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The path to the standardization of PTH: Is this a realistic possibility? a position paper of the IFCC C-BM

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Abstract

Parathyroid hormone (PTH) determination is of greatest importance for patients suffering from parathyroid gland disorders and for the follow-up of bone turnover in patients suffering from chronic kidney disease (CKD). Two generations of PTH assays are simultaneously present on the market for PTH quantification. As these assays are not yet standardized, this results in a significant level of confusion in the care of CKD patients. One key objective of the IFCC Committee for Bone Metabolism is to improve this situation. In this position paper, we will highlight the current state of PTH testing and propose a pathway to ultimately overcome issues resulting from PTH assay variability.

Keywords

Standardization; Parathyroid hormone; Immunoassays

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CRediT authorship contribution statement

EC and CZU have written the manuscript. HPB, SV, KM and ACH have read, amended and accepted the paper as members of the IOF-IFCC Committee on Bone metabolism.

5. Disclaimer

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention/the Agency for Toxic Substances and Disease Registry. Use of trade names is for identification only and does not imply endorsement by the Centers for Disease Control and Prevention, the Public Health Service and the US Department of Health and Human Services.

1. Introduction

Parathyroid hormone (PTH) is an 84 single chain amino acid (AA) peptide produced by the parathyroid gland. It is first synthesized as a pre-pro peptide of 115 AA and further cleaved to give a 90 AA pro-peptide, which is finally transformed into the biologically active 1–84 PTH. Both the pre-pro-PTH and pro-PTH peptides are undetectable in the blood [1]. PTH is released into the circulation when the plasma ionized calcium concentration, which is detected by calcium sensing receptors located on the parathyroid cells, decreases. Regulation of the production of PTH is mediated by a negative feed-back involving calcium, active vitamin D (calcitriol) and FGF-23 (Fig. 1). The main role of PTH is thus to maintain ionized calcium in a very tight concentration zone and to participate in the urinary excretion of phosphorus. To exert these actions, PTH binds to bone and kidney cells that express the type 1 PTH/PTHrP receptor (PTH1R). In the kidney distal tubule, PTH stimulates the reabsorption of calcium and in the proximal tubule, it stimulates the activity of 1-alpha hydroxylase to produce 1,25 dihydroxyvitamin D, the active metabolite of vitamin D. PTH also regulates phosphate metabolism by decreasing the renal reabsorption of phosphate in the proximal tubule [2]. In bone, PTH acts on chon-drocytes, osteoprogenitors, osteoblasts and osteocytes [3] and controls bone remodelling as well as the homeostasis of calcium and phosphorus, even if all mechanisms for these processes are not fully understood yet [4]. Although the biologically active form of PTH is 84 AA in length, the biological function of PTH is believed to be heavily influenced by the very first amino acids of the aminoterminal domain [5]. Truncated forms of PTH such as large C-terminal or mid-truncated fragments also circulate in blood as a result of liver metabolism of the active peptide or direct secretion by the parathyroid gland itself [6–8]. The biological half-life of 1–84 PTH is rather short (2–4 min) and the half-life of the large C-terminal fragments is longer, ranging between 8.1 and 24.0 min [9,10]. These fragments represent about 15–30% of total PTH in healthy individuals, but in the blood of patients suffering from chronic kidney diseases (CKD), these fragments bioaccumulate and can represent up to 70–80% of total PTH [11,12].

In clinical practice, PTH is routinely measured for the diagnosis of primary and secondary hyperparathyroidism in the general (sometimes even asymptomatic) population [13]. PTH is also frequently measured in patients suffering from CKD. Indeed, these patients tend to present systemic mineral and bone disorders called CKD-Mineral and Bone Disease (CKD-MBD). CKD-MBD is due to abnormalities in the phospho-calcic, PTH and vitamin D metabolism. This leads to high-turnover bone diseases (e.g., secondary hyperparathyroidism), low-turnover bone diseases (e.g., osteomalacia and adynamic bone disease) and/or vascular or soft-tissue calcification. The Kidney Disease Improving Global Out-comes (KDIGO) 2017 Clinical Practice Guidelines for the Diagnosis, Evaluation, Prevention and Treatment of CKD-MBD suggest maintaining PTH levels of hemodialyzed patients at approximately 2 to 9 times the upper normal limit (ULN) of the assay used [14]. However, it should be acknowledged that PTH values ranging from 100 to 500 pg/mL (as measured by the former Nichols IRMA 2nd generation PTH assay, for which the ULN was 65 pg/mL) cannot differentiate adynamic bone from “active” bone [15]. For example, PTH levels above this ULN have only an 86% specificity for high bone turnover bone disease and levels below the target values have a 66% sensitivity for low bone turnover [16]. The

relationship between PTH and all-cause mortality has been reported to follow a U-curve, where patients with PTH values falling roughly between these limits presented a lower mortality risk [17]. The recommendation that treatments be based on multiples of the ULN is quite unique and is a circumvolution due to the lack of standardization of PTH assays. This lack of standardization also impacts the use of common reference intervals [18], which have not always been adequately established by manufacturers [19,20]. In this work, we will thus highlight the critical importance of the reporting of standardized results for PTH assays to avoid further confusion in the treatment and diagnosis of diseases influenced by PTH levels.

2. PTH assays: Two “generations” of assays are coexisting on the market.

The first generation of PTH radio-immunoassays (RIAs) were developed by Berson and Yalow in 1963 [21]. These cumbersome RIA incorporated a single polyclonal antibody and suffered from an important lack of specificity, especially in CKD patients. As a result, PTH RIA were soon replaced by more specific assays.

2.1. Second generation PTH assays

In 1987, Nichols Diagnostics proposed a two-site IRMA assay called “Allegro” [22], which incorporated a capture antibody directed against the 39–84C-terminal epitope region and a recognition antibody directed towards the 13–24 N-terminal epitope region. This “sandwich” assay, also referred to as “intact” was considered more specific in the measurement of full-length PTH compared to the first-generation PTH assays. This “second-generation” assay, along with the subsequent automated chemiluminescent, ELISA and IRMA methods, were globally called “intact” PTH assays as they were thought to measure only the full-length (1–84) PTH. However, the expression “intact” is misleading (and should definitely be abandoned in favor of “2nd generation PTH assays”) because it was shown in 1998 that these assays recognized, with various cross-reactivities (from approximately 50% to 100%), a family of large C-terminal fragments referred to as “non-(1–84)” PTH [23]. This finding explained why these assays overestimated the degree of secondary hyperparathyroidism in CKD patients: in some patients the elevated “intact” PTH concentrations were in total contradiction with their bone biopsy, which classified them as suffering from low bone turnover [24,25]. Despite these limitations, 2nd generation PTH assays remain the most widely-used PTH assays to date [16].

2.2. Third generation PTH assays

Third generation immunoassays, also referred to as “whole” or “bioactive” PTH assays, were designed in 1999 to have a higher level of specificity for the full-length form of PTH. These PTH assays incorporate an anti-N-terminal antibody that is directed towards the first four amino acids of the peptide, which is believed to eliminate the issue of cross-reactivity with PTH fragments [26,27]. Several manufacturers (e.g., DiaSorin, Tosoh, Fujirebio, Roche, and bioMérieux) now propose to measure the 1–84 PTH with an automated third generation assay. Of note, these assays have been reported to cross-react with amino-PTH, a form of PTH that is not truncated, but modified in the (15–20) region, potentially by phosphorylation of the serine at position 17 [28], which is overproduced in parathyroid

carcinoma [29,30] and severe types of parathyroid hyperplasia in hemodialyzed patients [31].

A schematic representation of the different generations of PTH assays and their epitope regions is depicted in Fig. 2.

3. PTH standardization: A major problem in laboratory medicine. Could it be overcome?

To date, PTH assays are not standardized. To circumvent this unfortunate situation, the International Federation of Clinical Chemistry (IFCC) Working Group on PTH standardization, which has now become the IFCC Committee on Bone Metabolism, published in 2017, the perspectives and priorities for the improvement of PTH measurements [32]. This group has since proposed the use of a single internationally-recognized standard for PTH assays calibration. The World Health Organization (WHO) Expert Committee on Biological Standardization (ECBS) prepared a recombinant human PTH 1–84 standard (NIBSC 95/646) for the calibration of PTH assays. This recombinant material may be a good candidate. However, this standard cannot be imposed yet because its commutability must be formally assessed beforehand [33,34]. The first task of the IFCC C-BM will thus be to assess the commutability of this standard in a defined matrix. A study on this topic is underway with the collaboration of the UK-NEQAS (Edinburgh, Scotland) and the Laboratoire National de Métrologie et d'Essais (Paris, France). Once the commutability of the NIBSC 95/646 material is determined, the standard will be proposed to manufacturers. The IFCC C-BM will then ask manufacturers to align their assays (either 2nd or 3rd generation versions) to the internationally-recognized, commutable standard. The second step will be to develop one or more candidate reference measurement procedures (RMPs) for PTH. Such RMPs are not available yet, but could reasonably be expected in the upcoming years due to advancements in mass spectrometry. With the help of these RMPs, it will be possible to certify the value of secondary reference materials and external controls. LC-MS/MS methods for PTH will also help to clarify the real impact of the large C-terminal fragments on the total PTH concentrations, as well as the real presence (or not) of oxidized PTH in samples from hemodialyzed patients [35–37]. Finally, once standardization is established, the IFCC C-BM will propose multi-ethnic, well-designed studies to establish common reference intervals for PTH assays [38].

3.1. Non-CKD patients.

From a theoretical point of view, second and third generation PTH assays should not present discordant results in non-CKD patients. Common reference ranges intervals could even be proposed for all the different assays available on the market. Due to the lack of standardization, this is unfortunately not the case. However, evidence from relative recovery experiments performed by the UK-NEQAS with purified 1–84 PTH consistently shows that if PTH methods were accurately calibrated in terms of the same commutable international standard, the between-method agreement would improve [32]. Such studies generally also show that 3rd generation PTH assays report rather similar values. This is not the case of 2nd generation assays, which report very different recoveries that can be up to 150 or 200%. In

conclusion, for non-CKD patients, standardization of 2nd or 3rd generation PTH assays seems feasible and would greatly improve the clinical concordance of the different assays available on the market. This would also open the doors to new, correctly designed, studies aimed at establishing reference values in large cohorts of individuals of different ethnic origins.

3.2. CKD patients

In 2006, Jean-Claude Souberbielle alerted the nephrological community to the discrepancies in PTH results obtained in hemodialyzed patients and showed that, unacceptably, opposite therapeutic decisions could be reached in the same patient depending on the PTH assay used [39]. Fifteen years later, nothing has changed. Table 1 summarizes the 23 major studies where the results from 2nd or 3rd generation PTH assays were compared in CKD and hemodialyzed (HD) patients. The slopes and intercepts show some substantial variation across the studies, which could be explained by different factors such as changes in the vendor calibration standards over time, the use of a uremic matrix that can affect the reaction process and the renal status of the patients involved in the comparisons. The cross-reactivity of second generation PTH assays with non-(1–84) PTH have been shown using the 7–84 fragment as a surrogate, but it seems that this fragment is not present in humans [40], which can question the robustness of these models. Studies using high resolution mass spectrometers will certainly allow for a good cartography of the different fragments present in the serum of CKD patients. Such studies will be useful in understanding the impact of these fragments on their cross-reactivities with 1–84 PTH assays. Meanwhile, standardization of all the assays against a common standard will certainly reduce the inter-method variability, improve the care of CKD patients and ease the life of nephrologists.

4. Conclusions

Standardization of PTH assays is of primary importance and should be achieved as fast as possible to reduce the inter-assay variability that we still observe in PTH results today. This standardization will allow for the more accurate diagnosis and treatment of CKD and non-CKD patients. We do believe that this goal is totally achievable in the next few years with the emergence of LC-MS/MS (candidate reference) methods, commutable international standards (which could be the NIBSC 95/646) and accuracy-based external controls. This will probably require much effort from many IVD manufacturers, but this is necessary to improve the comparability of PTH results.

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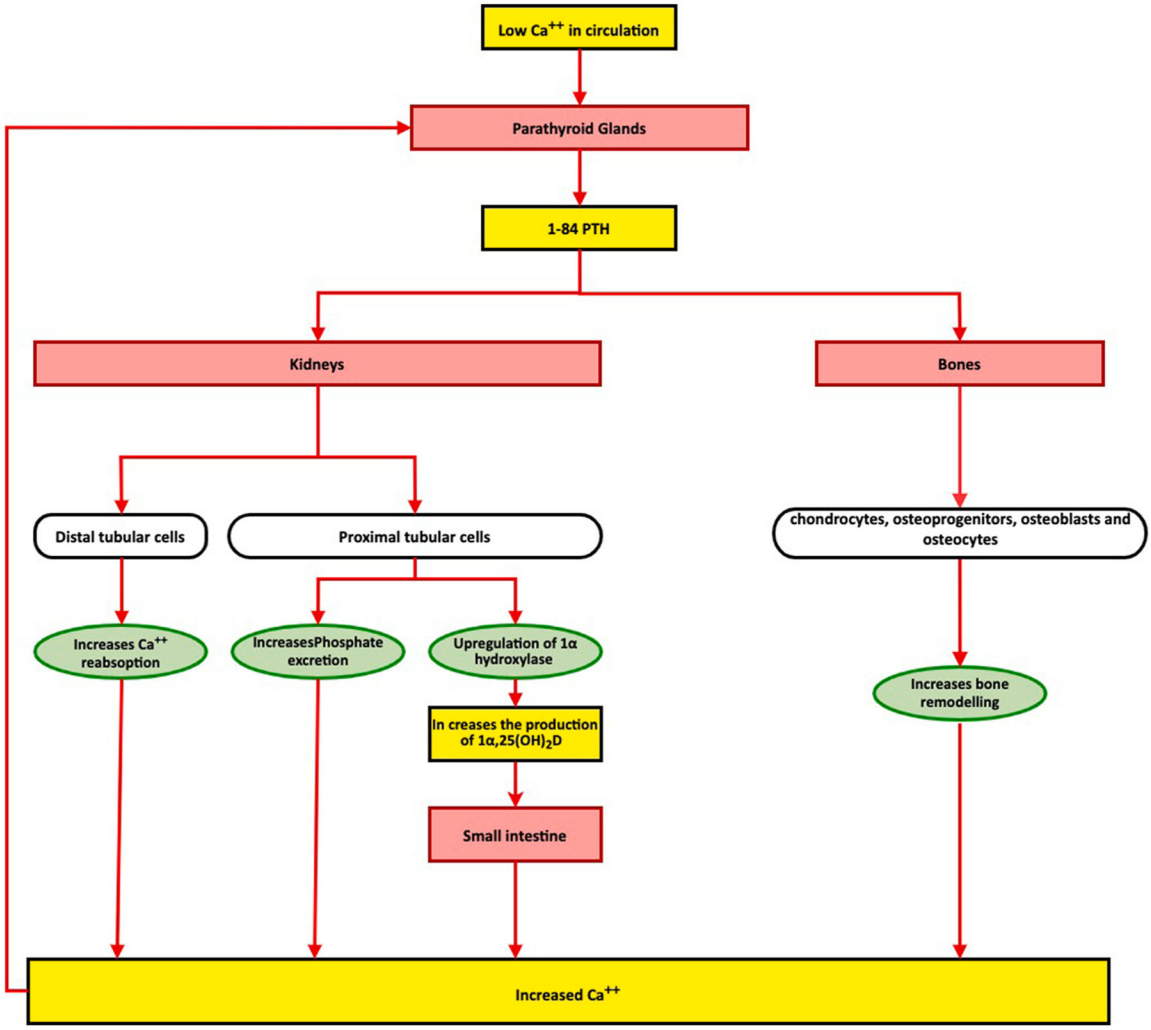

Fig. 1.

Regulation of the production of PTH mediated by a negative feed-back involving calcium, active vitamin D (calcitriol) and FGF-23.

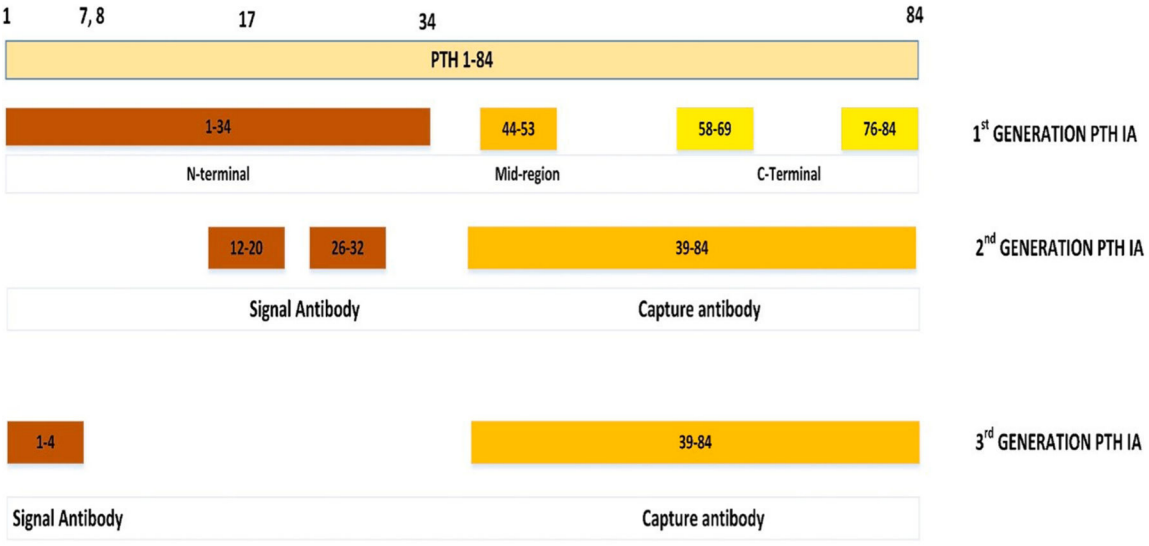

Fig. 2.

PTH assays and antibodies used. First generation assays used a single antibody directed against C-terminal region or mid region or N-terminal region. Second generation used two antibodies: one “capture” antibody directed against the C-terminal region and one “signal” antibody directed against N-terminal region (directed against epitopes AA 12–20 or aa 26–32 depending on manufacturer). Finally, in third generation assays while the “capture” antibody remained the same the “signal” antibody is directed against the first four aminoacids (AA 1–4).

Table 1

Summary of 23 studies where results from 2nd or 3rd generation PTH assays were compared for CKD and hemodialyzed (HD) patients. Third generation PTH assays are in bold.

Population	Y	X	Slope (a) [CI 95%]	Intercept (b) [CI 95%]	Reference
Pool from 47 HD	N-tact iPTH IRMA (DiaSorin)	Allegro iPTH(Nichols Institute Diagnostics)	0.51 (0.48;0.55)	6.5 (3.4;9.5)	[39]
	iPTH IRMA Immunotech (Beckman-Coulter)		1.21 (1.14;1.28)	6.1 (−0.5;12.7)	
	ELSA iPTH (Schering-Cis Bio)		0.94 (0.89;0.99)	7.7 (5.2;10.2)	
	Total iPTH IRMA (Scantibodies Laboratories)		0.85 (0.80;0.99)	6.6 (3.8;8.3)	
	DSL iPTH IRMA (Diagnostic System Laboratories)		2.10 (1.96;2.24)	8.1 (−5.3;21.5)	
	DSL iPTH ELISA (Diagnostic System Laboratories)		1.73 (1.56;1.9)	4.2 (−8.2;16.7)	
	Elecsys iPTH (Roche Diagnostics)		1.00 (0.95;1.04)	11.3 (9.4,13.3)	
	Immulite 2000 iPTH (Siemens Healthcare Diagnostics)		1.32 (1.25;1.39)	13.9 (11.2;16.5)	
	i PTH-ACS 180 (Bayer)		1.26 (1.08;1.43)	− 3.9 (−22.4,14.7)	
	ADVIA Centaur iPTH (Siemens Healthcare Diagnostics)		1.16 (0.95;1.36)	− 6.2 (−27.8;15.4)	
	iPTH advantage (Nichols Institute Diagnostics)		1.10 (1.04;1.14)	8.9 (6.0;11.9)	
	N-tact iPTH Liaison (DiaSorin)		0.75 (0.68;0.81)	− 1.9 (−8.5;4.7)	
	CA-PTH IRMA (Scantibodies Laboratories)		0.54 (0.50;0.57)	2.6 (1.1;4.1)	
	wPTH Advantage (Nichols Institute Diagnostics)		0.70 (0.64;0.76)	4.2 (−2.4;10.9)	
46 CKD stage 5	iPTH Advantage (Nichols Institute Diagnostics)	Allegro iPTH IRMA (Nichols Institute Diagnostics)	1.24	0	[41]
	Total iPTH IRMA (Scantibodies Laboratories)		1.02	0	
	N-tact iPTH IRMA (DiaSorin)		0.52	0	
	Coat-a-Count iPTH IRMA (DPC)		0.84	0	
	Elecsys iPTH (Roche Diagnostics)		0.94	0	
	DSL iPTH IRMA (Diagnostic System Laboratories)		1.46	0	
167 HD	N-tact iPTH Liaison (DiaSorin)	Allegro iPTH (Nichols Institute Diagnostics)	0.79	50.3	[42]
80 HD	N-tact iPTH Liaison (DiaSorin)	N-tact iPTH IRMA (DiaSorin)	1.21	28.3	
121 HD	**Liaison PTH 1-84 (DiaSorin)**	N-tact iPTH Liaison (DiaSorin)	0.66 (0.63;0.70)	− 9.1 (−15.7;−4.3)	[43]
	Elecsys PTH 1-84 (Roche)	Elecsys iPTH (Roche Diagnostics)	0.60 (0.58;0.62)	9.0 (4.8;12.7)	
22 HD	N-tact iPTH Liaison (DiaSorin)	Elecsys iPTH (Roche Diagnostics)	0.86	0	[44]
	Access Dxl iPTH (Beckman-Coulter)		0.91	0	

Population	Y	X	Slope (a) [CI 95%]	Intercept (b) [CI 95%]	Reference
	ADVIA Centaur iPTH (Siemens Healthcare Diagnostics)		1.09	0	
	Architect iPTH (Abbott Diagnostics)		1.12	0	
	Immulite 2000 iPTH (Siemens Healthcare Diagnostics)		1.59	0	
37 HD	Architect iPTH (Abbott Diagnostics)	Elecsys iPTH (Roche Diagnostics)	1.31	0	[45]
	ADV1A Centaur iPTH (Siemens Healthcare Diagnostics)		1.14	0	
	Access Dxl iPTH (Beckman-Coulter)		1.00	0	
	Immulite 2000/20005 iPTH (Siemens Healthcare Diagnostics)		1.14	0	
98CKD	**Liaison PTH 1–84 (DlaSorin)**	Elecsys iPTH (Roche Diagnostics)	0.55	0.5	[46]
20 CKD stage 3	**Liaison PTH 1–84 (DiaSorin)**		0.45	6.1	
40 CKD stage 4	**Liaison PTH 1–84 (DiaSorin)**		0.68	−23.4	
38 CKD stage 5	**Liaison PTH 1–84 (DiaSorin)**		**0.53**	**8.0**	
53 CKD stage 3	**Elecsys PTH 1–84 (Roche Diagnostics)**	Elecsys iPTH (Roche Diagnostics)	0.68	10.5	[47]
35 CKD stage 4	**Elecsys PTH 1–84 (Roche Diagnostics)**		0.63	16.8	
15 CKD stage 5	**Elecsys PTH 1–84 (Roche Diagnostics)**		0.50	36.2	
73 HD	**Elecsys PTH 1–84 (Roche Diagnostics)**		0.58	6.1	
79 CKD stages 1–4	**Elecsys PTH 1–84 (Roche Diagnostics)**	Elecsys iPTH (Roche Diagnostics)	0.82	2.7	[48]
61 End stage renal disease	**Elecsys PTH 1–84 (Roche Diagnostics)**		0.62	9.9	
216 HD	Architect iPTH (Abbott Diagnostics)	Elecsys iPTH (Roche Diagnostics)	1.30	0	[49]
290 HD	Architect iPTH (Abbott Diagnostics)	Elecsys iPTH (Roche Diagnostics)	1.27	27.4	[50]
83 CKD (44 non dialysis CKD, 15 HD, 15 PD, 9 post TX)	Architect iPTH (Abbott Diagnostics)	**Elecsys PTH 1–84 (Roche Diagnostics)**	2.2 (2.1;2.4)	− 1.8 (−2.5;−0.7)	[51]
	ADV1A Centaur iPTH (Siemens Healthcare Diagnostics)		2.2 (2.0–2.4)	− 1.6 (−2.6;−0.5)	
	VitrosiPTH (Ortho Clinical Diagnostics)		1.6 (1.4;1.7)	− 0.6 (−1.2;−0.2)	
	Access Dxl iPTH (Beckman-Coulter)		1.6 (1.4;1.7)	− 1.3 (−2.1;−0.6)	
56 HD	**Liaison PTH 1–84 (DiaSorin)**	**Elecsys PTH 1–84 (Roche Diagnostics)**	0.97	−23.1	[52]
	Liaison PTH 1–84 (DiaSorin)		0.98	9.0	
129 HD	**Liaison PTH 1–84 (DiaSorin)**	**Lumipulse G wPTH (Fujirebio)**	1.01 (0.96;1.04)	−2.4 (−6.0;0.1)	[53]
92 HD	**Liaison PTH 1–84 (DiaSorin)**	EUSAiPTH (Schering-Cis Bio)	0.70 (0.40;2.00)	0	[54]
40 HD	ADV1A Centaur iPTH (Siemens Healthcare Diagnostics)	ELSAiPTH (Schering-Cis Bio)	1.34 (1.27;1.43)	−0.6 (−14.3;14.5)	[55]
	iSYS iPTH (IDS)		1.07 (1.02;1.11)	−2.6 (−11.6;7.2)	
	N-tact iPTH Liaison (DiaSorin)		0.71 (0.65;0.77)	10.0 (1.6;26.2)	

Population	Y	X	Slope (a) [CI 95%]	Intercept (b) [CI 95%]	Reference
55 Plasma samples eGFR < 30	Access Dxl iPTH (Beckman-Coulter)	Architect iPTH (Abbott Diagnostics)	0.76 (0.73;0.81)	−5.3	[56]
	ADVIA Centaur iPTH (Siemens Healthcare Diagnostics)		0.90 (0.85;0.93)	−5.0	
	Elecsys iPTH (Roche Diagnostics)		0.78 (0.76;0.79)	3.4	
	Immulite 2000 iPTH (Siemens Healthcare Diagnostics)		1.43 (1.35;1.48)	−7.1	
	N-tact iPTH Liaison (DiaSorin)		0.90 (0.84;0.96)	−2.9	
100 CKD stages 4 et 5 (60.6 y.o.)	iSYS iPTH (IDS)	ADVIA Centaur iPTH (Siemens Healthcare Diagnostics)	1.09	4.4	[57]
70 HD	ADVIA Centaur CP iPTH (Siemens Healthcare Diagnostics)	ADVIA Centaur XP iPTH (Siemens Healthcare Diagnostics)	0.96 (0.94;0.99)	0.1 (−0.5;0.5)	[58]
738 HD	Intact PTH (?)	**Whole PTH (?)**	1.59	0	[59]
	Whole PTH (?)	Intact PTH (?)	0.63	0	
51 HD	**wPTH (Nichols Institute Diagnostics)**	iPTH (Nichols Institute Diagnostics)	0.52	−10.9	[60]
138 HD	iPTH (Nichols Institute Diagnostics)	**wPTH (Scantibodies Laboratories)**	1.66	6.2	[61]
19 HD	Elecsys iPTH (Roche Diagnostics)	ST AIA iPTH (Tosoh Biosciences)	0.7	0	[62]