NATIONAL QUALITY FORUM

Measure Submission and Evaluation Worksheet 5.0

This form contains the information submitted by measure developers/stewards, organized according to NQF's measure evaluation criteria and process. The evaluation criteria, evaluation guidance documents, and a blank online submission form are available on the submitting standards web page.

NQF #: 1655 NQF Project: Renal Endorsement Maintenance 2011

(for Endorsement Maintenance Review)
Original Endorsement Date: Most Recent Endorsement Date:

BRIEF MEASURE INFORMATION

De.1 Measure Title: ESRD patients with PTH >400pg/mL and not treated with a calcimimetic or vitamin D analog.

Co.1.1 Measure Steward: Amgen Inc.

De.2 Brief Description of Measure: Percentage of end stage renal disease (ESRD) patients aged 18 years and older with serum intact PTH levels >400pg/mL who are NOT treated with a calcimimetic agent or vitamin D analog to lower the PTH during the 3-month reporting period.

2a1.1 Numerator Statement: Number of patients from the denominator with serum intact PTH >400pg/mL who are NOT being treated with a calcimimetic agent or vitamin D analog to lower the PTH.

2a1.4 Denominator Statement: All hemodialysis and peritoneal dialysis patients aged 18 years and older at the dialysis facility for at least 30 days who have been on dialysis for greater than 90 days and who have not been discharged from the facility prior to the last day of the most recent month of the 3-month reporting period.

2a1.8 Denominator Exclusions: None.

1.1 Measure Type: Process
2a1. 25-26 Data Source: Electronic Clinical Data : Electronic Health Record, Electronic Clinical Data : Laboratory
2a1.33 Level of Analysis: Facility

1.2-1.4 Is this measure paired with another measure? No

De.3 If included in a composite, please identify the composite measure (*title and NQF number if endorsed*):
Not applicable.

STAFF NOTES (*issues or questions regarding any criteria*)

Comments on Conditions for Consideration:

Is the measure untested? Yes☐ No☐ If untested, explain how it meets criteria for consideration for time-limited endorsement:

1a. Specific national health goal/priority identified by DHHS or NPP addressed by the measure (*check De.5*):
5. Similar/related endorsed or submitted measures (*check 5.1*):
Other Criteria:

Staff Reviewer Name(s):

1. IMPACT, OPPORTUITY, EVIDENCE - IMPORTANCE TO MEASURE AND REPORT

Importance to Measure and Report is a threshold criterion that must be met in order to recommend a measure for endorsement. All three subcriteria must be met to pass this criterion. See guidance on evidence.
Measures must be judged to be important to measure and report in order to be evaluated against the remaining criteria.

(evaluation criteria)

1a. High Impact: H☐ M☐ L☐ I ☐
(*The measure directly addresses a specific national health goal/priority identified by DHHS or NPP, or some other high impact aspect of healthcare.*)

De.4 Subject/Topic Areas *(Check all the areas that apply)*: Renal, Renal : End Stage Renal Disease (ESRD)
De.5 Cross Cutting Areas (*Check all the areas that apply)*: Access, Care Coordination, Disparities, Functional Status, Infrastructure Supports : Health IT, Patient and Family Engagement, Safety : Complications

1a.1 Demonstrated High Impact Aspect of Healthcare: Affects large numbers, A leading cause of morbidity/mortality, High resource use, Patient/societal consequences of poor quality, Severity of illness

1a.2 If "Other," please describe:

1a.3 Summary of Evidence of High Impact *(Provide epidemiologic or resource use data)*:
In 2008, the adjusted incident rate of end-stage renal disease (ESRD) cases in the United States was 350.8 per million population, and the adjusted rate of prevalent cases rose 1.9 percent to 1,699 per million population. This rate is nearly 20 percent greater than that seen in 2000, and the annual rate of increase has remained between 1.9 and 2.3 percent since 2003. Total Medicare costs rose nearly 11 percent in 2008—up from a 7 percent rise the previous year—to $454 billion. ESRD costs rose 13.2 percent to $26.8 billion, and accounted for 5.9 percent of the Medicare budget.(1)

Among patients with ESRD, secondary hyperparathyroidism (SHPT) is a common and serious co-morbid condition that can develop long before dialysis is initiated. The disorder occurs early in the course of chronic kidney disease (CKD), progresses in severity over time, and affects the majority of patients when renal replacement therapy with dialysis is begun. It is characterized by persistent and often markedly elevated concentrations of parathyroid hormone (PTH) in blood.(2,3)

SHPT is an adaptive response that serves initially to maintain calcium homeostasis as kidney function declines. When kidney disease becomes more advanced, however, SHPT increases in severity and it becomes a progressive disorder if left untreated. Among patients with ESRD, SHPT contributes to important biochemical disturbances such as episodes of hypercalcemia and hyperphosphatemia, to abnormal bone pathology, and to reductions in bone mass.(4,5) Because high blood levels of PTH are the hallmark of SHPT, PTH measurements are used most widely in clinical practice to assess the presence and severity of SHPT and to monitor evolution of the disorder over time, particularly in the setting of dialysis.(5) No other biochemical determination can be used for this purpose.

Although recognized for many years as a discrete clinical entity, SHPT has recently come to be considered as an integral component of the newly defined syndrome of chronic kidney disease-mineral and bone disorder, or CKD-MBD.(6) Despite this development, SHPT remains a major cause of renal bone disease, or renal osteodystrophy, leading to pathological changes in bone known as osteitis fibrosa cystica. The bone disease of SHPT is characterized by high rates of skeletal remodeling and turnover, by changes in bone structure and bone mass, and by prominent clinical manifestations that include bone pain, muscle pain and weakness, arthalgia, and skeletal fractures.(7-12)

Therapeutic interventions that attenuate even modestly the severity of SHPT among patients with CKD diminish or reverse the pathological features of hyperparathyroidism in bone(13) and substantially attenuate reductions in bone mass.(14) Conversely, if SHPT remains untreated before dialysis is initiated, PTH concentrations increase progressively due in part to the development of parathyroid gland hyperplasia with attendant increases parathyroid gland mass.(15) These components of the disease continue to advance after renal replacement therapy with dialysis is initiated. Once established, parathyroid gland enlargement is largely irreversible, resulting in persistent and marked elevations in serum or plasma PTH levels that worsen over time.(16) The progressive nature of SHPT is documented in reports demonstrating that both the prevalence and severity of SHPT increase with the duration of CKD and as a function of the number of years of treatment with dialysis.(17-19)

Overt SHPT contributes materially to systemic disturbances in calcium and phosphorus metabolism among patients with little or no residual kidney function who require treatment with dialysis. Importantly, these biochemical abnormalities contribute to the development of soft-tissue and vascular calcification, including cardiovascular calcification, among persons with CKD, particularly in those managed with dialysis.(20-22) Results from observational studies indicate that elevations in plasma PTH levels are

associated consistently with morbidity and with an increased risk of cardiovascular and all-cause mortality among patients undergoing dialysis.(23-28)

1a.4 Citations for Evidence of High Impact cited in 1a.3:

1. U.S. Renal Dialysis System, USRDS 2009 Annual Data Report: Atlas of Chronic Kidney Disease and End-Stage Renal Disease in the United States. 2009.

2. Levin A, Bakris G, Molitch M et al. Prevalence of abnormal serum vitamin D, PTH, calcium, and phosphorus in patients with chronic kidney disease: results of the study to evaluate early kidney disease. Kidney Int. 2007;71:31-8.

3. Rix M, Andreassen H, Eskildsen P et al. Bone mineral density and biochemical markers of bone turnover in patients with predialysis chronic renal failure. Kidney Int. 1999;56(3):1084-93.

4. Goodman W and Quarles L. Development and progression of secondary hyperparathyroidism in chronic kidney disease: lessons from molecular genetics. Kidney Int. 2008;74(3):276-88.

5. Goodman, W. Renal Osteodystrophy: Pathogenic Mechanisms and Therapeutic Options. In: Principles of Bone Biology, edited by J. P. Bilezikian, L. G. Raisz, and T. J. Martin. New York:Elsevier. 2008:1479-1510.

6. Moe S, Drueke T, Cunningham J et al. Definition, evaluation, and classification of renal osteodystrophy: a position statement from Kidney Disease Improving Global Outcomes (KDIGO). Kidney Int. 2006;69(11):1945-53.

7. Danese M, Kim J, Doan Q et al. PTH and the risks for hip, vertebral, and pelvic fractures among patients on dialysis. Am J Kidney Dis. 2006;47(1):149-56.

8. Block G, Hulbert-Shearon T, Levin N, Port F. Association of serum phosphorus and calcium x phosphate product with mortality risk in chronic hemodialysis patients: a national study. Am J Kidney Dis. 1998;31:607–17.

9. Ganesh S, Stack A, Levin N et al. Association of elevated serum PO4, Ca x PO4 product, and parathyroid hormone with cardiac mortality risk in chronic hemodialysis patients. J Am Soc Nephrol. 2001;12:2131–8.

10. London G, Guerin A, Marchais S et al. Arterial media calcification in end-stage renal disease: impact on all-cause and cardiovascular mortality. Nephrol Dial Transplant. 2003;18:1731–40.

11. Block G, Klassen P, Lazarus J et al. Mineral metabolism, mortality, and morbidity in maintenance hemodialysis. J Am Soc Nephrol. 2004;15:2208–18.

12. Cunningham J, Danese M, Olson K, Klassen P, Chertow G. Effects of the calcimimetic cinacalcet HCl on cardiovascular disease, fracture, and health-related quality of life in secondary hyperparathyroidism. Kidney International. 2005;68:1793-1800.

13. Hamdy N, Kanis J, Beneton C et al. Effect of alfacalcidol on natural course of renal bone disease in mild to moderate renal failure. Br Med J. 1995;310:358-63.

14. Rix M, Eskildsen P, and Olgaard K. Effect of 18 months of treatment with alfacalcidol on bone in patients with mild to moderate chronic renal failure. Nephrol Dial Transplant. 2004;19(4):870-6.

15. De Francisco A, Ellis H, Owen J et al. Parathyroidectomy in chronic renal failure. Q J Med. 1985;55:289-315.

16. Lloyd H, Parfitt A, Jacobi D et al. The parathyroid glands in chronic renal failure: a study of their growth and other properties made on the basis of findings in patients with hypercalcemia. J Lab Clin Med. 1989;114:358-67.

17. De Boer I, Gorodetskaya I, Young B, Hsu C, and Chertow G. The severity of secondary hyperparathyroidism in chronic renal insufficiency is GFR-dependent, race-dependent, and associated with cardiovascular disease. J Am Soc Nephrol. 2002;13(11):2762-9.

18. Chertow G, Plone M, Dillon M, Burke S, and Slatopolsky E. Hyperparathyroidism and dialysis vintage. Clin Nephrol. 2000;54(4):295-300.

19. Malberti F, Marcelli D, Conte F et al. Parathyroidectomy in patients on renal replacement therapy: an epidemiologic study. J Am Soc Nephrol. 2001;12:1242-8.

20. Qunibi W and Kalantar-Zadeh K. Target levels for serum phosphorus and parathyroid hormone. Seminars in Dialysis. 2011;2:4-7.

21. Spasovski G, Bervets A, Behets G et al. Spectrum of renal bone disease in end-stage renal failure patients not yet on dialysis. Nephrol Dial Transplant. 2003;18:1159–66.

22. Rostand S, Drueke T. Parathyroid hormone, vitamin D, and cardiovascular disease in chronic renal failure. Kidney Int. 1999;56:383–92.

23. Piergiorgio M, Fernando M, Magdi Y et al. The OPTIMA study: assessing a new cinacalcet treatment algorithm for secondary hyperparathyroidism. Clin J Am Soc Nephrol. 2008;3:36-45.

24. Martinez I, Saracho R, Montenegro J, Liach F. The importance of dietary calcium and phosphorus in the secondary hyperparathyroidism of patients with early renal failure. Am J Kidney Dis. 1997;29:496–502.

25. Slatopolsky E, Brown A, Dusso A. Pathogenesis of secondary hyperparathyroidism. Kidney Int. 1999;56[Suppl 73]:S14–S19.

26. Salem M. Hyperparathyroidism in the dialysis population: a survey of 612 patients. Am J Kidney Dis. 1997;29:862–5.

27. Billa V, Zhong A, Bargman J et al. High prevalence of hyperparathyroidism among peritoneal dialysis patients: a review of 176 patients. Perit Dial Int. 2000;20:315–21.

28. Hruska K, Teitelbaum S. Renal osteodystrophy. N Engl J Med. 1995;333:166–74.

1b. Opportunity for Improvement: H☐ M☐ L☐ I ☐
(*There is a demonstrated performance gap - variability or overall less than optimal performance*)

1b.1 Briefly explain the benefits (improvements in quality) envisioned by use of this measure:
High serum intact PTH level in dialysis patients is a risk factor for bone fractures and a predictor of all-cause and cardiovascular mortality. Reduction in serum PTH levels with vitamin D analogs or calcimimietic agents will contribute to improved outcomes for dialysis patients.

1b.2 Summary of Data Demonstrating Performance Gap *(Variation or overall less than optimal performance across providers)*:
[*For Maintenance – Descriptive statistics for performance results for this measure - distribution of scores for measured entities by quartile/decile, mean, median, SD, min, max, etc.*]
Testing of the measure's data elements was conducted through a retrospective review of information in an electronic health record (EHR) database maintained by a large dialysis organization (LDO) in the United States. Data from 43,057 dialysis patients recorded during 2007 were evaluated. (The LDO database referred to in this submission is comprised of a random selection of all patients with a cinacalcet prescription in 2007 and a random selection of equal numbers of patients with no cinacalcet prescription; the LDO had approximately 100,000 patients at the time. Overall, then, the dataset for these analyses was comprised of 50% of patients receiving cinacalcet, compared to the approximately 20% receiving the medication within the LDO in 2007. The data are weighted to account for this over-selection.) An additional assessment was done using data from the 2007 Dialysis Outcomes and Practice Study (DOPPS) report (N=6,927). When examining serum PTH levels and the corresponding use of vitamin D analogs and/or calcimimetics, it was observed that 16% of patients in LDO facilities and 25% of patients in DOPPS with serum PTH values >400pg/mL were not being treated with a vitamin D analog or a calcimimetic agent as recommended in current clinical practice guidelines. (See Table 1A and Table 1B [Prevalence of PTH >400pg/mL and Selected Lab Parameters by Treatment Status] in the accompanying Attachment A.)

An assessment of the same sets of data for variation in performance among facilities also revealed that more than 39% of LDO and

42% of DOPPS facilities had patients with documented PTH values >400pg/mL who were not being treated. (See Table 2 [Percent of Facilities with Patients with PTH >400 Who Are Not Treated] in Attachment A.)

Such findings indicate that a substantial proportion of hemodialysis patients with biochemical evidence of SHPT are not receiving treatment for SHPT that would be considered clinically appropriate, and that this shortcoming occurs in a substantial percentage of dialysis facilities. The results identify an important gap in clinical performance that requires attention. This gap also provides an opportunity to offer guidance to clinicians for improved clinical care.

In this regard, Tentori reported data from DOPPS that compared PTH levels among countries over three discreet surveillance intervals, noting substantial variation both within and among countries including the United States. No overt trend in serum PTH levels over time was apparent. (See Figure 1 [DOPPS Distributions of Serum PTH Levels by Country and Study Phase] in Attachment A.)

1b.3 Citations for Data on Performance Gap: [*For Maintenance – Description of the data or sample for measure results reported in 1b.2 including number of measured entities; number of patients; dates of data; if a sample, characteristics of the entities included*]

1. Amgen. Unpublished review of large U.S. dialysis provider medical records-based database (N = 43,057; 2007). March 2011.

2. Tentori F. Mineral and bone disorder and outcomes in hemodialysis patients: results from the DOPPS. Semin Dial. 2010;23(1):10-14.

1b.4 Summary of Data on Disparities by Population Group: [*For Maintenance –Descriptive statistics for performance results for this measure by population group*]

Testing of the measure's data elements was conducted through a retrospective review of 2007 data in an EHR database from 43,057 dialysis patients from an LDO in the United States and through an assessment of data from the 2007 DOPPS report (N=6,927). As an examination of the data for disparities trends was not conducted because the database does not have race/ethnicity information, we instead provide the findings of two peer-reviewed studies that demonstrate that SHPT in chronic renal disease is race-dependent and that among ESRD patients, African Americans may be at increased risk for hyperparathyroid bone disease and Caucasians for adynamic bone disease.

• Gupta et al. examined racial differences in the severity of uremic hyperparathyroidism among 1,270 patients (61.1% African American, 51% male, and 31.1% diabetic) receiving hemodialysis or peritoneal dialysis, with onset of ESRD after 1993. Maximum PTH levels were analyzed as a function of race, gender, age, diabetic status, and levels of serum calcium, phosphorus, alkaline phosphatase, and aluminum. Using a stepwise multiple regression model, the determinants of maximum PTH in the order of their importance were African American race, serum phosphorus, absence of diabetes, younger age, serum calcium, and female gender. The maximum PTH levels averaged 641.7pg/mL in African Americans and 346.0pg/mL in Caucasians after adjusting for age, gender, diabetic status, serum calcium, and phosphorus (P <0.0001). In African Americans compared with Caucasians, the odds ratio for adynamic bone disease (maximum PTH <150pg/mL) was 0.26 (95% confidence interval = 0.17 to 0.41), whereas the odds ratio for hyperparathyroid bone disease (mean PTH >500pg/mL) was 4.4 (95% confidence interval = 2.10 to 9.25). The study demonstrates that race is a major independent determinant of uremic SHPT and that among ESRD patients African Americans may be at increased risk for hyperparathyroid bone disease and Caucasians for adynamic bone disease.

• De Boer et al. similarly demonstrated that SHPT in chronic renal insufficiency is race-dependent. This study evaluated 218 patients in an ethnically diverse ambulatory nephrology practice at the University of California San Francisco during calendar years 1999 and 2000. Demographic data, comorbid diseases, medications, and laboratory parameters were collected, and independent correlates of intact PTH were identified using multiple linear regression. The adjusted mean PTH was higher among African Americans and lower among Asian/Pacific Islanders compared with Caucasian patients (233 versus 95 versus 139pg/mL; P <0.0001). Moreover, among the 196 patients with GFR <60mL/min per 1.73m2, the slope of GFR versus PTH was significantly steeper among African Americans than among Caucasian patients (10.6 versus 3.9pg/mL per 1.73m2; P = 0.01). After adjusting for age and diabetes, PTH was associated with a history of myocardial infarction (OR, 1.6; 95% CI, 1.1 to 2.3 per unit natural log PTH) and congestive heart failure (OR, 2.0; 95% CI, 1.3 to 2.9 per unit natural log PTH) and was not associated with other co-morbid conditions. (See Table 3 [PTH Variations by Race] in Attachment A.)

We posit that as both the LDO and DOPPS data used in our patient sample can be viewed as valid representations of the U.S. ESRD population (see Table 4 [Comparison of Patient Characteristics] in Attachment A), information on disparities can be

extrapolated from the data presented in the Gupta and De Boer studies.

1b.5 Citations for Data on Disparities Cited in 1b.4: [*For Maintenance – Description of the data or sample for measure results reported in 1b.4 including number of measured entities; number of patients; dates of data; if a sample, characteristics of the entities included*]

1. Gupta A, Kallenbach L, Zasuwa G, Divine G. Race is a major determinant of secondary hyperparathyroidism in uremic patients. J Am Soc Nephrol. 2000;11:330-4.

2. De Boer I, Gorodestskaya I, Young B, Hsu C, Chertow G. The severity of secondary hyperparathyroidism in chronic renal insufficiency is GFR-dependent, race-dependent, and associated with cardiovascular disease. J Am Soc Nephrol. 2002;13:2762-9.

1c. Evidence (*Measure focus is a health outcome OR meets the criteria for quantity, quality, consistency of the body of evidence.*)
Is the measure focus a health outcome? Yes☐ No☐ If not a health outcome, rate the body of evidence.

Quantity: H☐ M☐ L☐ I☐ Quality: H☐ M☐ L☐ I☐ Consistency: H☐ M☐ L☐ I☐

Quantity	Quality	Consistency	Does the measure pass subcriterion1c?
M-H	M-H	M-H	Yes☐
L	M-H	M	Yes☐ IF additional research unlikely to change conclusion that benefits to patients outweigh harms: otherwise No☐
M-H	L	M-H	Yes☐ IF potential benefits to patients clearly outweigh potential harms: otherwise No☐
L-M-H	L-M-H	L	No ☐

Health outcome – rationale supports relationship to at least one healthcare structure, process, intervention, or service	Does the measure pass subcriterion1c? Yes☐ IF rationale supports relationship

1c.1 Structure-Process-Outcome Relationship *(Briefly state the measure focus, e.g., health outcome, intermediate clinical outcome, process, structure; then identify the appropriate links, e.g., structure-process-health outcome; process- health outcome; intermediate clinical outcome-health outcome)*:
ANTECEDENTS: Dialysis patients with reduced plasma levels of vitamin D, hypocalcemia, and suppressed PTH synthesis leading to secondary hyperparathyroidism (SHPT) >> PROCESS: Measure PTH >> Identify patients with PTH >400pg/mL >> Start vitamin D analog and/or calcimimetic >> OUTCOME: Normalization of PTH and related biomarkers >> Bone turnover decreased and hypocalcemia minimized >> Reduced high turnover bone lesions and lower fracture and all-cause and cardiovascular mortality rates.

Renal bone disease is a common complication of ESRD that has an important impact on morbidity and mortality in dialysis patients. Patients undergoing dialysis have reduced plasma levels of vitamin D, leading to decreased intestinal absorption of calcium and impaired suppression of the parathyroid gene that initiates the synthesis of PTH.(1-8) During the past two decades, numerous large studies and reviews have demonstrated that this secondary hyperparathyroidism (SHPT) of ESRD leads to an increased risk of high turnover bone lesions, fracture-related hospitalization, and all-cause and cardiovascular mortality.(1-3,7,9-14) The inflection point or range at which PTH becomes significantly associated with increased mortality varies among studies, but evidence suggests that the risk of increased mortality starts at 400pg/mL.(13) Moderate to severe hyperparathyroidism (PTH >600pg/mL) has been associated with an increase in the relative risk of all-cause and cardiovascular death and fracture-related hospitalization.(9)

SHPT in ESRD can be treated with calcitriol, with any of several synthetic vitamin D analogs, or with calcimimetic agents, either alone or in combination. Each therapeutic strategy has been shown to lower plasma PTH levels among patients with biochemical evidence of SHPT as judged by elevated pre-treatment PTH values.(15-20) Treatment with vitamin D analogs and/or calcimimetic compounds improves many of the clinical manifestations classically associated with SHPT such as bone pain, muscle weakness, and arthralgia. It also diminishes or corrects the pathological changes of hyperparathyroidism in bone among patients with ESRD, a population with very high risk of skeletal fracture.(15-20)

Inadequately controlled SHPT is characterized not only by persistently high PTH levels in blood, but also by important disturbances in calcium and phosphorus metabolism that include recurrent episodes of hypercalcemia and hyperphosphatemia.(1-9) These biochemical abnormalities can arise not only from uncontrolled SHPT per se but also from certain therapeutic interventions used

widely to manage the disorder, which include the use of large oral doses of calcium-containing, phosphate-binding agents and pharmacological doses of vitamin D analogs.(5-9) In this regard, elevated serum levels of calcium and phosphorus have been associated consistently in observational studies with adverse cardiovascular outcomes and increases in all-cause mortality among patients receiving dialysis.(9-14) Such observations highlight the need for, and pivotal role of, adequate biochemical surveillance in the ongoing clinical management of bone disease and mineral metabolism among patients with ESRD.

Recent retrospective analyses suggest that the use of vitamin D analogs and/or calcimimetic improves survival among patients undergoing hemodialysis.(15,17-20) A secondary analysis of prospective RCT data also indicates that treatment with cinacalcet compared with placebo reduces the risk of hospitalization from cardiovascular causes.(19) Results such as these underscore the importance of improving management strategies to favorably affect key clinical outcomes among patients with ESRD and associated disorders of bone and mineral metabolism.

1c.2-3 Type of Evidence *(Check all that apply)*:
Clinical Practice Guideline, Systematic review of body of evidence (other than within guideline development)

1c.4 Directness of Evidence to the Specified Measure *(State the central topic, population, and outcomes addressed in the body of evidence and identify any differences from the measure focus and measure target population)*:
Central Topic: Treatment of abnormal PTH levels in ESRD patients.

Population: Adult ESRD patients in the United States.

Outcomes Addressed: Chronic Kidney Disease Mineral and Bone Disorder (CKD-MBD), dialysis adequacy, all-cause mortality rates, cardiovascular-related mortality rates, hospitalization rates, skeletal fracture rates.

Differences Between Measure Focus and Measure Target Population: None.

1c.5 Quantity of Studies in the Body of Evidence *(Total number of studies, not articles)*: The body of evidence presented above cites nine peer-reviewed publications encompassing 15 clinical studies.

1c.6 Quality of Body of Evidence (*Summarize the certainty or confidence in the estimates of benefits and harms to patients across studies in the body of evidence resulting from study factors. Please address: a) study design/flaws; b) directness/indirectness of the evidence to this measure (e.g., interventions, comparisons, outcomes assessed, population included in the evidence); and c) imprecision/wide confidence intervals due to few patients or events*): The following nine studies address the etiology, clinical course, and sequellae of secondary hyperparathyroidism in renal disease. The strengths and weaknesses of each study are presented below; the consistency of the evidence across these nine studies is discussed in Section 1c.7. (Numbered according to Citations sequence in Section 1c.14.)

Block G, Hulbert-Shearon T, Levin N, Port F. Association of serum phosphorus and calcium x phosphate product with mortality risk in chronic hemodialysis patients: a national study. Am J Kidney Dis. 1998;31:607–17. (Citation 11.)
Data on 40,538 hemodialysis patients with at least one determination of serum PTH during the last three months of 1997 were analyzed. Unadjusted, case mix-adjusted, and multivariable-adjusted relative risks of death were calculated for categories of intact PTH using proportional hazards regression. Also determined was whether disorders of mineral metabolism were associated with all-cause, cardiovascular, infection-related, fracture-related, and vascular access-related hospitalization. After adjustment for case mix and laboratory variables, moderate to severe hyperparathyroidism (PTH concentrations >600pg/mL) was associated with an increase in the relative risk of death, whereas more modest increases in PTH were not. Hyperparathyroidism was significantly associated with all-cause, cardiovascular, and fracture-related hospitalization.

De Boer I, Gorodestskaya I, Young B, Hsu C, Chertow G. The severity of secondary hyperparathyroidism in chronic renal insufficiency is GFR-dependent, race-dependent, and associated with cardiovascular disease. J Am Soc Nephrol. 2002;13:2762-9. (Citation 12.)
This study evaluated 218 patients in an ethnically diverse ambulatory nephrology practice at the University of California San Francisco during calendar years 1999 and 2000. Demographic data, comorbid diseases, medications, and laboratory parameters were collected, and independent correlates of intact PTH were identified by using multiple linear regression. The mean estimated

GFR was 34mL/min/1.73m2; PTH was inversely related to GFR (P <0.0001). After adjusting for age and diabetes, PTH was associated with a history of myocardial infarction (OR = 1.6; 95% CI = 1.1 to 2.3 per unit natural log PTH) and congestive heart failure (OR = 2.0; 95% CI = 1.3 to 2.9 per unit natural log PTH) and not associated with other co-morbid conditions.

Kalantar-Zadeh K, Kuwae N, Regidor D et al. Survival predictability of time-varying indicators of bone disease in maintenance hemodialysis patients. Kidney Int. 2006;70:771–80. (Citation 13.)
The authors examined associations between survival and quarterly laboratory values and administered paricalcitol in a two-year (July 2001-June 2003) cohort of 58,058 maintenance hemodialysis patients from all DaVita dialysis clinics in the United States using both time-dependent Cox models with repeated measures and fixed-covariate Cox models with only baseline values. Associations between high serum PTH and increased death risk were masked by case-mix characteristics of the patients, but multivariate adjustments disclosed a strong association between incrementally higher serum PTH values and increased death risk. Risk of death increased beginning at 400pg/mL. Administration of any dose of paricalcitol was associated with improved survival in time-varying models.

Tentori F. Mineral and bone disorder and outcomes in hemodialysis patients: results from the DOPPS. Semin Dial. 2010;23(1):10-14. (Citation 14.)
The authors described changes in serum concentrations of mineral bone disease markers over time among international participants in the first three phases of the Dialysis Outcomes and Practice Patterns Study (DOPPS), from 1996–2007. The study sample comprised 25,558 patients from 925 dialysis units across the 12 DOPPS countries. The lowest mortality risk was found for PTH values of 101 to 300pg/mL; PTH >600pg/mL was associated with the greatest mortality risk.

Martin K, Gonzalez E, Gellens M et al. 19-Nor-1-alpha-25-dihydroxyvitamin D2 (Paricalcitol) safely and effectively reduces the levels of intact parathyroid hormone in patients on hemodialysis. J Am Soc Nephrol. 1998;9:1427-32. (Citation 15.)
Paricalcitol, a vitamin D analog developed for the treatment of SHPT, was evaluated in three double-blind, placebo-controlled, dose-escalating, randomized multicenter trials. A total of 78 patients (40 Paricalcitol injection, 38 placebo) achieved treatment phase eligibility, which included intact PTH >400pg/mL, normalized serum calcium levels between 8.0 and 10.0mg/dL, and calcium x phosphorus product values less than 75. Study end points included a decrease in intact PTH of at least 30% or a maximum of five dose escalations. Of 40 patients receiving paricalcitol, 27 (68%) had at least a 30% decrease in serum intact PTH for four consecutive weeks, compared with three of 38 patients (8%) receiving placebo (P <0.001). For patients who received 12 weeks of treatment with paricalcitol, the levels of intact PTH decreased significantly from 795+/-86 to 406+/-106pg/mL (P <0.001), whereas the values for PTH were 679+/-41pg/mL before and 592+/-41pg/mL after 12 weeks of therapy in patients receiving placebo. Also, there was a significant difference between treatment groups for the change from baseline PTH levels (P <0.001). Importantly, hypercalcemia did not occur before achieving target serum intact PTH levels in any of the paricalcitol-treated patients, and there was no significant difference in adverse events between the paricalcitol and placebo-treated groups.

Baker L, Muir J, Sharman V et al. Controlled trial of calcitriol in hemodialysis patients. Clin Nephrol. 1986;26:185-91. (Citation 17.)
A five-year, prospective, double-blind trial of calcitriol versus placebo in 76 hemodialysis patients without biochemical or radiological evidence of bone disease. Calcitriol, 1 microgram daily, regularly induced hypercalcemia. Doses of 0.25 micrograms daily or less proved satisfactory in most patients. During calcitriol treatment, serum PTH concentration was significantly lower than on placebo. Calcitriol appeared to protect against the development of histological evidence of osteitis fibrosa but not of osteomalacia.

Cunningham J, Danese M, Olson K, Klassen P, Chertow G. Effects of the calcimimetic cinacalcet HCl on cardiovascular disease, fracture, and health-related quality of life in secondary hyperparathyroidism. Kidney International. 2005;68:1793-1800. (Citation 18.)
This combined analysis of safety data (parathyroidectomy, fracture, hospitalizations, and mortality) from four similarly designed randomized, double-blind, placebo-controlled clinical trials enrolled 1184 subjects (697 on cinacalcet, 487 control) with ESRD and uncontrolled SHPT (intact PTH = 300pg/mL). Cinacalcet or placebo was administered to subjects receiving standard care for hyperphosphatemia and SHPT (i.e., phosphate binders and vitamin D). Relative risks (RR) and 95% confidence intervals were calculated using proportional hazards regression with follow-up times from six to twelve months. Randomization to cinacalcet resulted in significant reductions in the risk of parathyroidectomy (RR = 0.07, 95% CI = 0.01–0.55), fracture (RR = 0.46, 95% CI = 0.22–0.95), and cardiovascular hospitalization (RR = 0.61, 95% CI = 0.43–0.86) compared with placebo.

Block G, Martin K, de Francisco A et al. Cinacalcet for secondary hyperparathyroidism in patients receiving hemodialysis. NEJM. 2004;350:1516-25. (Citation 19.)

The authors report the combined results of two identical randomized, double-blind, placebo-controlled clinical trials to determine the safety and effectiveness of cinacalcet for treating SHPT in patients undergoing hemodialysis. The trials were conducted at 63 sites in North America and 62 sites in Europe and Australia between December 20, 2001, and January 16, 2003. A total of 741 patients satisfied eligibility criteria (410 in North America and 331 in Europe and Australia) and were randomly assigned to receive cinacalcet (371 patients) or placebo (370 patients). Randomization was stratified according to disease severity and baseline values for the calcium–phosphorus product. No more than 20% of the study population could have PTH levels exceeding 800pg/mL. The treatment phase of both studies lasted 26 weeks and consisted of a 12-week dose-titration phase followed by a 14-week efficacy-assessment phase. The primary study end point was the proportion of randomized patients who had a mean PTH level <250pg/mL during the efficacy-assessment phase. Secondary end points included the proportion of patients with a reduction from base line of at least 30% in mean PTH levels and the percent change in the values for PTH, calcium, phosphorus, and the calcium–phosphorus product. In stratified analyses, the likelihood of achieving the primary end point was greater among patients given cinacalcet than among those given placebo and was not influenced by sex, race, age, duration of dialysis, base-line biochemical variables, the presence of diabetes, or the use of vitamin D sterols. Multivariate logistic-regression analysis showed that the odds of achieving at least a 30% reduction in PTH were 15 times as great among patients who received cinacalcet as among patients who received placebo (odds ratio =15.38; 95% CI = 10.31-22.95).

Lindberg J, Culleton B, Wong G et al. Cinacalcet HCL, an oral calcimimetic agent for the treatment of secondary hyperparathyroidism in hemodialysis and peritoneal dialysis: a randomized, double-blind, multicenter study. J Am Soc Nephrol. 2005;16:800-7. (Citation 20.)
This Phase 3, multicenter, randomized, placebo-controlled, double-blind study evaluated the efficacy and safety of cinacalcet in HD and PD patients with PTH >300pg/mL despite traditional therapy. A total of 395 patients received once-daily oral cinacalcet (260 HD, 34 PD) or placebo (89 HD, 12 PD) titrated from 30 to 180mg to achieve a target intact PTH level <250pg/mL. During a 10-week efficacy assessment phase, cinacalcet was more effective than control for PTH reduction outcomes, including proportion of patients with mean intact PTH levels <300pg/mL (46 versus 9%), proportion of patients with >30% reduction in intact PTH from baseline (65 versus 13%), and proportion of patients with >20, >40, or >50% reduction from baseline. Cinacalcet had comparable efficacy in HD and PD patients; 50% of PD patients achieved a mean intact PTH <300pg/mL. Cinacalcet also significantly reduced serum calcium, phosphorus, and Ca x P levels compared with control treatment.

Study Design/Flaws:
We note that there are no RCTs showing that treatment to achieve a speci?c PTH level directly results in improved outcomes, as a treatment/placebo RCT in that regard would be unethical given the potential dire consequences of these metabolic abnormalities. Despite this, the body of evidence summarized previously demonstrates that vitamin D analogs and calcimimetic agents effectively reduce PTH levels compared to placebo,(15-20) that survival on dialysis may be improved by vitamin D therapy,(9,14,15) and that use of cinacalcet is associated with a reduction in cardiovascular-related hospitalization compared to placebo.(17-20) We likewise provide strong evidence of the association between incrementally higher serum PTH values and increased risk of death and improved survival with administration of paricalcitol in the Kalantar study of 58,058 maintenance hemodialysis patients in the United States.(13)

1c.7 Consistency of Results across Studies *(Summarize the consistency of the magnitude and direction of the effect):* The studies described demonstrate that vitamin D analogs and calcimimetic agents effectively reduce PTH levels compared to placebo,(15-20) that there is an association between the use of vitamin D analogs and improved survival,(9,14,15) that use of calcimimetic agents is associated with a reduction in cardiovascular-related hospitalization compared to placebo,(17-20) and that incrementally higher serum PTH values are associated with increased risk of death.(13)

1c.8 Net Benefit *(Provide estimates of effect for benefit/outcome; identify harms addressed and estimates of effect; and net benefit - benefit over harms)*:
A potential harm associated with the identification and treatment of SHPT in ESRD patients is the development of adynamic bone disease, which has been linked with a number of adverse outcomes, including fractures, hypercalcemia, vascular and myocardial calcifications, and increased mortality.(1-4,7,9-14) Specifically, the use of vitamin D analogs and calcimimetic compounds to treat SHPT in ESRD patients can reduce plasma PTH levels substantially and result in adynamic bone if treatment is not monitored regularly and adjusted appropriately.(1,2,8,16) With the expanded use of these medications during the past 15 to 20 years, adynamic bone has become increasingly common and is now considered by some to be the predominant type of renal osteodystrophy in both adult hemodialysis and peritoneal dialysis patients. The prevalence of adynamic renal osteodystrophy approaches 70% in patients with diabetes, who now comprise approximately 38% of the ESRD population.(1-4,7,9)

Adynamic bone is highly prevalent among dialysis patients with PTH levels below 65pg/mL, but risk for the disease increases when PTH levels fall below 150pg/mL.(1-4,7,9) Thus, to ensure that PTH values are monitored regularly and medications are adjusted as clinically appropriate, two measures are recommended to address performance across the range of renal parathyroid disease:

• ESRD patients with PTH >400pg/mL and not treated with a calcimimetic or vitamin D analog

• ESRD patients with PTH <130pg/mL and continued treatment with a calcimimetic or vitamin D analog

1c.9 Grading of Strength/Quality of the Body of Evidence. Has the body of evidence been graded? Yes

1c.10 If body of evidence graded, identify the entity that graded the evidence including balance of representation and any disclosures regarding bias: Three of the publications included in the body of evidence (see Table 5 [KDIGO Quality of Evidence Ratings for Specific Publications] in Attachment A) were graded by the Kidney Disease Improving Global Outcomes (KDIGO). KDIGO utilizes a structured approach to grading the quality of evidence for outcomes in individual studies, modeled after the Grades of Recommendations Assessment, Development, and Evaluation (GRADE) system and facilitated by the use of evidence profiles and evidence matrices. (See Table 6 [KDIGO Ratings for Quality of Evidence] in Attachment A.)

KDIGO is a global organization managed by the National Kidney Foundation (NKF) that works to improve care and outcomes through the development and implementation of evidence-based clinical practice guidelines. KDIGO's guideline development process is modeled on NKF's Kidney Disease Outcomes Quality Initiative (KDOQI) CKD guideline series and employs an independent work group and three international methodology centers to examine the evidence and formulate practice guidelines. Draft guidelines undergo internal review by the KDIGO Board of Directors, organizational review by key patient, medical, and health organizations, and a public review period prior to finalization and publication in peer-reviewed journals.

KDIGO notes that it makes all efforts to avoid any actual or reasonably perceived conflicts of interest that may arise as a result of an outside relationship or a personal, professional, or business interest of a member of a Work Group involved in developing guidelines. All members of the Work Groups are required to complete, sign, and submit a disclosure and attestation form showing all such relationships that might be perceived or actual conflicts of interest. The disclosure document is updated annually, and all reported information is published in its entirety at the end of the publication documents in the Work Group members' Biographical and Disclosure Information section.

In regards to the CKD-MBD guidelines, KDIGO acknowledges the following consortium of sponsors: Abbott, Amgen, Belo Foundation, Coca-Cola Company, Dole Food
Company, Genzyme, JC Penney, NATCO—The Organization for Transplant Professionals, National Kidney Foundation—Board of Directors, Novartis, Robert and Jane Cizik Foundation, Roche, Shire, Transwestern Commercial Services, and Wyeth.

1c.11 System Used for Grading the Body of Evidence: GRADE

1c.12 If other, identify and describe the grading scale with definitions:

1c.13 Grade Assigned to the Body of Evidence: Three studies cited in the Quality of Body of Evidence section (1c.6) have been graded by KDIGO (see Table 5 in Attachment A): Cunningham (18) = C; Block (19) = B; Lindberg (20) = B

1c.14 Summary of Controversy/Contradictory Evidence: We note that there are no RCTs showing that treatment to achieve a specific PTH level results in improved outcomes, as a treatment/placebo RCT in that regard would be unethical given the potential dire consequences of these metabolic abnormalities. Despite this and the conclusions drawn by Palmer and colleagues (discussion follows), we have provided evidence demonstrating that vitamin D analogs and calcimimetic agents effectively reduce PTH levels compared to placebo,(15-20) that survival on dialysis may be improved by vitamin D therapy,(9,14,15) and that use of cinacalcet is associated with a reduction in cardiovascular-related hospitalization compared to placebo.(17-20) We have likewise provided strong evidence of the association between incrementally higher serum PTH values and increased risk of death and improved survival with administration of paricalcitol in the Kalantar study of 58,058 maintenance hemodialysis patients in the United States.(13)

Additionally, Palmer et al. (21) recently published a summary analysis of 14 cohort studies (N=109,670 patients) assessing the quality of evidence for the association between levels of serum phosphorus, PTH, and calcium and risks of death, cardiovascular mortality, and nonfatal cardiovascular events in individuals with CKD. While a subgroup analysis revealed higher mortality rates among CKD patients with elevated PTH levels who were not yet receiving dialysis, the study was unable to demonstrate a strong or consistent association between all-cause mortality and serum levels of PTH in dialyzed patients (RR per 100pg/mL increase, 1.01 [95% CI = 1.00-1.02]). The authors concluded that the data informing current clinical guideline targets is poor.

The analysis by Palmer et al. correctly highlights some of the limitations in current methods of examining associations between phosphorus, calcium, and PTH in CKD patients—i.e., inconsistent adjustment of covariates, variability in how the biomarkers are categorized, and variation in the identification of clinical outcomes. However, a number of issues raise questions about the validity of the analysis and challenge the authors' conclusions:

• The study populations included and combined in the analysis are heterogeneous, and the analysis assumes that CKD, dialysis, and transplant patients are a homogenous population, which is clearly not found in practice. Tests for heterogeneity in meta-analyses are designed only to detect statistical differences, are often underpowered, and do not justify the inclusion of clinically diverse patient populations.

• Many published studies have reported a non-linear (e.g., J-shaped) association between PTH, phosphorus, and calcium. By extrapolating these potentially non-linear effects and excluding studies for which no linear extrapolation could be computed, the analysis is subject to biased estimates and selection bias.

• Only 14 studies were considered evaluable by the authors and were included in the analysis. Only four of these assessed the association between PTH levels and all-cause mortality (n=101,058), two the association between PTH and cardiovascular mortality (n=22,367), and none considered the association between PTH and nonfatal cardiovascular events. The authors further noted that data for the association between serum level of phosphorus, PTH, and calcium and cardiovascular death were each available in only one adequately adjusted cohort study. These small numbers yield potentially biased estimates that rely on single studies (thereby defeating the purpose of a meta-analysis) or lead to non-estimable summary estimates.

• Most studies in this area adjust for the independent effects of PTH, phosphorus, and calcium, and the adjusted factors are often on the causal pathway between the biomarker and the clinical outcome(s) being studied. The authors fail to acknowledge such adjustments or to identify which studies did and which did not adjust for other biochemical parameters.

• The review considered only the association between values of the three biomarkers and cardiovascular disease and mortality, discounting other important outcomes. Neither fracture nor hospitalization rates (cardiovascular or all-cause) were assessed.

• An editorial by Bryan Kestenbaum published in the same issue noted that many of the studies cited in the Palmer review are limited by the use of registry or EHR data, which might imprecisely characterize comorbid conditions and lead to bias. The use of questionnaires or diagnosis codes to assign comorbidites can result in the misclassification of these conditions, limiting the ability to properly adjust for them in the analyses. Kestenbaum also suggests that obtaining serum measurements for phosphorus, calcium, and PTH from EHRs might have obscured the validity of Palmer's findings by preferentially focusing on patients who undergo more frequent clinical laboratory testing, possibly due to illness.(22)

1c.15 Citations for Evidence other than Guidelines*(Guidelines addressed below)*:

1. Hercz G, Pei Y, Greenwood C et al. Aplastic osteodystrophy without aluminum: the role of "suppressed" parathyroid function. Kidney Int. 1993;44:860-6.

2. Sherrard D, Hercz G, Pei Y et al. The spectrum of bone disease in end-stage renal failure—an evolving disorder. Kidney Int. 1993;43:436–42.

3. Qi Q, Monier-Faugere M, Geng Z, Malluche H. Predictive value of serum parathyroid hormone levels for bone turnover in patients on chronic maintenance dialysis. Am J Kidney Dis. 1995;26:622-31.

4. Martinez I, Saracho R, Montenegro J, Liach F. The importance of dietary calcium and phosphorus in the secondary hyperparathyroidism of patients with early renal failure. Am J Kidney Dis. 1997;29:496–502.

5. Slatopolsky E, Brown A, Dusso A. Pathogenesis of secondary hyperparathyroidism. Kidney Int. 1999;56[Suppl 73]:S14–S19.

6. Billa V, Zhong A, Bargman J et al. High prevalence of hyperparathyroidism among peritoneal dialysis patients: a review of 176 patients. Perit Dial Int. 2000;20:315–21.

7. Malluche H, Mawad H, Monier-Faugere M. The importance of bone health in end-stage renal disease: out of the frying pan, into the fire. Nephrol Dial Transplant. 2004;19(Suppl1):i9-i13.

8. Qunibi W and Kalantar-Zadeh K. Target levels for serum phosphorus and parathyroid hormone. Seminars in Dialysis. 2011;2:4-7.

9. Block G, Klassen P, Lazarus J, Ofsthun N, Lowrie E, Chertow G. Mineral metabolism, mortality, and morbidity in maintenance hemodialysis. J Am Soc Nephrol. 2004;15(8);2208-18.

10. London G, Marty C, Marchais S et al. Arterial calcifications and bone histomorphometry in end-stage renal disease. J Am Soc.Nephrol. 2004;15(7):1943-51.

11. Block G, Hulbert-Shearon T, Levin N, Port F. Association of serum phosphorus and calcium x phosphate product with mortality risk in chronic hemodialysis patients: a national study. Am J Kidney Dis. 1998;31:607–17.

12. De Boer I, Gorodestskaya I, Young B, Hsu C, Chertow G. The severity of secondary hyperparathyroidism in chronic renal insufficiency is GFR-dependent, race-dependent, and associated with cardiovascular disease. J Am Soc Nephrol. 2002;13:2762-9.

13. Kalantar-Zadeh K, Kuwae N, Regidor D et al. Survival predictability of time-varying indicators of bone disease in maintenance hemodialysis patients. Kidney Int. 2006;70:771–80.

14. Tentori F. Mineral and bone disorder and outcomes in hemodialysis patients: results from the DOPPS. Semin Dial. 2010;23(1):10-14.

15. Martin K, Gonzalez E, Gellens M et al. 19-Nor-1-alpha-25-dihydroxyvitamin D2 (Paricalcitol) safely and effectively reduces the levels of intact parathyroid hormone in patients on hemodialysis. J Am Soc Nephrol. 1998;9:1427-32.

16. Goodman W, Ramirez J, Belin T et al. Development of adynamic bone in patients with secondary hyperparathyroidism after intermittent calcitriol therapy. Kidney Int. 1994;46:1160-6.

17. Baker L, Muir J, Sharman V et al. Controlled trial of calcitriol in hemodialysis patients. Clin Nephrol. 1986;26:185-91.

18. Cunningham J, Danese M, Olson K, Klassen P, Chertow G. Effects of the calcimimetic cinacalcet HCl on cardiovascular disease, fracture, and health-related quality of life in secondary hyperparathyroidism. Kidney International. 2005;68:1793-1800.

19. Block G, Martin K, de Francisco A et al. Cinacalcet for secondary hyperparathyroidism in patients receiving hemodialysis. NEJM. 2004;350:1516-25.

20. Lindberg J, Culleton B, Wong G et al. Cinacalcet HCL, an oral calcimimetic agent for the treatment of secondary hyperparathyroidism in hemodialysis and peritoneal dialysis: a randomized, double-blind, multicenter study. J Am Soc Nephrol. 2005;16:800-7.

21. Palmer S, Hayen A, Macaskill P et al. Serum levels of phosphorus, parathyroid hormone, and calcium and risks of death and cardiovascular disease in individuals with chronic kidney disease. A systematic review and meta-analysis. JAMA. 2011;305(11):1119-27.

22. Kestenbaum B. Mineral metabolism disorders in chronic kidney disease. Editorial. JAMA. 2011;305(11):1138-9.

1c.16 Quote verbatim, the specific guideline recommendation *(Including guideline # and/or page #)*:

KDOQI Clinical Practice Guidelines for Bone Metabolism and Disease in Chronic Kidney Disease:

• Guideline 13A.2: In CKD patients (Stage 5) who have elevated plasma levels of intact PTH (>300pg/mL), calcitriol (EVIDENCE) or 1 of its analogs (doxercalciferol, alfacalcidol, or paricalcitol) (OPINION) should be used to reverse the bone features of PTH overactivity (i.e., high-turnover bone disease), and to treat defective mineralization.

• Guideline 8B.1: Patients treated with hemodialysis or peritoneal dialysis with serum levels of intact PTH levels >300pg/mL (33.0pmol/L) should receive an active vitamin D sterol (such as calcitriol, alfacalcidol, paricalcitol, or doxercalciferol) to reduce the serum levels of PTH to a target range of 150 to 300pg/mL. (EVIDENCE)

KDIGO Clinical Practice Guidelines for the Diagnosis, Evaluation, Prevention and Treatment of Chronic Kidney Disease—Mineral Bone Disorder (CKD—MBD):

• Recommendation 4.2.4: In patients with CKD stage 5D and elevated or rising PTH, we suggest calcitriol, or vitamin D analogs, or calcimimetics, or a combination of calcimimetics and calcitriol or vitamin D analogs be used to lower PTH (2B).

1c.17 Clinical Practice Guideline Citation: 1. National Kidney Foundation: KDOQI Clinical Practice Guidelines for Bone Metabolism and Disease in Chronic Kidney Disease. American Journal of Kidney Disease. 2003:42:S1-S20(suppl 3).

2. Kidney Disease Improving Global Outcomes: KDIGO Clinical Practice Guideline for the Diagnosis, Evaluation, Prevention and Treatment of Chronic Kidney Disease—Mineral Bone Disorder (CKD—MBD). Kidney Int. 2009;76:S1–S130.

1c.18 National Guideline Clearinghouse or other URL: Not applicable.

1c.19 Grading of Strength of Guideline Recommendation. Has the recommendation been graded? Yes

1c.20 If guideline recommendation graded, identify the entity that graded the evidence including balance of representation and any disclosures regarding bias:

1c.21 System Used for Grading the Strength of Guideline Recommendation: GRADE

1c.22 If other, identify and describe the grading scale with definitions:

1c.23 Grade Assigned to the Recommendation: KDOQI Guideline 13A.2 = Evidence/Opinion; KDOQI Guideline 8B.1 = Evidence; KDIGO Recommendation 4.2.4 = Level 2.

1c.24 Rationale for Using this Guideline Over Others: The KDOQI and KDIGO guidelines present the most up-to-date summary of available knowledge in the field of mineral and bone disorder. As stated in their mission statement, KDIGO guidelines were developed to "improve the care and outcomes of kidney disease patients worldwide through promoting coordination, collaboration and integration of initiatives to develop and implement clinical practice guidelines." Likewise, KDOQI has provided evidence-based clinical practice guidelines for all stages of chronic kidney disease (CKD) and related complications since 1997 and is recognized throughout the world for improving the diagnosis and treatment of kidney disease.

Based on the NQF descriptions for rating the evidence, what was the <u>developer's assessment</u> of the quantity, quality, and consistency of the body of evidence?
1c.25 Quantity: High 1c.26 Quality: High1c.27 Consistency: Moderate

Was the threshold criterion, *Importance to Measure and Report*, met?
(*1a & 1b must be rated moderate or high and 1c yes*) Yes☐ No☐
Provide rationale based on specific subcriteria:

For a new measure if the Committee votes NO, then STOP.
For a measure undergoing endorsement maintenance, if the Committee votes NO because of 1b. (no opportunity for improvement), it may be considered for continued endorsement and all criteria need to be evaluated.

2. RELIABILITY & VALIDITY - SCIENTIFIC ACCEPTABILITY OF MEASURE PROPERTIES

Extent to which the measure, as specified, produces consistent (reliable) and credible (valid) results about the quality of care when implemented. (evaluation criteria)
Measure testing must demonstrate adequate reliability and validity in order to be recommended for endorsement. Testing may be conducted for data elements and/or the computed measure score. Testing information and results should be entered in the appropriate field. Supplemental materials may be referenced or attached in item 2.1. See guidance on measure testing.

S.1 Measure Web Page *(In the future, NQF will require measure stewards to provide a URL link to a web page where current detailed specifications can be obtained*). Do you have a web page where current detailed specifications for this measure can be obtained? Yes

S.2 If yes, provide web page URL: www.amgen.com/pdfs/pthmeasurespecifications.pdf

2a. RELIABILITY. Precise Specifications and Reliability Testing: H☐ M☐ L☐ I ☐

2a1. Precise Measure Specifications. (*The measure specifications precise and unambiguous.*)

2a1.1 Numerator Statement *(Brief, narrative description of the measure focus or what is being measured about the target population, e.g., cases from the target population with the target process, condition, event, or outcome)*:
Number of patients from the denominator with serum intact PTH >400pg/mL who are NOT being treated with a calcimimetic agent or vitamin D analog to lower the PTH.

2a1.2 Numerator Time Window *(The time period in which the target process, condition, event, or outcome is eligible for inclusion)*:
3-month reporting period.

2a1.3 Numerator Details *(All information required to identify and calculate the cases from the target population with the target process, condition, event, or outcome such as definitions, codes with descriptors, and/or specific data collection items/responses*:
• Serum intact PTH laboratory result (numerical value)
• Date serum intact PTH lab test performed
• Calcimimetic and/or vitamin D analog prescribed (yes/no)

2a1.4 Denominator Statement *(Brief, narrative description of the target population being measured)*:
All hemodialysis and peritoneal dialysis patients aged 18 years and older at the dialysis facility for at least 30 days who have been on dialysis for greater than 90 days and who have not been discharged from the facility prior to the last day of the most recent month of the 3-month reporting period.

2a1.5 Target Population Category *(Check all the populations for which the measure is specified and tested if any)*: Adult/Elderly Care

2a1.6 Denominator Time Window *(The time period in which cases are eligible for inclusion)*:
3-month reporting period.

2a1.7 Denominator Details (*All information required to identify and calculate the target population/denominator such as definitions, codes with descriptors, and/or specific data collection items/responses)*:
• Identification of all patients on hemodialysis or peritoneal dialysis (including home dialysis) assigned to a facility
• Patient Date of Birth
• Date Regular Chronic Dialysis Began
• Facility Admission Date
• Facility Discharge Date, if applicable

2a1.8 Denominator Exclusions *(Brief narrative description of exclusions from the target population)*:
None.

2a1.9 Denominator Exclusion Details *(All information required to identify and calculate exclusions from the denominator such as definitions, codes with descriptors, and/or specific data collection items/responses)*:

Not applicable.

2a1.10 Stratification Details/Variables *(All information required to stratify the measure results including the stratification variables, codes with descriptors, definitions, and/or specific data collection items/responses)*:
Not applicable.

2a1.11 Risk Adjustment Type *(Select type. Provide specifications for risk stratification in 2a1.10 and for statistical model in 2a1.13)*: No risk adjustment or risk stratification 2a1.12 If "Other," please describe:

2a1.13 Statistical Risk Model and Variables *(Name the statistical method - e.g., logistic regression and list all the risk factor variables. Note - risk model development should be addressed in 2b4.)*:
Not applicable.

2a1.14-16 Detailed Risk Model Available at Web page URL (or attachment). Include coefficients, equations, codes with descriptors, definitions, and/or specific data collection items/responses. Attach documents only if they are not available on a webpage and keep attached file to 5 MB or less. NQF strongly prefers you make documents available at a Web page URL. Please supply login/password if needed:

2a1.17-18. Type of Score: Rate/proportion

2a1.19 Interpretation of Score *(Classifies interpretation of score according to whether better quality is associated with a higher score, a lower score, a score falling within a defined interval, or a passing score)*: Better quality = Lower score

2a1.20 Calculation Algorithm/Measure Logic*(Describe the calculation of the measure score as an ordered sequence of steps including identifying the target population; exclusions; cases meeting the target process, condition, event, or outcome; aggregating data; risk adjustment; etc.)*:
DENOMINATOR
Patients are included in the denominator if they meet the following criteria:

• Patient's primary Type of Dialysis is hemodialysis, home hemodialysis, continuous ambulatory peritoneal dialysis (CAPD), or continuous cycling peritoneal dialysis (CCPD) in the most recent month of the reporting period.

AND

• Patient's age is 18 years or older as of the first day of the most recent month of the reporting period. (Patient's age will be determined by subtracting the patient's Date of Birth from the first day of the most recent month of the reporting period.)

AND

• Patient has been on dialysis for more than 90 days as of the first day of the most recent month of the reporting period. (Patient's time on dialysis will be determined by subtracting the patient's Date Regular Chronic Dialysis Began from the first day of the most recent month of the reporting period.)

AND

• Patient has been in the facility for at least 30 days as of the last day of the most recent month of the reporting period. (Patient's time within a facility is calculated from the Admission Date to the last day of the most recent month of the reporting period.)

AND

• Patient has not been discharged from the facility prior to the last day of the most recent month of the 3-month reporting period.

(Patient's time within a facility is calculated from the Admission Date to the last day of the most recent month of the reporting period. Patients discharged prior to the last day of the most recent month of the 3-month reporting period are excluded from the calculation.)

NUMERATOR
The numerator will be determined by counting the patients in the denominator who meet the following criteria:

• Serum intact PTH >400pg/mL. (If there is more than one serum intact PTH measurement within the 3-month reporting period, the first value for the period shall be used.)

AND

• Calcimimetic and/or Vitamin D Analog Prescribed is equal to 'No' in each of the three months of the reporting period during which the serum intact PTH >400pg/mL.

2a1.21-23 Calculation Algorithm/Measure Logic Diagram URL or attachment:
Attachment
HyperPTH_CalcAlgorithm.pdf

2a1.24 Sampling (Survey) Methodology. If measure is based on a sample (or survey), provide instructions for obtaining the sample, conducting the survey and guidance on minimum sample size (response rate):
Not applicable.

2a1.25 Data Source *(Check all the sources for which the measure is specified and tested*). If other, please describe:
Electronic Clinical Data : Electronic Health Record, Electronic Clinical Data : Laboratory

2a1.26 Data Source/Data Collection Instrument (*Identify the specific data source/data collection instrument, e.g. name of database, clinical registry, collection instrument, etc.*): The denominator can be constructed from data that is scheduled for collection via the Centers for Medicare and Medicaid Services' (CMS) CROWNWeb data repository (Kidney Data Dictionary [KDD] version 3.0). We note that the current medication data element label refers only to prescriptions for Vitamin D analogs. Believing that this was an oversight in nomenclature given there are clearly other therapeutic options, we have been in contact with CMS and have been advised that while the development of CROWNWeb won't allow for a change to the data field at this time, the implementation guidance will instruct facilities to record BOTH vitamin D analog and calcimimetic use in this data field during data entry.

2a1.27-29 Data Source/data Collection Instrument Reference Web Page URL or Attachment: URL
http://www.projectcrownweb.org/crown/index.php

2a1.30-32 Data Dictionary/Code Table Web Page URL or Attachment:
URL
http://www.projectcrownweb.org/crown/index.php?page=Public_Documents&subPage=Release_Documents

2a1.33 Level of Analysis (*Check the levels of analysis for which the measure is specified and tested)*: Facility

2a1.34-35 Care Setting *(Check all the settings for which the measure is specified and tested)*: Dialysis Facility

2a2. Reliability Testing. (*Reliability testing was conducted with appropriate method, scope, and adequate demonstration of reliability*.)

2a2.1 Data/Sample *(Description of the data or sample including number of measured entities; number of patients; dates of data; if a sample, characteristics of the entities included)*:
Testing of the measure's data elements was conducted on 2007 data from a U.S. large dialysis organization (LDO) for 43,057

dialysis patients using an electronic health record (EHR) database. As noted in the NQF report, Guidance for Measure Testing and Evaluating Scientific Acceptability of Measure Properties, data elements for quality measures that are extracted from EHRs are, by virtue of automation, repeatable (i.e., reliable). Because different uses of an EHR data field by a clinician or different data extraction protocols in different EHRs can produce different performance scores, testing at the data element level should thus focus on validity. If empirical validity testing of the data elements is conducted, as is the case with this measure, separate reliability testing of the data elements is not required. Please see Section 2b. for information on validity testing.

2a2.2 Analytic Method *(Describe method of reliability testing & rationale)*:
Please see Section 2b for information on validity testing.

2a2.3 Testing Results *(Reliability statistics, assessment of adequacy in the context of norms for the test conducted)*:
Please see Section 2b for information on validity testing.

2b. VALIDITY. Validity, Testing, including all Threats to Validity: H☐ M☐ L☐ I ☐

2b1.1 Describe how the measure specifications *(measure focus, target population, and exclusions)* are consistent with the evidence cited in support of the measure focus (*criterion 1c)* and identify any differences from the evidence:
The measure focus and target population are consistent with the evidence cited in Section 1c; no differences have been identified. In both the body of evidence and the measure specifications, the central topic is the assessment and treatment of abnormal PTH levels in ESRD patients, the target population is adult ESRD patients in the United States, and the outcomes of interest are CKD-MBD, dialysis adequacy, all-cause mortality rates, cardiovascular-related mortality rates, hospitalization rates, skeletal fracture rates.

2b2. Validity Testing. (*Validity testing was conducted with appropriate method, scope, and adequate demonstration of validity.)*

2b2.1 Data/Sample *(Description of the data or sample including number of measured entities; number of patients; dates of data; if a sample, characteristics of the entities included)*:
Validity of the measure's data elements was empirically established using 2007 medical record-derived data from a U.S. large dialysis organization (LDO) database. Data were collected on 43,057 patients.

2b2.2 Analytic Method *(Describe method of validity testing and rationale; if face validity, describe systematic assessment)*:
Validity of the data elements was empirically established by analyzing agreement with an authoritative source of the same information. The necessary data elements for the measure—i.e., serum PTH value and vitamin D analog and/or calcimimetic agent use—have not to date been collected and reported by CMS. Thus, to establish validity of the data elements, data collected from a large U.S. dialysis provider database were compared to DOPPS data. DOPPS is a prospective cohort study of hemodialysis practices based on the collection of observational longitudinal data for a random sample of patients from a representative and random sample of units in 12 countries (Australia, Belgium, Canada, France, Germany, Japan, Italy, New Zealand, Spain, Sweden, the United Kingdom, and the United States). Data collection for the study has been ongoing since 1996 and has yielded detailed data on more than 38,000 patients in more than 900 dialysis facilities.

2b2.3 Testing Results *(Statistical results, assessment of adequacy in the context of norms for the test conducted; if face validity, describe results of systematic assessment)*:
To first establish that both the DOPPS data and the data collected from the LDO database can be viewed as valid representations of the U.S. ESRD population, Table 9 (see Attachment A) compares patient characteristics in 81 DOPPS U.S. facilities in 2007 (N=4,740) with 2007 prevalent (>60 days on dialysis) Medicare hemodialysis patients (N=341,906) and the 2007 LDO patients (N=43,057). Both the DOPPS and the LDO patients mirror the dialysis population for which CMS is the primary payer, which is approximately 90% of all dialysis patients in the United States. Given this, it can be concluded that these data are a valid and accurate representation of the U.S. ESRD hemodialysis population.

Next, a retrospective review of 2007 data from the medical record-derived LDO database was performed to determine the validity of the serum PTH and vitamin D analog/calcimimetic agent use data elements. Results were compared to 2007 DOPPS data (N=6,927) to analyze agreement between the two data sources. (See Tables 10A and B [Prevalence of PTH >400pg/mL and Selected Lab Parameters by Treatment Status] in Attachment A.) Again, PTH values and information on use of the pharmacotherapies are quite similar in the two data sets, indicating that the data elements can be viewed as a valid representation of the information and that the measure can be used to discriminate performance and assess outcomes.

POTENTIAL THREATS TO VALIDITY. (*All potential threats to validity were appropriately tested with adequate results.*)

2b3. Measure Exclusions. (*Exclusions were supported by the clinical evidence in 1c or appropriately tested with results demonstrating the need to specify them.*)

2b3.1 Data/Sample for analysis of exclusions *(Description of the data or sample including number of measured entities; number of patients; dates of data; if a sample, characteristics of the entities included)*:
Not applicable.

2b3.2 Analytic Method (*Describe type of analysis and rationale for examining exclusions, including exclusion related to patient preference)*:
Not applicable.

2b3.3 Results *(Provide statistical results for analysis of exclusions, e.g., frequency, variability, sensitivity analyses):*
Not applicable.

2b4. Risk Adjustment Strategy. (*For outcome measures, adjustment for differences in case mix (severity) across measured entities was appropriately tested with adequate results.*)

2b4.1 Data/Sample *(Description of the data or sample including number of measured entities; number of patients; dates of data; if a sample, characteristics of the entities included)*:
Not applicable.

2b4.2 Analytic Method (*Describe methods and rationale for development and testing of risk model or risk stratification including selection of factors/variables)*:
Not applicable.

2b4.3 Testing Results *(Statistical risk model: Provide quantitative assessment of relative contribution of model risk factors; risk model performance metrics including cross-validation discrimination and calibration statistics, calibration curve and risk decile plot, and assessment of adequacy in the context of norms for risk models. Risk stratification: Provide quantitative assessment of relationship of risk factors to the outcome and differences in outcomes among the strata)*:
Not applicable.

2b4.4 If outcome or resource use measure is not risk adjusted, provide rationale and analyses to justify lack of adjustment: This measure assesses provider management of high serum intact PTH level—a modifiable risk factor in ESRD patients that is associated with adverse patient outcomes including increased rates of bone fractures, hospitalization, and all-cause and cardiovascular mortality. The goal of treatment is to achieve laboratory values as close to normal as possible for all ESRD patients, regardless of age, race, gender, co-morbidities, socioeconomic factors, and other variables typically addressed through risk adjustment. This measure is similar in construct, for example, to the NQF-endorsed® diabetes measure, "HbA1c >9mg/dL" (NQF Measure 0059), which is also not risk-adjusted.

2b5. Identification of Meaningful Differences in Performance. (*The performance measure scores were appropriately analyzed and discriminated meaningful differences in quality.*)

2b5.1 Data/Sample *(Describe the data or sample including number of measured entities; number of patients; dates of data; if a sample, characteristics of the entities included)*:
Testing of the measure's data elements was conducted on 2007 data from a U.S. large LDO for 43,057 dialysis patients using an EHR database.

2b5.2 Analytic Method *(Describe methods and rationale to identify statistically significant and practically/meaningfully differences in performance)*:
The data elements collected from the LDO database permit calculation of performance for the measure as follows:

Performance Rate =
(Patients with serum intact PTH >400pg/dL who are NOT treated with a calcimimetic agent or vitamin D analog) / (Total ESRD patients aged 18 years and older)

2b5.3 Results *(Provide measure performance results/scores, e.g., distribution by quartile, mean, median, SD, etc.; identification of statistically significant and meaningfully differences in performance)*:
LDO Performance Rate =
(Patients with serum intact PTH >400pg/dL who are NOT treated with a calcimimetic agent or vitamin D analog) / (Total ESRD patients aged 18 years and older)
= 1,541 / 9,425 = 16.4%

Table 11 (see Attachment A) displays the LDO mean and median (with standard deviation) PTH values by treatment status.

2b6. Comparability of Multiple Data Sources/Methods. (*If specified for more than one data source, the various approaches result in comparable scores.*)

2b6.1 Data/Sample *(Describe the data or sample including number of measured entities; number of patients; dates of data; if a sample, characteristics of the entities included)*:
Not applicable.

2b6.2 Analytic Method *(Describe methods and rationale for testing comparability of scores produced by the different data sources specified in the measure)*:
Not applicable.

2b6.3 Testing Results *(Provide statistical results, e.g., correlation statistics, comparison of rankings; assessment of adequacy in the context of norms for the test conducted)*:
Not applicable.

2c. Disparities in Care: H☐ M☐ L☐ I ☐ NA☐ (*If applicable, the measure specifications allow identification of disparities.*)

2c.1 If measure is stratified for disparities, provide stratified results *(Scores by stratified categories/cohorts)*: Research indicates that PTH levels in chronic renal insufficiency is race-dependent and that race is a major independent determinant of uremic SHPT. Among ESRD patients, African Americans typically have the highest mean PTH values and may be at increased risk for hyperparathyroid bone disease, while Caucasians have lower values and may be at greater risk for adynamic bone disease. The measure could be reported in a stratified manner to monitor disparities.

2c.2 If disparities have been reported/identified (e.g., in 1b), but measure is not specified to detect disparities, please explain:
The measure could be reported in a stratified manner to monitor the disparities in mean PTH values by race/ethnicity.

2.1-2.3 Supplemental Testing Methodology Information:
Attachment
AttachmentA_TablesandGraphs.pdf

Steering Committee: Overall, was the criterion, *Scientific Acceptability of Measure Properties*, met?
(*Reliability and Validity must be rated moderate or high*) Yes☐ No☐
Provide rationale based on specific subcriteria:

If the Committee votes No, STOP

3. USABILITY

Extent to which intended audiences (e.g., consumers, purchasers, providers, policy makers) can understand the results of the measure and are likely to find them useful for decision making. (evaluation criteria)

C.1 Intended Purpose/ Use *(Check all the purposes and/or uses for which the measure is intended)*: Payment Program, Public Reporting, Quality Improvement (Internal to the specific organization), Quality Improvement with Benchmarking (external benchmarking to multiple organizations)

3.1 Current Use *(Check all that apply; for any that are checked, provide the specific program information in the following*

questions): Quality Improvement (Internal to the specific organization)

3a. Usefulness for Public Reporting: H☐ M☐ L☐ I ☐
(*The measure is meaningful, understandable and useful for public reporting.*)

3a.1. Use in Public Reporting - disclosure of performance results to the public at large *(If used in a public reporting program, provide name of program(s), locations, Web page URL(s)).* If not publicly reported in a national or community program, state the reason AND plans to achieve public reporting, potential reporting programs or commitments, and timeline, e.g., within 3 years of endorsement: [*For Maintenance – If not publicly reported, describe progress made toward achieving disclosure of performance results to the public at large and expected date for public reporting; provide rationale why continued endorsement should be considered.*]
The measure is intended to be used by the Centers for Medicare and Medicaid Services (CMS) for its public reporting and payment initiatives.

3a.2.Provide a rationale for why the measure performance results are meaningful, understandable, and useful for public reporting. If usefulness was demonstrated (e.g., focus group, cognitive testing), describe the data, method, and results: The measure results have not been tested for interpretability in public reporting, however we have consulted with leadership from the National Kidney Foundation (NKF), and they concur that the availability of performance data on this PTH measure is an important indicator of quality of care and believe the measure will be readily interpreted by dialysis patients. Clinic personnel should be encouraged to stimulate discussion as to the role that patients can play in achieving higher scores, thereby improving the outcomes of the care they receive.

3.2 Use for other Accountability Functions (payment, certification, accreditation). If used in a public accountability program, provide name of program(s), locations, Web page URL(s): The measure can be constructed from data that is scheduled for collection via the CMS CROWNWeb data repository (Kidney Data Dictionary [KDD] version 3.0) and is intended to be used by CMS for its public reporting and payment initiatives.

3b. Usefulness for Quality Improvement: H☐ M☐ L☐ I ☐
(*The measure is meaningful, understandable and useful for quality improvement.*)

3b.1. Use in QI. If used in quality improvement program, provide name of program(s), locations, Web page URL(s):
[*For Maintenance – If not used for QI, indicate the reasons and describe progress toward using performance results for improvement*].
The measure can be constructed from data that will be collected via the CMS CROWNWeb data repository. The ESRD Conditions for Coverage (section ß494.180 [h]) state that data collected through CROWNWeb are to be used in a national ESRD information system and in compilations relevant to performance assessment and quality improvement.

3b.2. Provide rationale for why the measure performance results are meaningful, understandable, and useful for quality improvement. If usefulness was demonstrated *(e.g., QI initiative),* describe the data, method and results:
The measure results have not been tested for interpretability in quality improvement, however we have consulted with leadership from NKF, and they concur that the availability of performance data on this PTH measure is an important indicator of quality of care and believe the measure results are basic clinical concepts that are well understood by the provider community. Clinic personnel should be encouraged to stimulate discussion as to the role that patients can play in achieving higher scores, thereby improving the outcomes of the care they receive.

Overall, to what extent was the criterion, *Usability*, met? H☐ M☐ L☐ I ☐
Provide rationale based on specific subcriteria:

4. FEASIBILITY

Extent to which the required data are readily available, retrievable without undue burden, and can be implemented for performance measurement. (evaluation criteria)

4a. Data Generated as a Byproduct of Care Processes: H☐ M☐ L☐ I ☐

4a.1-2 How are the data elements needed to compute measure scores generated? *(Check all that apply).*
Data used in the measure are:

generated by and used by healthcare personnel during the provision of care, e.g., blood pressure, lab value, medical condition

4b. Electronic Sources: H☐ M☐ L☐ I ☐

4b.1 Are the data elements needed for the measure as specified available electronically *(Elements that are needed to compute measure scores are in defined, computer-readable fields)*: ALL data elements in electronic health records (EHRs)

4b.2 If ALL data elements are not from electronic sources, specify a credible, near-term path to electronic capture, OR provide a rationale for using other than electronic sources:

4c. Susceptibility to Inaccuracies, Errors, or Unintended Consequences: H☐ M☐ L☐ I ☐

4c.1 Identify susceptibility to inaccuracies, errors, or unintended consequences of the measurement identified during testing and/or operational use and strategies to prevent, minimize, or detect. If audited, provide results:
We note that much of the literature and recommendations from the KDOQI Bone and Mineral guidelines were based on use of the second-generation Allegro PTH assay from Nichols, which is no longer available. Currently, there are a number of commercially available kits that measure intact PTH with second-generation assays. Research indicates that there is inter-method variability in results because of standardization and antibody specificity. In addition, there are differences in PTH results when samples are measured on plasma, serum, or citrate, and depending on whether the samples are on ice or are allowed to sit at room temperature. These sample collection and assay variability issues(1) have raised concerns with regard to absolute levels of PTH and their strict use as a clinically relevant biomarker coupled to specific target values. (For instance, the inflection point at which PTH becomes significantly associated with increased all-cause mortality varies among studies, ranging from 400 to 600pg/mL.)

Nevertheless, KDIGO notes that the clinical consequences of NOT measuring PTH and treating SHPT are of equal concern. To balance the methodological issues of PTH measurement with the known risks and benefits of excess PTH and treatment strategies, the KDIGO Work Group concluded that PTH should be measured, with standardization within clinics and dialysis units in the methods of sample collection, processing, and assay used. To that end, there are four laboratories (SPECTRA, DaVita Laboratory Services, Nationwide Laboratories, and Satellite Laboratory Services) that provide laboratory services for the majority of dialysis patients within the United States. Our understanding is that these four laboratories all currently utilize the Siemens Advia Centaur PTH assay platform, and have been utilizing the Advia Centaur Platform for the past five years. The Advia Centaur assay could arguably be considered the de-facto standard among dialysis providers in the United States. However, in the case where other assays are used, values can be converted or corrected. Correction factors for PTH results have been identified in several peer-reviewed publications:

No correction:
• PTH Advia Centaur (Siemens)(2,3)
• Access Intact PTH (Beckman Coulter)(2)
• Roche Elecsys PTH(3)
• Schering CisBio ELSA(3)
• Scantibodies Total Intact PTH(3)

Divide by the following factor:
• Architect PTH Abbott: /1.3 (4)
• Beckman Coulter PTH IRMA: /1.2 (3)
• DiaSorin Intact PTH IRMA: /0.55 (3)
• LIAISON N-tact PTH: /0.90 (3)
• Scantibodies Ca-PTH IRMA (the only third-generation assay): /0.55 (3)

Special case:
• Immulite 2000 Intact PTH (Siemens): If in serum, no change; if in plasma, divide by 1.25 (2)

The inter-method variability between the commercially available PTH kits is an issue that must be addressed on a national level to allow valid facility-to-facility comparisons for this important clinical biomarker. However, this is an issue of measure implementation that does not diminish the measure's potential to significantly improve the quality of care delivered to patients with ESRD. Notably, CMS's Implantable Cardioverter-Defibrillator (ICD) Complication Rate measure faces a similar implementation barrier due to the

National Cardiovascular Data Registry's (NCDR) unique patient identifier restriction, but was nonetheless recognized by NQF as an important performance standard and was endorsed.(5) We posit that this PTH measure should likewise be viewed as a critical and scientifically valid performance measure that, if endorsed, can overcome implementation issues through the application by CMS of correction factors and/or standardization of PTH assays. We are engaged in conversations with CMS to address the issue of applying the correction factor in conjunction with the PTH data elements it proposes to collect based on the 2011 KDD for CROWNWeb.

Citations:
1. Cantor T, Yang Z, Caraiani N et al. Lack of comparability of intact parathyroid hormone measurements among commercial assays for end-stage renal disease patients: Implications for treatment. Clinical Chem. 2006;52(9):1771-76.

2. Joly D, Drueke T, Alberti C et al. Variation in serum and plasma PTH levels in second-generation assays in hemodialysis patients: a cross-sectional study. Am J Kidney Dis. 2008;51:987-95.

3. Souberbielle J, Boutten A, Carlier M et al. Inter-method variability in PTH measurement: implication for the care of CKD patients. Kidney Int. 2006;70:345-50.

4. Monge M, Jean G, Bacri J et al. Higher parathyroid hormone (PTH) concentrations with the Architect PTH assay than with the Elecsys assay in hemodialysis patients, and a simple way to standardize these two methods. Clin Chem Lab Med. 2009;47:362-6.

5. National Quality Forum. National Voluntary Consensus Standards for Patient Outcomes, First Report for Phases 1 and 2: A Consensus Report. Washington, DC; NQF: 2010.

4d. Data Collection Strategy/Implementation: H☐ M☐ L☐ I ☐

A.2 Please check if either of the following apply (*regarding proprietary measures*): Proprietary measure
4d.1 Describe what you have learned/modified as a result of testing and/or operational use of the measure regarding data collection, availability of data, missing data, timing and frequency of data collection, sampling, patient confidentiality, time and cost of data collection, other feasibility/implementation issues *(e.g., fees for use of proprietary measures)*:
All data required to calculate the measure will be collected via the CROWNWeb data repository. Data collection is required by CMS of all dialysis facilities for clinical performance measures. This measure will use data elements that will be collected via CROWNWeb and will pose no additional burden or costs to users beyond what CMS estimates are the costs associated with facility compliance in providing all CROWNWeb data.

Overall, to what extent was the criterion, *Feasibility*, met? H☐ M☐ L☐ I ☐
Provide rationale based on specific subcriteria:

OVERALL SUITABILITY FOR ENDORSEMENT

Does the measure meet all the NQF criteria for endorsement? Yes☐ No☐
Rationale:

If the Committee votes No, STOP.
If the Committee votes Yes, the final recommendation is contingent on comparison to related and competing measures.

5. COMPARISON TO RELATED AND COMPETING MEASURES

If a measure meets the above criteria and there are endorsed or new related measures (either the same measure focus or the same target population) or competing measures (both the same measure focus and the same target population), the measures are compared to address harmonization and/or selection of the best measure before a final recommendation is made.

5.1 If there are related measures *(either same measure focus or target population)* or competing measures *(both the same measure focus and same target population*), list the NQF # and title of all related and/or competing measures:
1658 : ESRD patients with PTH <130pg/mL and continued treatment with a calcimimetic or vitamin D analog.

5a. Harmonization

5a.1 If this measure has EITHER the same measure focus OR the same target population as NQF-endorsed measure(s): Are the measure specifications completely harmonized?

5a.2 If the measure specifications are not completely harmonized, identify the differences, rationale, and impact on interpretability and data collection burden:

5b. Competing Measure(s)

5b.1 If this measure has both the same measure focus and the same target population as NQF-endorsed measure(s): Describe why this measure is superior to competing measures *(e.g., a more valid or efficient way to measure quality);* OR provide a rationale for the additive value of endorsing an additional measure. *(Provide analyses when possible)*:
Not applicable.

CONTACT INFORMATION

Co.1 Measure Steward (Intellectual Property Owner): Amgen Inc., One Amgen Center Drive, Thousand Oaks, California, 91320-1799

Co.2 Point of Contact: Joshua, Ofman, MD, MSHS, jofman@amgen.com, 805-447-0787-

Co.3 Measure Developer if different from Measure Steward: Amgen Inc., One Amgen Center Drive, Thousand Oaks, California, 91320-1799

Co.4 Point of Contact: William, Goodman, MD, wgoodman@amgen.com, 807-447-0511-

Co.5 Submitter: Holly, Owens, howens@amgen.com, 202-585-9648-, Amgen Inc.

Co.6 Additional organizations that sponsored/participated in measure development:
Not applicable.

Co.7 Public Contact: William, Goodman, MD, wgoodman@amgen.com, 807-447-0511-, Amgen Inc.

ADDITIONAL INFORMATION

Workgroup/Expert Panel involved in measure development
Ad.1 Provide a list of sponsoring organizations and workgroup/panel members' names and organizations. Describe the members' role in measure development.
Not applicable.

Ad.2 If adapted, provide title of original measure, NQF # if endorsed, and measure steward. Briefly describe the reasons for adapting the original measure and any work with the original measure steward: Not applicable.

Measure Developer/Steward Updates and Ongoing Maintenance
Ad.3 Year the measure was first released: 2011
Ad.4 Month and Year of most recent revision: 04, 2011
Ad.5 What is your frequency for review/update of this measure? Annual
Ad.6 When is the next scheduled review/update for this measure? 05, 2012

Ad.7 Copyright statement/disclaimers:

Ad.8 Additional Information/Comments: Not applicable.

Date of Submission (*MM/DD/YY*): 06/03/2011

AMGEN INC.
ESRD PATIENTS WITH PTH >400PG/ML AND NOT TREATED WITH A CALCIMIMETIC OR VITAMIN D ANALOG

ATTACHMENT A: TABLES AND GRAPHS

Table 1A and B: Prevalence of PTH >400pg/mL and selected lab parameters by treatment status.

A. LDO (Total N=24,495)

Variable	N (%)	PTH (Mean ± SD)	PTH (Median)
All ≥400pg/mL (38% of total)	9,425 (100)	863 ± 436	662 (502;997)
Vitamin D + Cinacalcet	1,493 (16)	999 ± 360	752 (539;1,185)
Vitamin D or Cinacalcet	7,884 (84)	842 ± 407	650 (498;967)
No Vitamin D or Cinacalcet	**1,541 (16)**	969 ± 601	742 (524;1,176)

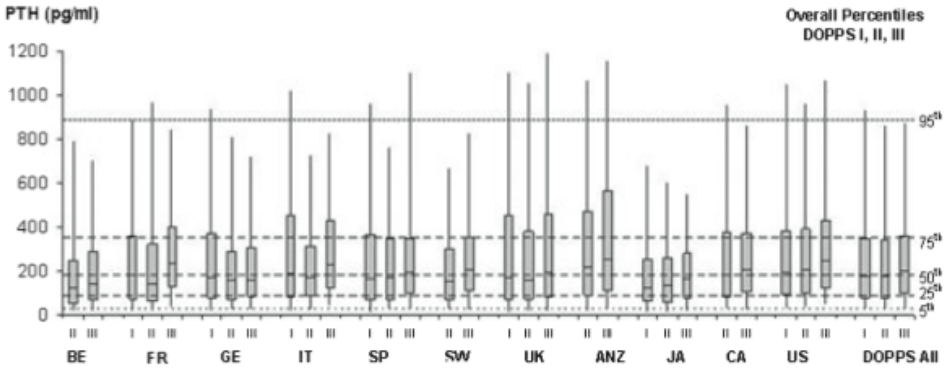
B. DOPPS III (Total N=6,927)

Variable	N (%)	PTH (Mean ± SD)	PTH (Median)
All ≥400pg/mL (21% of total)	1,449 (100)	766 ± 533	600 (473;847)
Vitamin D + Cinacalcet	177 (12)	921 ± 834	680 (508;1,013)
Vitamin D or Cinacalcet	1,082 (75)	773 ± 541	600 (473;852)
No Vitamin D or Cinacalcet	**364 (25)**	746 ± 509	597 (472;834)

Table 2: Percent of facilities with patients with PTH >400pg/mL who are not treated.

	Total Patients	Patients with PTH >400pg/mL	% Facilities with Untreated Patients
LDO	24,495	9,425	39.4
DOPPS III	6,927	1,449	42.0

Figure 1: DOPPS distributions of serum PTH levels by country and study phase.



Distributions of serum PTH levels at study entry by DOPPS country and phase. Box plots show weighted 25th to 75th percentiles (box) with median (line) and 5th and 95th percentiles (whiskers) for each country and phase of DOPPS. Horizontal lines indicate these percentiles for serum PTH (percentiles: 5th = 28, 25th = 83, 50th = 177, 75th = 342, and 95th = 893pg/ml) for the overall DOPPS study sample. BE, Belgium; FR, France;

GE, Germany; IT, Italy; SP, Spain; SW, Sweden; UK, United Kingdom; ANZ, Australia-New Zealand; JP, Japan; CA, Canada; US, United States.

Table 3: PTH variations by race (De Boer et al.)

	All (n = 218)	White (n = 95)	African American (n = 48)	Asian or Pacific Islander (n = 58)	Hispanic (n = 17)	P
Mean PTH (pg/ml)	146	130	249	93	130	<0.0001
Adjusted mean PTH (pg/ml)[a]	NA	139	233	95	131	<0.0001
% above 65 pg/ml	69%	65%	90%	60%	59%	0.005
% above 130 pg/ml	38%	33%	67%	21%	33%	<0.0001
% above 195 pg/ml	24%	20%	48%	9%	29%	<0.0001

[a] Adjusted for age, gender, estimated GFR, and serum bicarbonate concentration.

Table 4:* Comparison of patient characteristics in 81 U.S. DOPPS facilities in 2007 (N=4,740) with 2007 prevalent (>60 days on dialysis) Medicare hemodialysis patients (N=341,906) and 2007 LDO patients (N=21,023). NOTE: The LDO data are weighted to account for an oversampling of patients prescribed cinacalcet in the dataset.

	2007 Medicare	2007 DOPPS III (U.S. Facilities	2007 LDO Provider
Age, Mean	62.3 years	62.11 years	---
Race, White	188,052 (55%)	2,427 (51.6%)	10,652 (50.7%)
Race, Black	129,964 (38.0%)	1,602 (34.1%)	8,594 (40.9%)
Race, Asian	15,591 (4.6%)	214 (4.6%)	536 (2.6%)
Race, Other	2,964 (2.4%)	457 (9.7%)	1,241 (5.9%)
Gender, Female	153,561 (44.9%)	2,120 (44.7%)	9,677 (46.0%)
Gender, Male	188,345 (55.1%)	2,619 (55.3%)	11,346 (54.0%)
Primary Diagnosis, Diabetes Mellitus	151,477 (44.3%)	2,345 (50.0%)	8,948 (42.6%)

* Both the DOPPS and the LDO patients mirror the dialysis population for which CMS is the primary payer, which is approximately 90% of all dialysis patients in the United States. Given this, it can be concluded that these data are a valid and accurate representation of the U.S. ESRD hemodialysis population.

Table 5: KDIGO quality of evidence ratings for specific publications

INVESTIGATORS	TITLE	GRADE
Cunningham (14)	Effects of the calcimimetic cinacalcet HCl on cardiovascular disease, fracture, and health-related quality of life in secondary hyperparathyroidism	C
Block (15)	Cinacalcet for secondary hyperparathyroidism in patients receiving hemodialysis	B
Lindberg (16)	Cinacalcet HCL, an oral calcimimetic agent for the treatment of secondary hyperparathyroidism in hemodialysis and peritoneal dialysis: a randomized, double-blind, multicenter study	B

*See Section 1c.15 for full citations.

Table 6: KDIGO ratings for the quality of evidence

Grade	Quality of evidence	Meaning
A	High	We are confident that the true effect lies close to that of the estimate of the effect
B	Moderate	The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
C	Low	The true effect may be substantially different from the estimate of the effect
D	Very low	The estimate of effect is very uncertain, and often will be far from the truth

Table 7: KDOQI ratings for the strength of guideline recommendations

Grade	Recommendation
A	It is strongly recommended that clinicians routinely follow the guideline for eligible patients. There is strong evidence that the practice improves health outcomes.
B	It is recommended that clinicians routinely follow the guideline for eligible patients. There is moderately strong evidence that the practice improves health outcomes.
CPR	It is recommended that clinicians consider following the guideline for eligible patients. This recommendation is based on either weak evidence or on the opinions of the Work Group and reviewers that the practice might improve health outcomes.

Health outcomes are health-related events, conditions, or symptoms that can be perceived by individuals to have an important effect on their lives. Improving health outcomes implies that benefits outweigh any adverse effects.

Table 8: KDIGO grades for the strength of recommendations

	Implications		
Grade	Patients	Clinicians	Policy
Level 1 'We recommend'	Most people in your situation would want the recommended course of action and only a small proportion would not	Most patients should receive the recommended course of action	The recommendation can be adopted as a policy in most situations
Level 2 'We suggest'	The majority of people in your situation would want the recommended course of action, but many would not	Different choices will be appropriate for different patients. Each patient needs help to arrive at a management decision consistent with her or his values and preferences	The recommendation is likely to require debate and involvement of stakeholders before policy can be determined

Table 9: Comparison of 2007 total Medicare prevalent (>60 days) hemodialysis population data to 2007 U.S. DOPPS data and 2007 data from a large U.S. dialysis provider

	2007 Medicare	2007 DOPPS III (U.S. Facilities	2007 LDO Provider
Age, Mean	62.3 years	62.11 years	---
Race, White	188,052 (55%)	2,427 (51.6%)	20,198 (46.9%)
Race, Black	129,964 (38.0%)	1,602 (34.1%)	19,422 (45.1%)
Race, Asian	15,591 (4.6%)	214 (4.6%)	998 (2.3%)
Race, Other	2,964 (2.4%)	457 (9.7%)	2,170 (5.7%)
Gender, Female	153,561 (44.9%)	2,120 (44.7%)	20,089 (46.7%)
Gender, Male	188,345 (55.1%)	2,619 (55.3%)	22,968 (53.3%)

Primary Diagnosis, Diabetes Mellitus	151,477 (44.3%)	2,345 (50.0%)	17,297 (40.2%)

Table 10A and B: Prevalence of PTH >400pg/mL and selected lab parameters by treatment status.

A. LDO (Total N=24,495)

Variable	N (%)	PTH (Mean ± SD)	PTH (Median)
All ≥400pg/mL (38% of total)	9,425 (100)	863 ± 436	662 (502;997)
Vitamin D + Cinacalcet	1,493 (16)	999 ± 360	752 (539;1,185)
Vitamin D or Cinacalcet	7,884 (84)	842 ± 407	650 (498;967)
No Vitamin D or Cinacalcet	1541 (16)	969 ± 601	742 (524;1,176)

B. DOPPS III (Total N=6,927)

Variable	N (%)	PTH (Mean ± SD)	PTH (Median)
All ≥400pg/mL (21% of total)	1,449 (100)	766 ± 533	600 (473;847)
Vitamin D + Cinacalcet	177 (12)	921 ± 834	680 (508;1,013)
Vitamin D or Cinacalcet	1,082 (75)	773 ± 541	600 (473;852)
No Vitamin D or Cinacalcet	364 (25)	746 ± 509	597 (472;834)

Table 11: Prevalence of PTH >400pg/mL by treatment status in LDO.

Variable	N (%)	PTH (Mean ± SD)	PTH (Median)
All ≥400pg/mL (38% of total)	9,425 (100)	863 ± 436	662 (502;997)
Vitamin D + Cinacalcet	1,493 (16)	999 ± 360	752 (539;1,185)
Vitamin D or Cinacalcet	7,884 (84)	842 ± 407	650 (498;967)
No Vitamin D or Cinacalcet	1,541 (16)	969 ± 601	742 (524;1,176)

AMGEN INC.
ESRD PATIENTS WITH PTH >400PG/ML AND NOT TREATED WITH A CALCIMIMETIC OR VITAMIN D ANALOG

CALCULATION ALGORITHM

Measure scores are calculated by dividing the total number of patients included in the numerator by the total number of patients included in the denominator.

IDENTIFICATION OF DENOMINATOR CASES
To identify patients to be included in the denominator, first calculate the following:

- Patient *Age* = (Date of first day of most recent month of study period) — (Patient's *Date of Birth*)
- Patient *Time on Dialysis* = (Date of first day of most recent month of study period) — (Patient's *Date Regular Chronic Dialysis Began*)
- Patient *Time Within Facility* = (Date of last day of most recent month of study period) — (Patient's *Admission Date*)

Include in the denominator all patients who meet the following criteria in the most recent month of the 3-month study period:

- *Type of Dialysis* = Hemodialysis, Home Hemodialysis, Continuous Ambulatory Peritoneal Dialysis (CAPD), or Continuous Cycling Peritoneal Dialysis (CCPD)

  AND

- *Age* = ≥18 years

  AND

- *Time on Dialysis* = >90 days

  AND

- *Time at Facility* = ≥30 days

  AND

- Patient has not been discharged from the facility prior to the last day of the most recent month of the 3-month study period

IDENTIFICATION OF NUMERATOR CASES
Include in the numerator all patients from the denominator who meet the following criteria:

- *Serum Intact PTH* = >400pg/mL[1]

  AND

[1] If there is more than one serum intact PTH measurement within the 3-month study period, the first value for the period is used.

- *Calcimimetic and/or Vitamin D Analog Prescribed* = No in each of the three months of the study period during which the serum intact PTH >400pg/mL.

MEASURE SCORE CALCULATION

Performance Rate = (Patients with serum iPTH >400pg/mL and not prescribed calcimimetic and/or vitamin D analog in any of the 3 months of the study period) ÷ (Total patients ≥18 years of age on HD, HHD, CAPD, or CCPD >90 days and at the facility ≥30 days and not discharged from the facility prior to the last day of the most recent month of the study period)