Total Intact PTH

Scantibodies

ImmunoChemiluminoMetric (ICMA) Assay
(Coated Plate-Technology)
For the quantitative determination of human Total Intact PTH
****For *In Vitro* Diagnostic Use Only****

(Part Number: 3KG008)
Store at 2 - 8° C

INTENDED USE

This kit has been designed for the quantitative determination of human total immunoreactive parathyroid hormone (Total Intact PTH) in blood samples. The Total Intact PTH level is the sum of PTH (1-84) and N-terminal truncated PTH fragments.

PHYSIOLOGY

The cyclase activating 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 kidneys and the skeleton. PTH binds to receptors, which stimulate adenylate-cyclase to produce cyclic adenosine monophosphate (cAMP) from adenosine triphosphate (ATP). The biological activity of PTH resides in the first three amino acids of the N-terminal portion of the molecule. PTH is metabolized either intra glandular or in the peripheral organs into fragments. Circulation PTH are immunologically heterogenous. A recent study of circulation immunoreactive PTH showed that significant amounts of a large carboxyl-terminal PTH fragment presented in blood samples from uremic patients. Biologically inactive fragments with molecular weights of 4000-7000 Daltons circulate with a half-life of 30 minutes in healthy persons.

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. 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 Total Intact PTH Kit is an immunochemiluminometric assay (ICMA) utilizing a polyclonal PTH 1-84 antibody with a tendency to bind in the N-terminal region of PTH 1-84 (Label Antibody), and a polyclonal PTH 1-84 antibody with a tendency to bind in the C-terminal region of PTH 1-84 (Capture Antibody). The use of these antibodies guarantees that Whole PTH (1-84) and truncated PTH fragments are detected. The anti-PTH 1-34 (N-Terminal region) antibody is labeled with isoluminol. The antibody directed against 39-84 (C-terminal PTH region) is bound to the wells of the micro titer plate. The Total Intact PTH in patient samples is bound both to the wells of the micro titer plate strips and to the isoluminol-PTH Antibody. After incubation, free and bound isoluminol-antibody fractions are separated by discarding the supernatant. 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 Total Intact PTH is directly proportional to the photons emitted from the wells upon addition of triggering reagents. The concentration of Total Intact PTH in unknown patient samples and controls is determined by interpolation using a calibration curve.[30]

REAGENTS

The Scantibodies Total Intact PTH Kit contains sufficient reagents for 96 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 PTH concentrations. The lyophilized calibrators are prepared in stabilized human serum containing sodium azide 0.1% (w/v). The PTH concentrations are declared on the vial label.

PTH CONTROLS

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

Total Intact PTH TRACER FOR ICMA

The tracer consists of one bottle of PTH 1-34 antibodies labeled with luminol and dissolved in 10 ml phosphate buffered saline with a non-azide, non-mercury preservative 0.2% (v/v) and protein stabilizers.

PTH (39-84) ANTIBODY COATED PLATE

One plate contains 12 strips (96 wells) in a frame plus desiccant. The strip wells are coated with goat anti-PTH (39-84). The desiccant contains silica.

WASH CONCENTRATE

One bottle contains 30 ml of a 10 fold concentrate of phosphate buffered saline with sodium azide 0.6% (w/v) and detergent.

TRIGGER 1

One bottle contains 28 mL of ready to use reagent.

CAUTION: Contains 1 M Sodium Hydroxide.

TRIGGER 2

One bottle contains 28 mL of ready to use reagent.

PREPARATION AND STORAGE OF REAGENTS

PTH CALIBRATORS

The Scantibodies Laboratory, Inc. Total Intact PTH ICMA Diagnostic Kit contains PTH standards prepared analytically on a mass basis from purified synthetic PTH (1-84). These standards are further evaluated against lyophilized "primary standards" which are stored at -70° C to maintain potency.

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.

TOTAL INTACT PTH ICMA TRACER

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

PTH (39-84) ANTIBODY COATED PLATE

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

WASH CONCENTRATE (10X)

Mix the contents of the wash concentrate thoroughly with 270 ml of distilled or deionized water (1:10). Store the diluted wash solution at room temperature (18° - 25° C) until the stated expiration date. **Note**: On occasion, the wash concentrate may partially crystallize depending on individual storage conditions. In his case, additional mixing may be required in order to achieve complete dissolution of the reagent.

TRIGGER 1

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

TRIGGER 2

The reagent is ready to use. Store at 2° - 8° C in the dark 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.

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.

Corrosive Warning
Trigger 1 reagent contains 1M sodium hydroxide which is very corrosive. Do not allow to contact skin or splash into eyes. Wear gloves and goggles when handling this reagent. Dispose of any unused reagent in a safe manner according to local regulations.

SAMPLE PREPARATION AND STORAGE

Specimen Collection
The determination of human Total Intact PTH should be made on EDTA-plasma. One hundred microliters of plasma are required to assay one sample in duplicate. To obtain plasma, collect blood by venipuncture into a tube containing EDTA. Centrifuge the sample and separate the plasma from the cells. Plasma should be stored at -20° C or lower. 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 Total Intact PTH Kit (Part No. 3KG008) is supplied with the following:

Description	Number
PTH Standards 3CA647, 3CB647, 3CC647, 3CD647, 3CE647, 3CF647, 3CG647	7 vials
PTH Controls Part Nos. 3CA648, 3CB648	2 vials
PTH (39-84) Antibody Coated Plate Part No. 3KP004	1 Plate (12 Strips)
Total PTH Tracer, ICMA Part No. 3KL107	1 vial
Wash Concentrate (10X), ICMA Part No. 3KW002	1 bottle
Trigger 1 Part No. 3KL057	1 bottle
Trigger 2 Part No. 3KL055	1 bottle
Directional Insert Part No. 7KI029	1 insert

Materials And Equipment Required But Not Provided:

Distilled or deionized water
Pipettors with disposable tips: 0.05 and 0.1 ml
Wash station
VWR orbital shaker Model DS-500 or equivalent
Microplate luminometer equipped with dual injectors capable of delivering 100 µl each.

Preparation for Assay
For each assay, prepare the following number of strips for double determination:

2 strips for calibrators A – G and control I
2 strips for control II and samples 1 through 7
2 strips for samples 8 through 15, etc.
Place any unused strips back into the resealable foil pouch and store at 2-8° C

Pipetting and Incubation Steps

1. Pipette 50 µl of calibrators, controls and samples into the bottom of the corresponding strip wells. (Plate mapping forms are useful for recording sample locations on the plate.)
2. Pipette 100 µl of Total Intact PTH tracer into each well changing pipet tips between each well.
3. Place the plate securely on an orbital shaker and rotate the plate for 2 hours to 2½ hours at 160 to 180 rpm at room temperature (18° – 25° C). There is no need to cover the plate or protect from the light.
4. After the incubation time is completed, wash the plate strips by aspirating the contents of each well completely and pipeting 350 to 400 µl of diluted wash concentrate into each well. Repeat this procedure 3 to 5 times aspirating the wash solution completely after the last washing step. (Slapping the plate on absorbent material after washing is **not** recommended).
5. While the plate is being washed, prime the luminometer with enough of the trigger solutions to fully expel any air or liquid in the system.
6. Set up a standard curve in the instrument using the concentrations listed on the standard vials for the determination of the unknown samples.
7. Set the luminometer to inject 100 µl of trigger 1 followed by 100 µl of trigger 2 with a 0.5 second delay prior to reading and an integration time of 1.5 seconds. The delay and integration settings are general guidelines. Different instruments may require some adjustments to obtain optimal results.
8. Read the plate within 5 minutes after the washing step is completed.

PIPETTING GUIDE

Additive to well	Calibrator Wells	Control Wells	Sample Wells
Calibrator	50 µl	-----	--------
Control	-----	50 µl	--------
Sample	-----	-----	50 µl
Tracer	100 µl	100 µl	100 µl
Rotate the uncovered plate at 160 to 180 rpm on an orbital shaker for 2 to 2½ hours.			
Wash the strips 3 to 5 times with the diluted wash solution.			
Read the strips on a luminometer equipped with dual injectors primed with the two trigger solutions and set to deliver 100 µl of trigger 1 followed by 100 µl of trigger 2 with a 0.5 second delay prior to reading and an integration time of 1.5 seconds, within 5 minutes after the washing step is completed.			

PROCEDURAL COMMENTS

Interferences:
Samples containing up to 250 mg/dl triglyceride, 15 mg/dl hemoglobin and 30 mg/dl bilirubin do not exhibit any significant effect on the assay. However, it is strongly recommended that grossly hemolyzed, icteric or lipemic samples not be used in this assay.

Reagents from different lot numbers must not be interchanged.
The patient sample or calibrator should be pipetted carefully into the very bottom of the assay wells. The tracer should be pipetted onto the side of the well just above the liquid level.

Accurate and complete reconstitution of the controls and standards is essential to achieving accurate assay results.

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. Washing the wells 5 times with the provided wash reagent is recommended.

It is recommended that calibrators and patient samples be assayed in duplicate. The average Relative Light Units 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.

Storage of plasma samples at refrigerated temperature for prolonged periods (one week) may adversely affect assay results.

CALCULATION OF RESULTS

Evaluation

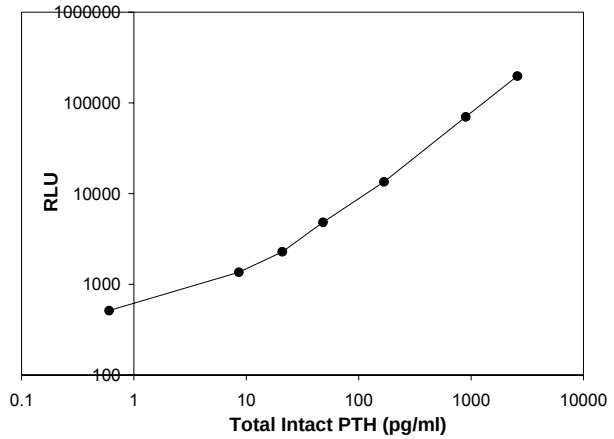
1. Calculate the average RLU for each double determination.
2. Draw the calibration curve by plotting the average RLU from each duplicate calibrator level (ordinate) against the respective concentration declared on the calibrator vial (abscissa) using log-log graph paper. Obtain sample concentrations by interpolation of average sample RLU on the calibration curve.
3. If samples were run with dilution, multiply the diluted sample assay results from the curve by the appropriate dilution factors to obtain the corrected sample assay results.

SAMPLE DATA

Wells	RLU	Ave. RLU
0.6 pg/ml	521 504	513
8.6 pg/ml	1357 1366	1362
20.9 pg/ml	2320 2248	2284
48 pg/ml	4950 4727	4839
168 pg/ml	13671 13316	13494
898 pg/ml	69650 70858	70254
2584 pg/ml	198730 196520	197625

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 below 2.0 pg/ml.

EXPECTED VALUES

The normal value range was determined following the NCCLS guidelines (C28-A) using 120 EDTA plasma 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	Total PTH RANGE (pg/ml)
Normal	14 - 66
Hyperparathyroidism	>66

PERFORMANCE CHARACTERISTICS

Accuracy, Recovery

Six different samples with known concentrations of PTH were spiked with known amounts of either 1-84 or 7-84 PTH. The % recovery was determined following assay of the spiked samples.

Sample value (pg/ml)	Added 1-84 PTH (pg/ml)	Measured value (pg/ml)	Expected value (pg/ml)	Recovery (%)
113.93	68.15	175.62	182.08	96.5
335.68	92.06	425.93	427.74	99.6
1137.10	301.87	1386.60	1438.97	96.4

Sample value (pg/ml)	Added 7-84 PTH (pg/ml)	Measured value (pg/ml)	Expected value (pg/ml)	Recovery (%)
102.65	123.01	236.82	225.66	104.9
219.73	112.37	338.10	332.10	101.8
661.70	72.19	811.04	733.89	110.5

Accuracy, Dilution

Different samples with high concentrations of PTH were diluted in a sample containing no PTH. The % recovery was determined following assay of the diluted samples.

Sample	Dilution	Measured value (pg/ml)	Expected value (pg/ml)	Recovery %
1	Neat	472.6		
	1:2	242.70	236.30	102.7
	1:4	129.92	118.15	110.0
	1:8	70.17	59.08	118.8
2	Neat	701.72		
	1:2	351.07	350.86	100.1
	1:4	185.73	175.43	105.9
	1:8	102.77	87.72	117.2
3	Neat	955.73		
	1:2	468.57	477.87	98.1
	1:4	237.46	238.93	99.4
	1:8	123.77	119.47	103.6
4	Neat	322.19		
	1:2	171.68	161.10	106.6
	1:4	94.05	80.55	116.8
	1:8	49.84	40.27	123.8
5	Neat	309.86		
	1:2	166.32	154.93	107.3
	1:4	90.55	77.47	116.9
	1:8	52.41	38.73	135.3
6	Neat	300.97		
	1:2	166.93	150.49	110.9
	1:4	93.21	75.24	123.9
	1:8	50.98	37.62	135.5
				112.9

High Dose Hook Response

This high dose hook response of the Scantibodies Laboratory, Inc. Total Intact PTH ICMA Diagnostic Kit was determined as 20,000 pg/ml of PTH. Samples greater than the highest standard (approximately 2300 pg/ml) and up to 20,000 pg/ml PTH will produce RLU values greater than that of the highest standard.

Precision

The inter-assay precision was evaluated by performing 20 separate Total PTH assays on three samples in duplicate over a two week period.

Sample	Mean value (pg/ml)	SD (pg/ml)	% CV
1	73.5	4.2	5.71
2	182.9	11.67	6.38
3	460.7	22.98	4.99

The intra-assay precision was evaluated by performing 20 replicates in the Total PTH assay on three samples.

Precision Intra-assay				
Kit Batch	Sample	Mean value (pg/ml)	SD (pg/ml)	% CV
E1	1	81.14	2.48	3.0
	2	200.74	6.72	3.4
	3	457.04	12.18	2.7
E2	1	67.92	2.31	3.4
	2	176.49	5.90	3.3
	3	439.84	15.52	3.5
E3	1	69.78	1.34	1.9
	2	186.49	4.37	2.3
	3	457.99	9.57	2.1

Sensitivity
The detection limit of the assay is defined as the lowest measurable value distinguishable from calibrator A. The sensitivity was determined by assaying calibrator A 20 times in the same assay. The minimum detectable dose was below 2.0 pg/ml calculated at 2 standard deviations above the first PTH calibrator.

Specificity
This Total Intact PTH assay does not show any cross-reaction to the following PTH fragments at 100,000 pg/ml:

PTH 1-34	undetectable
PTH 39-84	undetectable
PTH 39-68	undetectable
PTH 53-84	undetectable
PTH 44-68	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) Total Intact PTH ICMA Assay. A correlation coefficient (r) of 0.985 (n=240) was obtained with a slope of 0.957 and intercept of 12.8 where x represents the predicate device data and y represents the SLI Total Intact PTH ICMA data. Calculations were made with samples ranging from 2.48 – 1737.20 pg/ml.

Chemical Characterization:	1) Antibodies coated on to 96 well polystyrene plates packaged with silica desiccant.
	2) Antibody Tracer labeled with Luminol in a phosphate stabilizer with a mercury preservative @ 0.2%.
	3) Calibrators & Controls – Human Serum containing Sodium Azide @ 0.1%
	4) Wash Concentrate containing sodium azide @ 0.9%.
	5) Antibody Trigger containing Sodium Hydroxide @ 0.4%.
	6) Antibody Trigger containing Hydrogen Peroxide @ 0.5%.
Hazardous Ingredients:	Sodium Azide @ 0.1% CAS Number: 026628-22-8 Symbols: N/A R-phrases: N/A S-phrases: N/A
	Sodium Azide @ 0.9% CAS Number: 026628-22-8 Symbols: Toxic R-phrases: R25, R31, R52/53 S-phrases: S28, S45, S53, S60, S61
	Sodium Hydroxide @ 0.4% CAS Number: 1310-73-2 Symbols: Very Toxic; Corrosive R-phrases: R26/27/28, R32, R50/53 S-phrases: S28, S45, S53
	Hydrogen Peroxide @ 0.5% CAS Number: 7722-84-1 Symbols: Very Toxic; Corrosive; Oxidizing R-phrases: R20/21/22, R28, R32, R34, R50/53 S-phrases: S1/2, S3, S28, S36/39, S45, S53

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	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		Harmful

Symbol	Used for	Symbol	Used for
	Corrosive		Oxidizing

PTH LITERATURES

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