide with high doses of vitamin-D, milk-alkali-syndrome, Morbus Boeck, hyperthyreosis, ingestion of thiazide and hypercalcemia of malignancy. PTH concentration is also decreased with absorptive hypercalciuria and hypoparathyroidism.

PRINCIPLE OF PROCEDURE

Scantibodies 1-84 PTH or Whole PTH™ Kit is an immunoradiometric (IRMA) assay utilizing a polyclonal 1-84 PTH antibody with a tendency to bind in the N terminal region of 1-84 PTH (Label Antibody), and a polyclonal 1-84 PTH antibody with a tendency to bind in the C terminal region of 1-84 PTH (Capture Antibody). The use of these antibodies guarantees that only Whole PTH™ (CAP™) is detected. The Label Antibody is labeled with 125-I. The Capture Antibody is fixed to the beads. 1-84 PTH or Whole PTH™ (CAP™) in patient samples is bound both to the beads and the Label Antibody. Simple wash steps reduce the non-specific binding (NSB) to a minimum for increased precision at the low end of the calibration curve. The concentration of Whole PTH™ (CAP™) is directly proportional to the radioactivity bound to the beads after separation. The concentration of PTH in unknown patient samples and controls is determined by interpolation using a calibration curve.[30]

REAGENTS

The Scantibodies Whole PTH™ Kit contains sufficient reagents for 100 single determinations. The kit is stable at 2 - 8° C until the stated expiration date.

PTH CALIBRATORS

One set of calibrators consists of seven vials containing lyophilized human serum with nominal Whole PTH™ (CAP™) concentrations. The lyophilized calibrators are prepared in stabilized human serum containing sodium azide 0.1% (w/v). The Whole PTH™ (CAP™) concentrations are declared on the vial label.

PTH CONTROLS

One set of controls consists of two vials containing Whole PTH™ (CAP™) in lyophilized human serum with 0.1% (w/v) sodium azide. The concentration ranges of Whole PTH™ (CAP™) are declared on the vial labels.

^{125}I-ANTI N-TERMINAL PTH TRACER

One set of tracer consists of two bottles of ^{125}I-antibodies. Each bottle contains goat anti N-terminal PTH antibodies which are labeled with ^{125}I and dissolved in 5 ml phosphate buffered saline with sodium azide 0.1% (w/v) and protein stabilizers. The maximum radioactivity in a bottle is <370 kBq (<10 μCi). This kit contains ^{125}I (half life: 60 Days), emitting ionizing X (28 keV) and Gamma

γ (35,5 keV) radiations.

PTH (39-84) ANTIBODY COATED BEADS

One bottle contains 100 polystyrene beads (8 mm) plus desiccant. The beads are coated with goat anti-PTH (39-84). The desiccant contains silica.

WASH CONCENTRATE

One bottle contains 30 ml of a 30 fold concentrate of phosphate buffered saline with sodium azide 1.5% (w/v) and detergent.

PREPARATION AND STORAGE OF REAGENTS

PTH CALIBRATORS

The Scantibodies Laboratory, Inc. Whole PTH™ Coated Bead Diagnostic Kit contains the PTH standards prepared analytically on a mass basis from purified synthetic Whole PTH™ (1-84). These standards are further evaluated against "primary standards" which are stored at -70° C to maintain calibration.

Reconstitute the zero calibrator with 5 ml of distilled or deionized water. Reconstitute the remaining calibrators with 2 ml of distilled or deionized water. After addition of the water, mix each vial thoroughly but gently. Use the reconstituted calibrators within 1 hour. Store the unused portion of the calibrators below -20° C until the stated expiration date. Do not store the calibrators at room temperature for more than one hour at any given time. Do not thaw any calibrator vial more than two times.

PTH CONTROLS

Reconstitute the vials of controls with 2 ml of distilled or deionized water. After addition of the water, mix each vial thoroughly but gently. Use the reconstituted controls within 1 hour. Store the unused portion of the controls below -20° C until the stated expiration date. Do not store the controls at room temperature for more than one hour at any given time. Do not thaw any control vial more than two times.

^{125} I-ANTI N-TERMINAL PTH TRACER

The tracer is ready to use. Store the tracer at 2 - 8° C until the stated expiration date.

PTH (39-84) ANTIBODY COATED BEADS

The antibody coated beads are ready to use. Store the beads at 2 - 8° C until the stated expiration date. Allow the beads to equilibrate to ambient temperature prior to opening package. Reseal the package immediately after removing the required number of beads.

WASH CONCENTRATE

Mix the contents of the wash concentrate thoroughly with 870 ml of distilled or deionized water (1:30). Store the diluted wash solution at room temperature (18 - 25° C) until the stated expiration date.

WARNINGS AND PRECAUTIONS FOR USERS

Use of The Assay

The reagents are for in vitro diagnostic use only.

Human Serum Caution

The human serum in this kit has been prepared from human donors and it has been tested by FDA approved immunoassays and found to be non-reactive for Hepatitis B Surface Antigen (HBsAg), Anti HIV I/II and Anti HCV. However, it is recommended to consider the calibrators and controls as a potential biohazard and handle them with the same precautions as applied to any untested patient sample.

Radioactivity Warning

This radioactive material may be received, acquired, possessed, or used only by physicians, clinical laboratories, or hospitals and only for *in vitro* clinical or laboratory tests not involving internal or external administration of the material, or the radiation therefrom, to human beings or animals. Its receipt, acquisition, possession, use and transfer are subject to the regulations and a general license of the U.S. Nuclear Regulatory Commission or of a state with which the Commission has entered into an agreement for the exercise of regulatory authority.

All radioactive materials must be disposed of according to the regulations (regulations differ from country to country) and guidelines of the agencies with jurisdiction over the laboratory. Do not eat, drink, smoke or apply cosmetics in areas where radioactive materials are used. Storage of radioactive materials should be limited to specifically designated and appropriately secured areas. Access to radioactive materials should be limited to authorized and trained personnel only. Do not pipette radioactive solutions by mouth. Avoid direct contact with radioactive materials by using protective articles such as lab coats and disposable gloves. Radioactive materials must be stored in designated areas in their original containers or in containers providing equivalent radiation protection. A record of disposal of all radioactive materials must be kept. Immediately remove spilled solutions and decontaminate contaminated devices. Check laboratory equipment and glassware regularly to detect contamination with radioisotopes.

Sodium Azide (NaN_3) Warning

Some reagents in the Scantibodies PTH assay contain sodium azide. Sodium azide may react with lead and copper plumbing to form highly explosive metal azides. On disposal flush the drain with a large volume of water to prevent azide build-up. Avoid direct contact with skin and mucous membranes.

SAMPLE PREPARATION AND STORAGE

Specimen Collection

The determination of human PTH should be made on EDTA-plasma. Four hundred microliters of plasma are required to assay one sample in duplicate. To obtain plasma, collect blood by venipuncture into a tube containing EDTA. Invert the tube gently 5 - 6 times after collection to ensure adequate mixing. Whole blood may be stored refrigerated for up to 48 hours prior to centrifugation. Centrifuge the sample and separate the plasma from the cells. Plasma should be stored at -20° C or lower if not tested immediately. Avoid repeated freezing and thawing of plasma. Do not use patient samples which have been frozen and thawed more than two times.

Dilution of Patient Samples

Dilute plasma samples with PTH concentrations greater than the highest calibrator with Scantibodies PTH Zero Calibrator before assay. The dilution factor is applied to the diluted sample assay result in order to determine the PTH concentration in the undiluted sample.

Quality Control

Two levels of controls are provided with each assay kit. The values assigned to these controls are printed on the container label. The control value should fall within the specified range when tested in the same manner as the unknowns. Controls should be included in each assay. If the control values do not meet the established range, the assay may be invalid and should be repeated.

ASSAY PROCEDURE

Materials Provided

The Scantibodies Whole PTH™ Kit (Part No. 3KG056) is supplied with the following:

Description	Number
PTH Standards 3CA650, 3CB650, 3CC650, 3CD650, 3CE650, 3CF650, 3CG650	7 vials
PTH Controls Part Nos. 3CA651, 3CB651	2 vials
PTH (39-84) Antibody Coated Beads Part No. 3KB001	1 bottle of 100 beads
Goat Anti-N-Terminal PTH ^{125}I Antibody Part No. 3KL022	2 vials
Wash Concentrate Part No. 3KW001	1 bottle
Directional Insert Part No. 3KI086	1 insert

Materials And Equipment Required But Not Provided:

Distilled or deionized water
Round-bottomed polypropylene or polystyrene test tubes
(12 x 55, 12 x 75, 12 x 70 mm or equivalent)
Pipettor with disposable tips: 0.2 ml
Wash station
Vortex mixer
Gamma counter calibrated to detect ^{125}I

Preparation for Assay

For each assay, prepare the following groups of tubes and place them in a test tube rack (double determination):

2 total count tubes (optional for QC). Use non-coated tubes.
2 Bo tubes (NSB)
2 tubes for each calibrator concentration
2 tubes for each control concentration
2 tubes for each patient sample

Pipetting and Incubation Steps

1. Pipette 0.2 ml of calibrators, samples and controls into the corresponding tubes.
2. Pipette 0.1 ml of goat anti-N-terminal PTH ^{125}I antibody into each tube.
3. Gently vortex all tubes.
4. Dispense one antibody coated bead into each tube except for the total count tubes. To add the beads, tilt the test tube rack to approximately a 30 degree angle to prevent splashing.
5. Seal the tubes and incubate them for 18 - 24 hours at room temperature (18 - 25° C) and shaking 170 RPM.
6. Aspirate the supernatant from each tube except for the total count tubes. Wash the beads 3 times with 2 ml of diluted wash solution. After each addition of diluted wash solution aspirate all of the wash solution.
7. Count each tube for at least 1 minute in a gamma counter calibrated to detect ^{125}I. The total count tube should contain approximately 300,000 CPM (assuming the counter has an efficiency of 70% - 80%) when freshly iodinated ^{125}I-anti-N-terminal PTH tracer is used. The total activity of the tracer decreases according to the half-life of ^{125}I.

PIPETTING GUIDE

Additive to Tube	Total Count Tubes	Bo Tubes	Calibrator Tubes	Control Tubes	Sample Tubes
Calibrator	-	200 µl	200 µl		-
Control	-	-	-	200 µl	
Sample	-	-	-	-	200 µl
^{125}I anti-N-terminal PTH	100 µl	100 µl	100 µl	100 µl	100 µl
Beads	-	1	1	1	1
Vortex mix all tubes, except for the TC tubes. Incubate tubes for 18 - 24 hours at room temperature (18 - 25° C) and shaking at 170 RPM.					

Additive to Tube	Total Count Tubes	Bo Tubes	Calibrator Tubes	Control Tubes	Sample Tubes
Aspirate the supernatant from all of the tubes except the total count tubes. Wash all tubes except the total count tubes by adding 2 ml of diluted wash solution and aspirating the wash solution. Repeat this wash step two more times for a total of three times.					
Count each tube for at least 1 minute in a gamma counter.					

PROCEDURAL COMMENTS

Interferences:

Samples containing up to 250 mg/dl triglyceride, 15 mg/dl hemoglobin and 7.5 mg/dl bilirubin do not exhibit any effect on the assay.

Grossly hemolyzed or lipemic samples.

Samples from patients receiving radioisotopes for diagnostic or therapeutic purposes.

Contamination of the sample or assay tube with ^{125}I or other radioisotopes.

Reagents from different lot numbers must not be interchanged.

The patient sample or calibrator and the ^{125}I-anti-N-terminal PTH tracer should be pipetted carefully into the bottom one-fourth of the assay tube. This is to avoid losing liquid on the surface of the tube as the liquid runs down the tube.

The washing step is an important step in the assay procedure. Accurate dispensing of the wash solution and complete aspiration of the tube contents is essential to achieving assay sensitivity, low background and assay precision.

It is recommended that calibrators and patient samples be assayed in duplicate. The average counts per minute of each duplicate should then be used for data reduction and the calculation of results.

Avoid sample to sample contamination by using a new pipette tip for each sample.

CALCULATION OF RESULTS

Evaluation

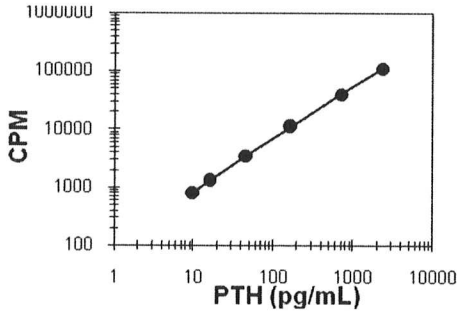
1. Calculate the average CPM for each double determination.
2. Subtract the average CPM of the zero calibrator tubes from the CPM's from all other tubes in order to obtain the corrected CPM for each tube.
3. Corrected CPM = average CPM of duplicate samples - average CPM of duplicate zero calibrators.
4. Draw the calibration curve by plotting the average corrected CPM from each duplicate calibrator level (ordinate) against the respective concentration declared on the calibrator vial (absolute) using log-log graph paper. Obtain sample concentrations by interpolation of average sample CPM on the calibration curve.
5. If samples were run with dilution, multiply the diluted sample assay results from the curve by the appropriate dilution factors to obtain the undiluted sample assay results.

SAMPLE DATA

Tube	CPM	Ave.CPM	Corrected CPM
Total Activity	331856 332975	332415	
0 pg/ml	246 283	264	
10 pg/ml	787 852	819	555
16 pg/ml	1349 1262	1306	1042
46 pg/ml	3490 3557	3523	3259
165 pg/ml	11178 11070	11124	10860
700 pg/ml	39835 39907	39871	39607
2300 pg/ml	110979 110168	110574	110310

NOTE: The data presented are for demonstration purposes only and must not be used in place of data generated at the time of the assay.

REPRESENTATIVE STANDARD CURVE



Automated data reduction can also be used to construct the Scantibodies PTH calibration curve. To program automated data reduction systems or to adapt an existing program consult the data processor manufacturer or the programmer.

LIMITATIONS OF THE PROCEDURE

For diagnostic purposes PTH values should be used in addition to other diagnostic data and clinical information available to the physician.

The assay procedure must be followed exactly; careful

technique must be used to obtain valid results. Any modification of the assay procedure is likely to alter the results.

Grossly hemolyzed, lipemic or icteric samples are likely to give non valid results.

The highest concentration of PTH measurable without sample dilution is the concentration of the highest calibrator. The lowest level measurable is approximately 1 pg/ml.

EXPECTED VALUES

The normal value range was determined following the NCCLS guidelines (C28-A) using 128 samples from apparently healthy individuals. It is recommended that each laboratory establish its own range of normal values. The values given are only indicative and may vary from other published data.

PATIENT CLASSIFICATION	Whole PTH™ RANGE (pg/ml)
Normal	5 - 39
Hyperparathyroidism	> 39

PERFORMANCE CHARACTERISTICS

Accuracy, Recovery

Different samples with low concentrations of PTH were spiked with 2 amounts of PTH. The % recovery was determined following assay of the spiked samples.

Sample value (pg/ml)	Added PTH (pg/ml)	Measured value (pg/ml)	Expected value (pg/ml)	Recovery (%)
36.05	- 50.07 141.51	- 43.11 90.62	- 43.06 88.78	- 100.12 102.07
77.09	- 41.34 130.31	- 66.9 108.72	- 59.22 103.7	- 112.98 104.84
126.2	- 39.23 130.33	- 91.42 127.38	- 82.72 128.27	- 110.52 99.31

Accuracy, Dilution

Different samples with high concentrations of PTH were diluted in a sample with low concentrations of PTH. The % recovery was determined following assay of the diluted samples.

Sample	Dilution	Measured value (pg/ml)	Expected value (pg/ml)	Recovery %
1	Neat 1:2 1:4 1:8	2057.5 1053.58 519.13 273.32	 1028.75 514.38 257.19	 102 101 106
2	Neat 1:2 1:4 1:8	1595.35 758.28 395.67 210.98	 797.68 398.84 199.42	 95 99 106
3	Neat 1:2 1:4 1:8	1006.36 485.9 256.29 140.6	 503.18 251.59 125.80	 97 102 112
4	Neat 1:2 1:4 1:8	646.09 333.07 168.56 87.11	 323.05 161.52 80.76	 103 104 108
5	Neat 1:2 1:4 1:8	573.91 303.99 159.69 86.04	 286.96 143.48 71.74	 106 111 120
6	Neat 1:2 1:4 1:8	181 97.82 48.02 20.42	 90.50 45.25 22.63	 108 106 90
7	Neat 1:2 1:4 1:8	153.12 91.05 49.59 22.28	 76.56 38.28 19.14	 119 130 116

High Dose Hook Response

This high dose hook response of the Scantibodies Laboratory, Inc. Whole PTH™ Specific Coated Bead Diagnostic Kit was determined as 20,000 pg/ml of Whole PTH™ (CAP™). Samples greater than the highest standard (approximately 2300 pg/ml) and up to 20,000 pg/ml Whole PTH™ (CAP™) will read CPM values greater than that of the highest standard.

Precision

The inter-assay precision was evaluated by performing 20 separate Whole PTH™ (CAP™) assays on two samples in duplicate over a two week period.

Precision Inter-assay				
Kit Batch	Sample	Mean value (pg/ml)	SD (pg/ml)	% CV
E2 E2	1 2	32.75 285.05	2.54 11.81	7.76 4.14
E3 E3	1 2	30.97 310.26	2.15 9.08	6.95 2.93

The intra-assay precision was evaluated by performing 20 replicates in the Whole PTH™ (CAP™) assays on two samples.

Precision Intra-assay				
Kit Batch	Sample	Mean value (pg/ml)	SD (pg/ml)	% CV
E1 E1	1 2	30.3 283.87	1.5 7.49	4.94 2.64
E2 E2	1 2	30.85 273.33	1.27 6.3	4.13 2.3
E3 E3	1 2	29.33 290.78	1.77 7.43	6.05 2.56

Sensitivity

The detection limit of the assay is defined as the lowest measurable value distinguishable from zero. This sensitivity was determined by assaying the zero calibrator 20 times in the same assay. The detection limit is approximately 1.0 pg/ml at 2 standard deviation above the PTH zero calibrator.

The functional sensitivity is defined as being the measured concentration by imprecision profile for a CV equal to 20%. It has been assessed as being 3 pg/mL.

Specificity

This Whole PTH™ (CAP™) assay does not show any cross-reaction to PTH (7-84) fragment when the synthetic PTH (7-84) peptide is serially diluted with standard zero matrix and assayed.

PTH (7 -84) Conc. Sample (pg/ml)	Measured PTH conc. (pg/ml)
2500	undetectable
5000	undetectable
10000	undetectable
20000	undetectable

A high degree of correlation exists between the PTH levels of duplicate samples measured by a commercially available predicate PTH kit and those levels measured by the Scantibodies Laboratory, Inc. (SLI) Whole PTH™ (1-84) (CAP™) Specific IRMA Assay. A correlation coefficient (r) of 0.98 (n=223) was obtained with a slope of 1.47 and intercept of -13.65 where x represents the predicate device data and y represents the SLI data. Calculations were made with samples ranging from 9.6 - 1808 pg/mL.

No correlation was made with the Nichols Advantage iPTH Assay nor the Nichols Bio-intact PTH Assay.

Chemical Characterization:	1) Antibodies coated on to polystyrene Beads.
	2) Radioactive Isotope containing Iodine-125 with radioactivity <10 µCi and Sodium Azide @ 0.1%.
	3) Calibrators & Controls – Human Serum containing Sodium Azide @ 0.1%
	4) Wash Concentrate containing sodium azide @ 1.5%.
Hazardous Ingredients:	Radioactive Isotope (Iodine-125) @ <10 µCi/Vial (<370 kBq) CAS Number: 7553-56-2 Symbols: Harmful Xn R-phrases: R22, R52/53 S-phrases: S28, S45, S53, S60, S61
	Sodium Azide @ 0.1% CAS Number: 026628-22-8 Symbols: N/A R-phrases: N/A S-phrases: N/A
	Sodium Azide @ 1.5% CAS Number: 026628-22-8 Symbols: Very Toxic T+; N R-phrases: R28, R32, R50/53 S-phrases: S28, S45, S53, S60, S61

Symbol	Used for	Symbol	Used for
	Do Not Reuse		Use By YYYY-MM-DD or YYYY-MM
LOT	Batch Code	SN	Serial Number
	Date of Manufacture	STERILE	Sterile
STERILE A	Sterilized Using Aseptic Processing Technique	REF	Catalog Number
	Caution, Consult Accompanying Documents		Biological Risks
	Manufacturer	EC REP	Authorized Representative in the European Community
Σ	Contains Sufficient for < n > Tests		For IVD Performance Evaluation Only
IVD	*In vitro* Diagnostic Medical Device		Upper Limit of Temperature
	Lower Limit of Temperature		Temperature Limitation
	Consult Instructions for Use	CONTROL +	Positive Control
CONTROL	Control	CONTROL −	Negative Control
CB	Antibody Coated Beads	CT	Antibody Coated Tubes
TRAC	Radioactive Iodine Tracer	WASH	Wash Solution
RCNS H_2O 2 mL	Reconstituted with 2 mL Water	RCNS H_2O 5 mL	Reconstituted with 5 mL Water
CE	European Conformity Mark		Radioactive
	Toxic	Xn	Harmful

PTH LITERATURES

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