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The Diagnosis of Normocalcaemic Hyperparathyroidism is Strikingly Dissimilar Using Different Commercial Laboratory Assays

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ABSTRACT

We assessed the impact of intact parathyroid hormone (iPTH) and adjusted calcium analyses on Abbott, Roche and Siemens analytical platforms in the diagnosis of normocalcaemic primary hyperparathyroidism (NCPHPT). These assays are used by over 85 % of clinical laboratories in the UK. Over five months, consecutive serum samples from outpatients with NCPHPT in the laboratory with Abbott assays were identified, aliquoted and stored at –80°C. Frozen aliquots were transported monthly to the other two laboratories. After thawing, samples were mixed and analysed immediately for calcium, albumin and iPTH in the laboratories with Abbott, Roche and Siemens analytical platforms. Adjusted calcium was calculated using the equation used in the respective laboratory. Diagnostic concordance of iPTH and adjusted calcium were assessed using manufacturer-provided assay-specific reference intervals and the pathology harmony reference interval respectively. Fifty-five patients with NCPHPT were identified using Abbott assays. Of these, 16 (29.1 %) and 11 (20.0 %) had NCPHPT, 9 (16.4 %) and 13 (23.6 %) had hypercalcaemic primary hyperparathyroidism, and 30 (54.6 %) and 31 (56.4 %) patients had normal results when analysed in laboratories with Roche and Siemens assays, respectively. The diagnosis of NCPHPT was strikingly different depending on the commercial assay used. There is a pressing need for iPTH assay harmonisation and robust reference intervals. Reference intervals may become invalid if an assay drifts, as exemplified by adjusted calcium in this study.

Introduction

Persistently elevated parathyroid hormone (PTH) concentrations with normal circulating calcium levels in the absence of secondary causes of hyperparathyroidism is classified as normocalcaemic primary hyperparathyroidism (NCPHPT) [1, 2], a well-established entity of primary hyperparathyroid disorders [1]. NCPHPT has been reported as carrying a significant co-morbidity with increased rates of osteoporosis, fractures and renal stones [3, 4].

The reported prevalence of NCPHPT ranges from 0.1 % to 6 % [3, 5–7]. The differing prevalence of NCPHPT has been attributed to different patient cohorts, study design especially non-rigorous exclusion of secondary hyperparathyroidism, nutritional factors, differing definitions of NCPHPT and normalisation or progression to hypercalcaemic primary hyperparathyroidism (PHPT) [3]. Many studies reporting NCPHPT prevalence have, however, provided little or no information about the calcium and PTH assays used [6, 7] and the specific generation of PTH assay used [6, 8].

Assay related differences in PTH are well-recognised [9] and evident from external quality assurance (UK NEQAS) data. It is generally believed, however, that between assay differences are accounted for by assay-specific reference intervals [10]. We suspected that the diagnosis of NCPHPT may be dependent on the laboratory site of sample analysis. Due to geographical and service provision reasons, patients seen in our regional endocrine services may have their blood samples analysed in any of six laboratories in the region. These laboratories have analytical platforms from either Abbott Laboratories, Roche Diagnostics or Siemens Healthineers. Calcium, albumin and PTH assays provided by these three manufacturers are used by 85 % of clinical laboratories in the UK.

In an institution approved service evaluation, we therefore, assessed the impact of Abbott, Roche and Siemens assays in the diagnosis of NCPHPT.

Patients and Methods

Three neighbouring hospital laboratories participated in a diagnostic test assessment study evaluating commutativity of Abbott, Roche and Siemens assay results in the diagnosis of NCPHPT.

Consecutive serum samples from outpatients with NCPHPT (adjusted calcium 2.2–2.6 mmol/l with an intact PTH (iPTH) > 7.2 pmol/l) were identified in the laboratory with Abbott assays for five months (February to June 2021). The diagnosis of NCPHPT requires confirmation of an elevated PTH on at least two further occasions [2]. However, for this study assessing the performance of diagnostic tests, patients with a single paired elevated iPTH with a normal serum albumin adjusted calcium were included after exclusion of secondary and tertiary hyperparathyroidism. Samples from patients with estimated glomerular filtration rate (eGFR, CKD-EPI equation) < 60 ml/min/1.73 m^2 [11], vitamin D < 50 nmol/l, pregnant women, children (< 18 years) and patients with malignancy, renal transplant, hypothyroidism with elevated thyroid stimulating hormone, Paget's disease of bone and on medication known to affect PTH calcium were identified based on information in the patients' laboratory, hospital and primary care records and excluded [2, 4, 12].

Samples from patients with possible NCPHPT were identified in real-time using automated data pulls from the laboratory information system in the laboratory with Abbott assays. Following the conclusion of requested tests, maximally within eight hours of sample collection, samples fulfilling the inclusion criteria were retrieved from refrigerated laboratory storage (2–8°C), anonymised, serum tipped off into three aliquots (one each for analysis by Abbott, Roche and Siemens assays) and stored at –80°C [8, 13].

Once a month, the serum aliquots for Roche and Siemens laboratories were transported frozen to the respective laboratory. On receipt, the sample aliquots were thawed, mixed and analysed within one hour for calcium, albumin and iPTH. The frozen sample aliquots in the laboratory with Abbott assays were similarly thawed and analysed on the same day every month as the aliquots in the other two laboratories. Calcium and albumin were measured on Architect c16000, cobas c702 and Atellica CH 930, and iPTH was measured on Architect i2000 SR, cobas e801 and Atellica IM 1600, respectively, in laboratories with Abbott, Roche and Siemens analytical platforms. All three PTH assays are second-generation (iPTH) immunoassays [9, 14]. The sample identification and exchange continued for five months.

Adjusted calcium (mmol/l) was calculated using the routinely used equation in each laboratory that was {total calcium (mmol/l) + 0.0152 [42.24 – albumin (g/l)]}, {total calcium (mmol/l) + 0.02 [40 – albumin (g/l)]} and {total calcium (mmol/l) + 0.015 [45 – albumin (g/l)]}, respectively, for laboratories with Abbott, Roche and Siemens methods. Laboratories with Abbott and Siemens methods use adjusted calcium equation derived in-house using previously published method [15, 16]. The calcium adjustment equation used by the laboratory with Abbott method was derived less than a year before the study. Adjusted calcium, and not ionised calcium, is used in all three laboratories in accordance with national guidance [17].

Adjusted calcium and iPTH assays were ISO 15189 accredited by the United Kingdom Accreditation Service (UKAS) for the participating laboratories. The inter-assay coefficient of variation (CV) for Abbott iPTH was 5.9 % at 4.6 pmol/l and 3.7 % at 25 pmol/l, for Roche iPTH was 7.4 % at 5.9 pmol/l and 2.6 % at 29.9 pmol/l and for Siemens iPTH was 6.4 % at 2.8 pmol/l and 4.5 % at 22.0 pmol/l. Inter-assay CV for Abbott adjusted calcium was 1.4 % and 1.1 %, respectively, at the calcium of 2.52 mmol/l and albumin of 32.4 g/l and calcium of 3.13 mmol/l and albumin of 39.3 g/l. Inter-assay CV for Roche adjusted calcium was 2.8 % and 2.8 %, respectively, at the calcium of 2.53 mmol/l and albumin of 25.5 g/l and calcium of 3.07 mmol/l and albumin of 41.9 g/l. Inter-assay CV for Siemens adjusted calcium was 2.3 and 2.1 %, respectively, at the calcium of 2.51 mmol/l and albumin of 32.3 g/l and calcium of 3.30 mmol/l and albumin of 39.5 g/l. All assays had satisfactory internal quality control performance on the days of sample measurement.

All three laboratories use UK Pathology Harmony consensus adjusted calcium reference intervals of 2.2 to 2.6 mmol/l [18]. The laboratories with Abbott and Roche assays use serum samples for iPTH analysis and both laboratories use the manufacturer provided assay-specific reference intervals, respectively, 1.6–7.2 pmol/l and 1.9–6.9 pmol/l. The preferred iPTH sample type in the laboratory with Siemens assay is EDTA plasma and results are interpreted using manufacturer-provided assay-specific reference intervals. Since serum was used in this study, the serum-specific iPTH reference range, provided by the manufacturer, was used (1.96–9.33 pmol/l). The manufacturer provided reference intervals for Abbott,

Roche and Siemens iPTH were derived from 143, 60 and 142 apparently health individuals respectively (package inserts). Additional details are not provided in Abbott and Roche iPTH package inserts. The Siemens iPTH package insert states that individuals had normal levels of calcium, creatinine, vitamin D and TSH.

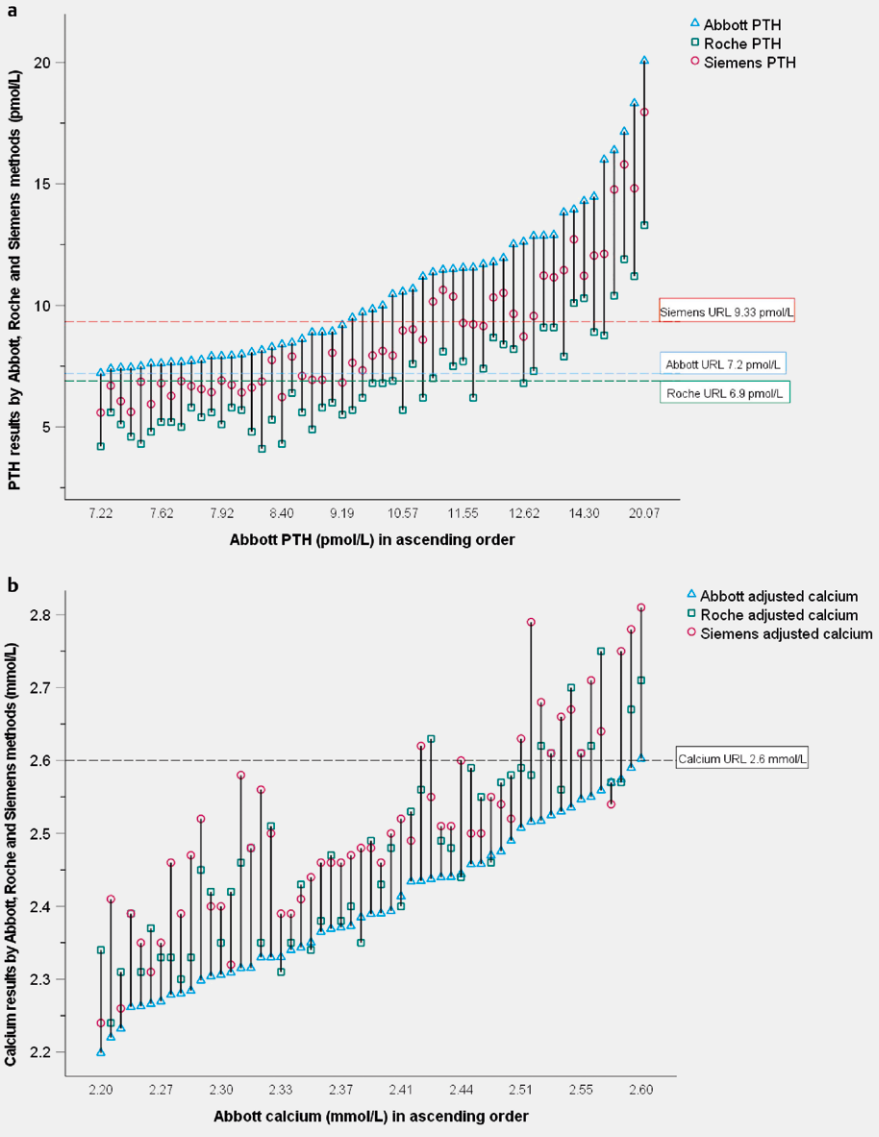
Data were tabulated in Excel (Microsoft corp.) and statistical analysis was performed using SPSS Statistics for Windows version 28 (IBM Corp.). Since data were non-parametric (Shapiro-Wilk test), Spearman rank correlation was used to measure the degree of association between results on different analytical platforms. Wilcoxon signed-rank test was used to assess the significance of the difference between paired data. Cohen's and Fleiss' kappa were used for assessing agreement in categorical diagnosis by two methods and three methods, respectively. The threshold for statistical significance was 5 %. Data are expressed as medians with inter-quartile ranges (IQR).

Results

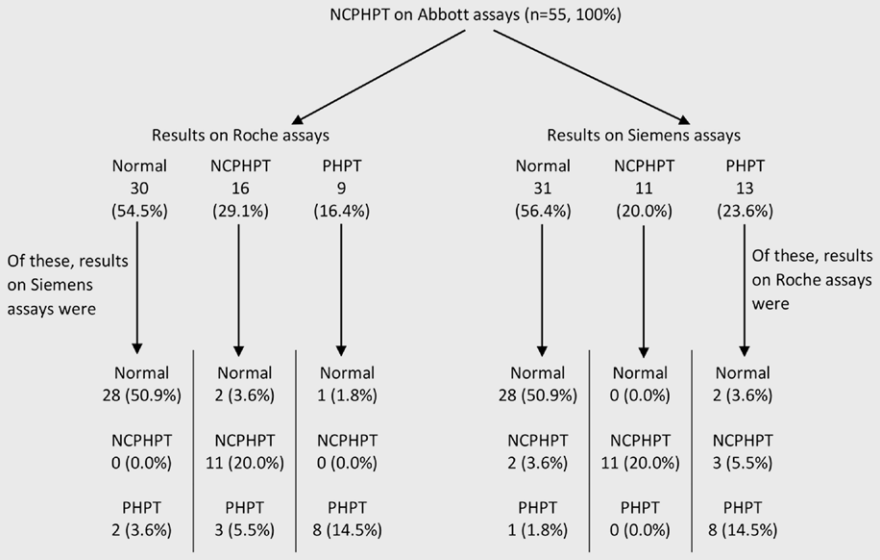
Samples from 55 patients (48 females, median age 71 years, IQR 64–77) indicative of NCPHPT were identified in the laboratory with Abbott assays over five months.

The Abbott adjusted calcium results correlated with the Roche (ρ 0.868, $p < 0.001$) and Siemens (ρ 0.855, $p < 0.001$) adjusted calcium results. The Roche adjusted calcium results correlated with the Siemens adjusted calcium results (ρ 0.828, $p < 0.001$). The Abbott iPTH results correlated with the Roche iPTH (ρ 0.911, $p < 0.001$) and Siemens iPTH (ρ 0.951, $p < 0.001$) results. The Roche iPTH results correlated with the Siemens iPTH results (ρ 0.920, $p < 0.001$).

Abbott iPTH results were 53.4 % (IQR 42.3–67.1, $p < 0.001$) and 21.4 % (IQR 12.1–28.1, $p < 0.001$) higher than Roche iPTH and Siemens iPTH results, respectively. Siemens iPTH results were 26.8 % (IQR 19.6–37.9, $p < 0.001$) higher than Roche iPTH results (▶ **Fig. 1 a**). The adjusted calcium results in the laboratory with Abbott methods were 3.0 % (IQR 0.9–4.4, $p < 0.001$) and 3.8 % (IQR 2.8–6.1, $p < 0.001$) lower than



▶ **Fig. 1** Intact PTH (**a**) and adjusted calcium (**b**) results on Abbott, Roche and Siemens assays for normocalcaemic hyperparathyroidism identified on Abbott assays (n = 55). URL is the upper reference limit.



▶ **Fig. 2** Comparison of Abbott, Roche and Siemens assays in the diagnosis of normocalcaemic primary hyperparathyroidism (NCPHPT) identified on Abbott assays (n = 55). PHPT is hypercalcaemic primary hyperparathyroidism and normal indicates both adjusted calcium and parathyroid hormone within respective reference intervals.

adjusted calcium results in laboratories with Roche and Siemens methods, respectively. Adjusted calcium results in the laboratory with Roche methods were 1.5 % (IQR –0.8 to 3.9, p = 0.002) lower than adjusted calcium results in the laboratory with Siemens methods (▶ **Fig. 1 b**).

Of the 55 patients with NCPHPT identified in the laboratory with Abbott assays, 16 (29.1 %) and 11 (20.0 %) had results consistent with NCPHPT when samples were analysed in laboratories with Roche and Siemens assays, respectively. Of the remaining patients, 9 (16.4 %) and 13 (23.6 %) had hypercalcaemic primary hyperparathyroidism (PHPT), and 30 (54.6 %) and 31 (56.4 %) had normal findings, based on results from the same laboratories, respectively (▶ **Fig. 2**).

Cohen's kappa for agreement in diagnosis for laboratories with Roche and Siemens assays was 0.756 (p < 0.001). Cohen's kappa for agreement in diagnosis was not significant (p > 0.05) for the laboratory with Abbott assays compared to laboratories with either Roche or Siemens assays. Overall, the laboratories did not agree with categorical diagnosis (Fleiss kappa 0.079, p = 0.189).

Discussion

We report striking differences in the diagnosis of NCPHPT depending on whether iPTH and adjusted calcium were analysed in laboratories with assays provided by Abbott Laboratories, Roche Diagnostics or Siemens Healthineers. Diagnostic categories when analysed in laboratories using Roche and Siemens methods were in moderate agreement but both were very different compared to the laboratory using Abbott methods. Of the 55 patients with NCPHPT defined using Abbott assays, only 16 (29.1 %) and 11 (20.0 %) had NCPHPT when analysed in laboratories using the Roche and Siemens assays respectively. The rest, 39 (70.9 %) and 44 (80.0 %) patients had discordant categorical clinical diagnoses when analysed in laboratories with Roche and Siemens assays, respectively.

The diagnostic differences in NCPHPT were largely due to iPTH assay differences and different assay-specific iPTH reference intervals. The diagnosis of NCPHPT was higher with Abbott than Roche assays because the Abbott iPTH results were 53.4 % higher than Roche iPTH results but their upper reference limits (URL) were similar. The diagnosis of NCPHPT was higher with Abbott than Siemens assays not only because the Abbott iPTH results were 23.4 % higher than Siemens iPTH results but also because the URL for Abbott iPTH was 29.5 % lower than the Siemens iPTH URL. The diagnosis of NCPHPT was slightly higher for Roche than Siemens assays because although Siemens iPTH results were 26.8 % higher than Roche iPTH results the URL for Siemens iPTH was 35 % higher than Roche iPTH URL.

The second-generation PTH assays, used in this study, are the most widely used PTH assays [14]. Second-generation PTH assays ("intact" PTH), unlike the third-generation PTH assays ("whole" or "bioactive" PTH), recognise biologically inactive large C-terminal PTH fragments to a variable extent which may explain some of the observed between assay variability [9, 14]. Although the International Federation of Clinical Chemistry (IFCC) Committee on Bone Metabolism is working towards improving PTH assay harmonisation including the development of a commutable international PTH standard [9, 14], PTH assays are not standardised [14]. In addition, our results indicate that current manufacturer-provided assay-specific reference intervals do not compensate for the inter-assay iPTH differences. Laboratories may, therefore, have to either derive or adopt appropriate iPTH reference intervals. Different inclusion and exclusion criteria and diverse statistical data handling in studies de-

riving PTH reference intervals, however, have led to large differences in published PTH reference intervals, which make it unclear which iPTH assay requires a re-evaluation of its reference intervals [19]. Notably, studies have reported higher upper reference limits (URL) for Abbott Architect iPTH assay, ranging from 9.4 pmol/l to 11.1 pmol/l compared to the manufacturer provided URL of 7.2 pmol/l [20]. A higher URL for the Abbott iPTH assay would have mitigated the observed differences in this study.

Of the 55 patients with NCPHPT identified in the laboratory with Abbott assays, 9 (16.4 %) and 13 (23.6 %) had hypercalcaemia with inappropriately elevated iPTH, diagnostic of PHPT, when analysed in laboratories using Roche and Siemens analytical platforms respectively. This diagnostic discordance was due to a significant negative bias in the Abbott calcium assay compared to the Roche and Siemens calcium assays during the study period since all the laboratories used the same UK Pathology Harmony consensus reference interval for adjusted calcium [18]. The negative bias for the Abbott assay reported in this study, which was evident since February 2021 (UK NEQAS for Clinical Chemistry external quality assessment report), prompted the laboratory with the Abbott assays to implement mitigative action by re-deriving the adjusted calcium equation [15, 16] until the issue was addressed and resolved by the manufacturer by October 2021 (UK NEQAS for Clinical Chemistry external quality assessment report). This study demonstrates how analytical issues with calcium or albumin can affect adjusted calcium and management of parathyroid disorders [21, 22]. The study also indicates limitation of current approach of derivation of adjusted calcium equation as it relies on previous patient data [22]. If calcium or albumin assay bias is introduced, derivation of updated adjustment equation is delayed until sufficient patient data is available. Additionally, small cumulative assay drift with successive lots may not be picked up by existing laboratory practise [23].

NCPHPT is considered to be an intermediate phenotype between the normal population and PHPT [3]. Studies in referral centres have reported a significant increase in the prevalence of osteoporosis, fragility fractures and nephrolithiasis in patients with NCPHPT whereas most population-based studies have reported little or no excess risk [3, 24]. Data on the natural history of NCPHPT are sparse and inconsistent and only a minority of NCPHPT patients, depending on the study 0 to 19 %, progress to PHPT [3–5].

In the absence of a strong evidence base, management of NCPHPT is guided by expert recommendation [24, 25] and includes nephrolithiasis screening, biochemical monitoring, periodic bone densitometry and regular clinical assessments in most centres [4, 25]. In this study, it is unclear whether Abbott iPTH and adjusted assays led to over-diagnosis of NCPHPT and under-diagnosis of PHPT or Roche and Siemens assays led to under-diagnosis of NCPHPT and over-diagnosis of PHPT. A misdiagnosis of NCPHPT and resultant additional investigations and periodic follow up not only generate additional expenditure but may also lead to patient anxiety, whereas a missed diagnosis of NCPHPT and PHPT may lead to increased patient co-morbidity through bone and renal stone disease.

This striking variability in the diagnosis of NCPHPT due to different iPTH assays is not addressed in guidelines [2, 17, 26]. Between assay differences in iPTH and differences in iPTH reference intervals may have contributed to observed differences in the prevalence, and therefore, epidemiology of NCPHPT but it is difficult to ascertain as many studies have not provided assay information [3, 6, 7].

In summary, this study draws attention to the pressing need for harmonisation of PTH assays [14] and the inclusion of assay-related factors in the clinical management guidelines of parathyroid conditions. This study also emphasises the importance to laboratories of selecting or deriving appropriate reference intervals and periodically assessing the fitness of existing assay-specific reference intervals and equations for calculated parameters. Clinicians and laboratorians should be aware that assay differences and variations in reference intervals will directly impact the diagnosis and therefore management of hyperparathyroidism.

Conflict of Interest

The authors declare that they have no conflict of interest.

References

[1] Bilezikian JP, Khan AA, Potts JT Jr et al. Guidelines for the management of asymptomatic primary hyperparathyroidism: summary statement from the third international workshop. J Clin Endocrinol Metab 2009; 94: 335–339

[2] Eastell R, Brandi ML, Costa AG et al. Diagnosis of asymptomatic primary hyperparathyroidism: proceedings of the Fourth International Workshop. J Clin Endocrinol Metab 2014; 99: 3570–3579

[3] Zavatta G, Clarke BL. Normocalcemic hyperparathyroidism: a heterogeneous disorder often misdiagnosed? JBMR Plus 2020; 4: e10391

[4] Corbetta S. Normocalcemic hyperparathyroidism. Front Horm Res 2019; 23–39

[5] Schini M, Jacques RM, Oakes E et al. Normocalcemic hyperparathyroidism: study of its prevalence and natural history. J Clin Endocrinol Metab 2020; 105: e1171–e1186

[6] Cusano NE, Maalouf NM, Wang PY et al. Normocalcemic hyperparathyroidism and hypoparathyroidism in two community-based nonreferral populations. J Clin Endocrinol Metab 2013; 98: 2734–2741

[7] García-Martín A, Reyes-García R, Muñoz-Torres M. Normocalcemic primary hyperparathyroidism: one-year follow-up in one hundred postmenopausal women. Endocrine 2012; 42: 764–766

[8] Hanon EA, Sturgeon CM, Lamb EJ. Sampling and storage conditions influencing the measurement of parathyroid hormone in blood samples: a systematic review. Clin Chem Lab Med 2013; 51: 1925–1941

[9] Sturgeon CM, Sprague S, Almond A et al. Perspective and priorities for improvement of parathyroid hormone (PTH) measurement - a view from the IFCC working group for PTH. Clin Chim Acta 2017; 467: 42–47

[10] Group KDIGO (KDIGO) C-MUW KDIGO 2017 Clinical practice guideline update for the diagnosis, evaluation, prevention, and treatment of chronic kidney disease-mineral and bone disorder (CKD-MBD). Kidney Int 2017; 7: 1–59

[11] Muntner P, Jones TM, Hyre AD et al. Association of serum intact parathyroid hormone with lower estimated glomerular filtration rate. Clin J Am Soc Nephrol 2009; 4: 186–194

[12] Makras P, Polyzos SA, Papatheodorou A et al. Parathyroid hormone changes following denosumab treatment in postmenopausal osteoporosis. Clin Endocrinol (Oxf) 2013; 79: 499–503

[13] Cavalier E, Delanaye P, Hubert P et al. Estimation of the stability of parathyroid hormone when stored at −80°C for a Long Period. Clin J Am Soc Nephrol 2009; 4: 1988 LP – 1992

[14] Cavalier E, Vasikaran S, Bhattoa HP et al. The path to the standardization of PTH: is this a realistic possibility? a position paper of the IFCC C-BM. Clin Chim Acta 2021; 515: 44–51

[15] James MT, Zhang J, Lyon AW et al. Derivation and internal validation of an equation for albumin-adjusted calcium. BMC Clin Pathol 2008; 8: 12

[16] Barth JH, Fiddy JB, Payne RB. Adjustment of serum total calcium for albumin concentration: effects of non-linearity and of regression differences between laboratories. Ann Clin Biochem 1996; 33: 55–58

[17] National Institute for Health and Care Excellence(2019). Hyperparathyroidism (primary): diagnosis, assessment and initial management. NICE Guidel [NG132] https//www.nice.org.uk/guidance/ng132 2019

[18] Berg J, Lane V. Pathology Harmony; a pragmatic and scientific approach to unfounded variation in the clinical laboratory. Ann Clin Biochem 2011; 48: 195–197

[19] Souberbielle J-C, Brazier F, Piketty M-L et al. How the reference values for serum parathyroid hormone concentration are (or should be) established? J Endocrinol Invest 2017; 40: 241–256

[20] Deckers MML, de Jongh RT, Lips PTAM et al. Prevalence of vitamin D deficiency and consequences for PTH reference values. Clin Chim Acta 2013; 426: 41–45

[21] Jassam N, Thomas A, Hayden K et al. The impact of the analytical performance specifications of calcium and albumin on adjusted calcium. Ann Clin Biochem 2020; 57: 382–388

[22] Weaving G. Calcium – An adjustment too far or not far enough? Ann Clin Biochem 2020; 57: 401–403

[23] Kalaria T, Sanders A, Ford C et al. Biochemical assessment of adequate Levothyroxine replacement in primary hypothyroidism differs with different TSH assays – potential clinical implications. J Clin Pathol 2021. doi:10.1136/jclinpath-2020-207316 Online ahead of print

[24] Cusano NE, Cipriani C, Bilezikian JP. Management of normocalcemic primary hyperparathyroidism. Best Pract Res Clin Endocrinol Metab 2018; 32: 837–845

[25] Silverberg SJ, Clarke BL, Peacock M et al. Current issues in the presentation of asymptomatic primary hyperparathyroidism: proceedings of the Fourth International Workshop. J Clin Endocrinol Metab 2014; 99: 3580–3594

[26] Wilhelm SM, Wang TS, Ruan DT et al. The American association of endocrine surgeons guidelines for definitive management of primary hyperparathyroidism. JAMA Surg 2016; 151: 959–968