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Intact PTH ELISA

Catalog Number M046016

For the quantitative determination of Intact-Parathyroid Hormone (PTH) in human serum samples.

For research use only.
This product insert must be read in its entirety before use.

INTENDED USE

The Intact-PTH ELISA is intended for the quantitative determination of Intact-PTH (Parathyroid Hormone) in human serum. This assay is intended for in vitro diagnostic use.

SUMMARY AND EXPLANATION

PTH (Parathyroid hormone, Parathormone, Parathyrin) is biosynthesized in the parathyroid gland as a pre-pro-parathyroid hormone, a larger molecular precursor consisting of 115 amino acids. Following sequential intracellular cleavage of a 25-amino acid sequence, preproparathyroid hormone is converted to an intermediate, a 90-amino acid polypetide, proparathyroid hormone. With additional proteolytic modification, proparathyroid hormone is then converted to parathyroid hormone, an 84 amino acid polypeptide. In healthy individuals, regulation of parathyroid hormone secretion normally occurs via a negative feedback action of serum calcium on the parathyroid glands. Intact PTH is biologically active and clears very rapidly from the circulation with a half-life of less than four minutes (1). PTH undergoes proteolysis in the parathyroid glands, but mostly peripherally, particularly in the liver but also in the kidneys and bone, to give N-terminal fragments and longer lived C-terminal and midregion fragments. In subjects with renal insufficiency, C-terminal and midregion PTH assays typically give elevated PTH results, as reflected by impaired renal clearance (2).

CLINICAL SIGNIFICANCE

Intact PTH assays are important for the differentiation of primary hyperparathyroidism from other (non-parathyroid-mediated) forms of hypercalcemia, such as malignancy, sarcoidosis and thyrotoxicosis (2). The measurement of parathyroid hormone is the most specific way of making the diagnosis of primary hyperparathyroidism. In the presence of hypercalcemia, an elevated level of parathyroid hormone virtually establishes the diagnosis. In over 90% of patients with primary hyperparathyroidism, the parathyroid hormone will be elevated (3). The most common other cause of hypercalcemia, namely hypercalcemia of malignancy, is associated with suppressed levels of parathyroid hormone (3) or PTH levels within the normal range (4). When intact PTH level is plotted against serum calcium, the intact PTH concentration for patients with hypercalcemia of malignancy is almost always found to be inappropriately low when interpreted in view of the elevated serum calcium (3,4,5). Unlike C-terminal and midregion PTH, which typically are grossly elevated in subjects with renal insufficiency, intact PTH assays are less influenced by the declining renal function (5). PTH values are typically undetectable in hypocalcemia due to total hypoparathyroidism, but are found within the normal range in hypocalcemia due to partial loss or inhibition of parathyroid function.

PRINCIPLE OF THE ASSAY

The Intact PTH Immunoassay is a two-site ELISA (Enzyme-Linked Immunosorbent Assay) for the measurement of the biologically intact 84 amino acid chain of PTH. Two different goat polyclonal antibodies to human PTH have been purified by affinity chromatography to be specific for well defined regions on the PTH molecule. One antibody is prepared to bind only the mid-region and C-terminal PTH 39-84 and this antibody is biotinylated. The other antibody is prepared to bind only the N-terminal PTH 1-34 and this antibody is labeled with horseradish peroxidase (HRP) for detection.

Streptavidin Well - Biotinylated Anti-PTH (39-84) - Intact PTH - HRP conjugated Anti-PTH (1-34)

Although mid-region and C-terminal fragments are bound by the biotinylated anti-PTH (39-84), only the intact PTH 1-84 forms the sandwich complex necessary for detection. The capacity of the biotinylated antibody and the streptavidin coated microwell both have been adjusted to exhibit negligible interference by inactive fragments, even at very elevated levels. In this assay, calibrators, controls, or patient samples are simultaneously incubated the enzyme labeled antibody and a biotin coupled antibody in a streptavidin-coated microplate well. At the end of the assay incubation, the microwell is washed to remove unbound components and the enzyme bound to the solid phase is incubated with the substrate tetramethylbenzidine (TMB). An acidic stopping solution is then added to stop the reaction and converts the color to yellow. The intensity of the yellow color is directly proportional to the concentration of intact PTH in the sample. A dose response curve of absorbance unit vs. concentration is generated using results obtained from the calibrators. Concentrations of intact PTH present in the controls and patient samples are determined directly from this curve.

KIT COMPONENTS

Microplate Plate - The plate contains 12 x 8-well strips coated with streptavidin. Ready for use.

Calibrator A - 1 vial (0 pg/mL) of a BSA solution with goat serum. Lyophilized.

Calibrators B through F - Synthetic human PTH (1-84) in a BSA solution with goat serum. Lyophilized. See vial label for concentrations.

Controls - Synthetic human PTH (1-84) in a BSA solution with goat serum. Lyophilized. See vial label for concentration ranges.

Biotinylated PTH Antibody - 1 vial of Biotinylated PTH Antibody. Ready to use.

Peroxidase labeled PTH Antibody - 1 vial of Peroxidase labeled PTH Antibody. Ready to use.

Patient Sample Diluent -1 vial of equine serum.

Reconstitution Solution - 1 vial of solution containing surfactant.

Wash Buffer Concentrate - 1 vial of 20-fold concentrated saline solution with surfactant.

Substrate - 1 vial of TMB Substrate. Ready to use.

Stop Solution - 1 vial of 1 N Sulfuric Acid. Ready to use.

STORAGE

<table>
<tr><td>Unopened Kit</td><td colspan="2">Store at 2 - 8 ºC. Do not use past the kit expiration date.</td></tr>
<tr><td rowspan="10">Opened Reagents</td><td>Calibrators</td><td rowspan="2">Store unused calibrators and controls at -20 ºC for up to 6 weeks.</td></tr>
<tr><td>Controls</td></tr>
<tr><td>Biotinylated PTH Antibody</td><td rowspan="5">Store at 2 - 8 °C.</td></tr>
<tr><td>Peroxidase Labeled PTH Antibody</td></tr>
<tr><td>Substrate</td></tr>
<tr><td>Patient Sample Diluent</td></tr>
<tr><td>Reconstitution Solution</td></tr>
<tr><td>Stop</td><td rowspan="2">Store at room temperature.</td></tr>
<tr><td>Wash Buffer</td></tr>
<tr><td>Microplate wells</td><td>Return unused wells to the foil pouch containing the desiccant and seal. Store at 2 - 8 ºC.</td></tr>
</table>

SUPPLIES REQUIRED BUT NOT PROVIDED

- Microplate Reader
- Microplate Washer
- Pipettes or pipetting equipment with disposable polypropylene tips (10 µL, 100 µL, 1 mL)
- Multi-channel pipette
- Disposable polypropylene test tubes
- Glass measuring cylinders
- Distilled or deionised water
- Orbital rotator or shaker

PRECAUTIONS

Although the reagents provided in this kit has been specifically designed to contain no human blood components, the human patient samples, which might be positive for HBsAg, HBcAg or HIV antibodies, must be treated as potentially infectious biohazard. Common precautions in handling should be exercised, as applied to any untested patient sample.

Stop Solution, consists of 1 N Sulfuric Acid. This is a strong acid. Although diluted, it still must be handled with care. It can cause burns and should be handled with gloves and eye protection, with appropriate protective clothing. Any spill should be wiped immediately with copious quantities of water. Do not breath vapor and avoid inhalation.

CRITICAL PARAMETERS

- Allow samples and all reagents to equilibrate to room temperature (22–25 °C) prior to performing the assay. This is especially important for the TMB Substrate.
- Adhere to recommended incubation temperatures in the protocol as variations may cause inconsistent or poor assay results.
- It is essential that all wells are washed thoroughly and uniformly. When washing is done by hand, use a squeeze bottle and ensure that all wells are completely filled and emptied at each step.

- Use only reagents from the same lot for each assay. This is especially important when running more than one plate per sample group.
- A separate standard curve must be run on each plate.
- Reagents can easily be trapped in the caps of small microfuge tubes. It is recommended to briefly centrifuge these reagents before use.
- Mix all reagents thoroughly prior to use, but avoid foaming!
- Keep the wells sealed with the plate sealer except when adding reagents and during reading.
- Any variation in the protocol can cause variation in binding!
- The kit should not be used beyond the expiration date on the kit label.
- The values obtained by the samples should be within the standard range. If this is not the case, dilute the sample and repeat the assay.
- We take great care to ensure that this product is suitable for all validated sample types, as designated in this manual. Other sample types may be tested and validated by the user.

SAMPLE COLLECTION AND STORAGE

The determination of Intact PTH should be performed with serum. EDTA plasma has been reported to be an acceptable sample (6). To assay the specimen in duplicate, 50 µL of serum or EDTA plasma is required. Col- lect whole blood without anticoagulant or lavender [EDTA] tube. After allowing blood to clot, the serum or plasma should be promptly separated, preferably in a refrigerated centrifuge, and stored at -20 °C or lower. Serum samples may be stored up to 8 hours at 2 - 8 °C. Serum samples frozen at -20 °C are stable for up to 4 months.

REAGENT PREPARATION

Note: All reagents should be stored at the recommended temperatures. Bring all reagents to room temperature (22 - 25 °C) before use. Reagents can easily be trapped in the caps of small microfuge tubes. It is recommended to briefly centrifuge these reagents before use.

Wash Buffer Concentrate - Bring to room temperature before use. Wash Buffer may exhibit precipitation when stored at cold temperatures. Mix thoroughly before use. If precipitate is present, dissolve by placing in a 37 °C water bath. Add 30 mL of Wash Buffer Concentrate to 570 mL deionized or distilled water and mix.

Calibrators - For Calibrators A through F, reconstitute each vial with 500 µL of Reconstitution Solution and mix. Allow the vial to stand for 10 minutes and then mix thoroughly by gentle inversion to ensure complete reconstitution. **Use immediately following reconstitution.** Store unused calibrators at -20 °C for up to 6 weeks. Avoid repeated freeze-thaw cycles.

Controls - Reconstitute each vial with 500 µL of Reconstitution Solution and mix. Allow the vial to stand for 10 minutes and then mix thoroughly by gentle inversion to ensure complete reconstitution. **Use immediately following reconstitution.** Store unused controls at -20 °C for up to 6 weeks. Avoid repeated freeze-thaw cycles.

ASSAY PROTOCOL

Read the entire protocol before beginning the assay. It is recommended that all standards and samples be assayed in dulplicate. Reagents can easily be trapped in the caps of small microfuge tubes. It is recommend- ed to briefly centrifuge these reagents before use. *Note: Reagents and samples may require specific handling temperatures and need preparation prior to the assay. See the Reagent and Sample Preparation sections before proceeding.*

1. Prepare all reagents and samples as described in the previous sections.
2. Remove any excess microplate strips from the plate frame and return them to the foil pouch containing the desiccant pack.

Calibrator/Sample/Antibody Incubation

3. Pipet 25 µL of calibrator, control or sample into duplicate wells. Freeze (-20 °C) the remaining calibrators and controls as soon as possible after use.
4. Pipette 50 µL of Biotinylated Antibody into each of the wells which already contain the sample.
5. Pipette 50 µL of Enzyme Labeled Antibody into each of the same wells. Mix wells by tapping plate frame gently.
6. Cover the microplate(s) with aluminum foil or a tray to avoid exposure to light. Incubate on an orbital shaker or rotator set at 170 ± 10 rpm for 3 hours ± 30 minutes at room temperature (22 - 25 °C).

Wash

7. Aspirate and wash each well five (5) times with the Working Wash Solution, using an automatic microplate washer. Blot dry by inverting the plate on an absorbent material. The wash solution volume should be set to dispense 350 µL into each well.

Substrate Incubation

8. Add or dispense 150 µL of the Substrate Solution into each of the wells. Mix wells by tapping plate frame gently.
9. With appropriate cover to avoid light exposure, place the microplate(s) on an orbital shaker or rotator set at 170 ± 10 rpm for 30 ±5 minutes at room temperature.

Stop Reaction

10. Add or dispense 100 µL of the Stop Solution into each of the wells. Mix gently.
11. Read the absorbance of the solution in the wells within 10 minutes, using a microplate reader set to 450 nm against 250 µL of distilled or deionized water. Read the plate again with the reader set to 405 nm against distilled or deionized water.
    Note: The second reading is designed to extend the analytical validity of the calibration curve to the value represented by the highest calibrator. Hence, patient samples with PTH > 200 pg/mL can be quantified against a calibration curve consisting of the readings all the way up to the concentration equivalent to the highest calibrator using the 405 nm reading, away from the wavelength of maximum absorbance. In general, patient and control samples should be read using the 450 nm for PTH concentrations up to 200 pg/mL. PTH concentrations above 200 pg/mL should be interpolated using the 405 nm reading.

SUMMARY

Prepare reagents and samples as previously described.

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Pipette 25 µL calibrator, control or sample in duplicate into the wells.

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Pipette 50 µL Biotinylated antibody into the wells.

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Pipette 50 µL Enzyme labeled antibody into the wells.

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Cover and Incubate 3 hours at RT (22 - 25 °C) on a shaker.

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Aspirate and wash 5 times.

↓

Add 150 µL of Substrate to each well. Cover and Incubate 30 minutes at RT on a shaker.

↓

Add 100 µL of Stop Solution to each well. Read at 450 nm and at 405nm.

PROCEDURAL NOTES

- Intact PTH 1-84 is a very labile molecule. Set up the assay immediately upon the reconstitution or the thawing of all calibrators, controls, and patient samples.
- It is recommended that all calibrators, controls, and patient samples are assayed in duplicate. The average absorbance units of duplicate sets should then be used for reduction of data and the calculation of results.
- The samples should be pipetted into the well with minimum amount of air-bubble. To achieve this, "reverse pipet" described in the package insert of the manufacturers of Pipettors is recommended.
- Patient samples with values greater than the highest calibrator (Calibrator F) may be diluted with Sample Diluent and reassayed. Multiply the result by the dilution factor.
- Reagents from different lot numbers must not be interchanged.
- If preferred, mix in equal volumes, in sufficient quantities for the assay, Biotinylated Antibody and Enzyme Labeled Antibody in a clean amber bottle. Then, use 100 µL of the mixed antibody into each well. This alternative method should replace Step (4) and (5), to be followed with the incubation with orbital shaker.

CALCULATION OF RESULTS

By using the final absorbance values obtained in the previous step, construct a calibration curve via cubic spline, 4 parameter logistics, or point-to-point interpolation to quantify the concentration of the intact PTH.

Manual Method

1. For the 450 nm readings, construct a dose response curve (calibration curve) using the first five calibrators provided, i.e. Calibrators A, B, C, D and E. For the 405 nm readings, construct a second dose response curve using the three calibrators with the highest concentrations, i.e. Calibrators D, E and F.
2. Assign the concentration for each calibrator stated on the vial in pg/mL. Plot the data from the calibration curve on linear graph paper with the concentration on the X-axis and the corresponding A.U. on the Y-axis.
3. Draw a straight line between 2 adjacent points. This mathematical algorithm is commonly known as the "point-to-point" calculation. Obtain the concentration of the sample by locating the absorbance unit on the Y-axis and finding the corresponding concentration value on the X-axis. Patient and control samples should be read using the 450 nm for PTH concentrations up to 200 pg/nm reading. PTH concentrations above 200 pg/mL should be interpolated using the 405 nm reading.

SAMPLE DATA

Data obtained at 450 nm (raw A.U. readout against distilled or deionized water):

Well	1st Reading (A.U.)	2nd Reading (A.U.)	Average A.U.	Intact PTH pg/mL	Intact PTH result to report (pg/mL)
Calibrator A	0.020	0.016	0.018		0
Calibrator B	0.056	0.051	0.054		7
Calibrator C	0.124	0.119	0.122		18
Calibrator D	0.388	0.393	0.391		55
Calibrator E	1.335	1.340	1.338		210
Control 1	0.200	0.200	0.200	27.6	27.6
Control 2	0.804	0.794	0.799	119	119
Sample 1	0.147	0.136	0.142	19.1	19.1
Sample 2	0.407	0.409	0.408	58.5	58.5
Sample 3	2.375	2.454	2.415	>200	*
Sample 4	3.725	3.725	3.725	>200	*

**Because the concentration is >200 pg/mL, it is recommended to use the data obtained at 405 nm.*

Data obtained at 405 nm (raw A.U. readout against distilled or deionized water):

Well	1st Reading (A.U.)	2nd Reading (A.U.)	Average A.U.	Intact PTH pg/mL	Intact PTH result to report (pg/mL)
Calibrator A	0.014	0.008	0.011		0
Calibrator D	0.124	0.128	0.126		55
Calibrator E	0.428	0.425	0.427		210
Calibrator F	1.309	1.317	1.313		700
Control 1	0.074	0.066	0.070	<200	
Control 2	0.260	0.251	0.256	121	
Sample 1	0.049	0.043	0.046	<200	
Sample 2	0.132	0.133	0.133	<200	
Sample 3	0.758	0.782	0.770	401	401
Sample 4	1.314	1.321	1.318	>700	

For samples with readout < 200 pg/mL, it is recommended to use the data obtained at 450 nm as shown in Sample Data at 450 nm in the table above. This practice should give the results with optimum sensitivity of the assay. Although the readout for Control 2 < 200 pg/mL, it is recommended that the actual result be read out and recorded for quality control evaluation purposes. Further, absorbance for Control 2 is sufficiently high to be analytically valid. The absorbance readout is off-scale or higher than the average absorbance of the highest calibrator. Sample should be repeated with dilution.

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

QUALITY CONTROL

Control serum or serum pools should be analyzed with each run of calibrators and patient samples. Results generated from the analysis of the control samples should be evaluated for acceptability using appropriate statistical methods. In assays in which one or more of the quality control sample values lie outside the acceptable limits, the results for the patient sample may not be valid.

LIMITATIONS OF THE PROCEDURE

The PTH ELISA kit has exhibited no“high dose hook effect” with samples spiked with 2,100,000 pg/mL of Intact PTH. Samples with intact PTH levels greater than the highest calibrator, however, should be diluted and reassayed for correct values. Like any analyte used as a diagnostic adjunct, intact PTH results must be interpreted carefully with the overall clinical presentations and other supportive diagnostic tests.

EXPECTED VALUES

Intact PTH levels were measured in one hundred and forty-eight (148) apparently normal individuals in the U.S. with the Intact PTH ELISA. The values obtained ranged from 9.0 to 94 pg/mL for serum. Based on statistical tests on skewness and kurtosis, the population, when transformed logarithmically, follows the normal or Gaussian distribution as shown in the histograms. The geometric mean ± 2 standard deviations of the mean were calculated to be 10.4 to 66.5 pg/mL for serum.

PERFORMANCE CHARACTERISTICS

Accuracy

Three hundred and nine (309) patient samples, with intact PTH values ranging from 1.0 to 833 pg/mL were assayed by the ELISA procedure and the first intact-PTH immunoradiometric Assay (IRMA) kit linear regression analysis gives the following statistics:

PTH ELISA = 1.06 1st IRMA kit + 1.49 pg/mL
r = 0.998 N = 309

SENSITIVITY

The sensitivity, or minimum detection limit, of this assay is defined as the smallest single value, which can be distinguished from zero at the 95% confidence limit. The PTH ELISA has a calculated sensitivity of 1.57 pg/mL.

SPECIFICITY AND CROSS-REACTIVITY

The antibodies used in the PTH ELISA were purified by affinity chromatography to be specific for well-defined regions on the PTH molecule. The peroxidase labeled antibody recognizes only the N-terminal region of the 1-34 amino acid sequence of the PTH molecule; whereas the biotinylated antibody is specific to the 39-84 segment. Accordingly, only intact PTH, which requires binding by both the enzyme conjugated and biotinylated antibodies, can be detected by this assay. To further achieve the specificity of this assay, conjugation and biotinylation and the molar ratios thereof, have been optimized to minimize detection of fragments of PTH. Human PTH 1-34 at levels up to 300 pg/mL and the C-terminal 39-84 fragment at levels up to 300,000 pg/mL give molar crossreactivites to PTH of less than 2% and 0.02%, respectively.

REPRODUCIBILITY

Intra-assay Precision (Precision within an assay) - The intra-assay precision was measured by assaying two control samples 25 times on one plate.
Inter-assay Precision (Precision between assays) - The inter-assay precison was assessed by repeated measurements of two samples obtained in 21 different assays, by 3 technicians on three different lots of reagents, over a three-week period.

	Intra-assay Precision		Inter-assay Precision	
Control	A	B	A	B
Mean (pg/mL)	32.4	178.2	30.3	159.1
CV (%)	6.08	3.68	3.6	2.8

RECOVERY

Various amounts of PTH 1-84 were added to three different patient sera to determine the recovery. The results are described in the following table:

Serum Sample	Endogenous PTH (pg/mL)	PTH Added (pg/mL)	Expected Value (pg/mL)	Observed Value (pg/mL)	% Recovery
A	32.7	132	165	168	102%
	20.6	264	285	288	101%
	13.5	396	410	413	101%
B	68.6	132	201	191	95%
	51.7	264	316	344	109%
	45.0	396	441	462	105%
C	19.9	132	152	165	109%
	15.4	264	279	275	99%
	13.3	396	409	424	104%

Linearity of Patient Sample Dilutions: Parallelism

Four patient serum samples were diluted with the Diluent for Patient Samples (read off-scale). Results in pg/mL are shown below:

Serum Sample	Dilution	Expected (pg/mL)	Observed (pg/mL)	% Observed / Expected
A	Undiluted	-	322	-
	1:2	161	148	92%
	1:4	80.5	73.1	91%
	1:8	40.3	41.5	103%
B	Undiluted	-	230	-
	1:2	115	97	84%
	1:4	58	55	95%
	1:8	29	30	103%
C	Undiluted	-	176	-
	1:2	88	82	93%
	1:4	44	45	102%
	1:8	22	24	109%
D	Undiluted	-	426	-
	1:2	213	192	90%
	1:4	107	90	84%
	1:8	53	47	89%

TROUBLESHOOTING

Problem	Recommendation
Low Absorbance	• Check reagents for proper storage. • Control expiration date. • Check preparation of reagents. • Control incubation times and temperature. • Check reader wavelength.
High Absorbance/high zero standard value	• Check preparation of reagents. • Control incubation times and temperature. • Equilibrate ELISA reagents to room temperature (22 - 25 °C). • Ensure that every well of the ELISA plate is completely filled and emptied at every wash step. • Check that plates are blotted on tissue paper after washing.
Flat cure/poor reproduciblity	• Check reagents for proper storage. • Control expiration date. • Check preparation of working standards. • Check incubation times and temperatures. • Use separate reservoirs for pipetting different solutions with multichanned pipettes. Always use new pipette tips. • Check pipette calibration. • Ensure efficient washing procedure.

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Further Suggested Reading

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