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 #: 1658 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 <130pg/mL and continued treatment 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 <130pg/mL who continue to be treated with a calcimimetic agent or vitamin D analog during the 3-month reporting period.

2a1.1 Numerator Statement: Number of patients from the denominator with serum intact PTH <130pg/mL who continue to be treated with a calcimimetic agent or vitamin D analog.

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)

Renal bone disease, or renal osteodystrophy, is common among patients with ESRD, and it is an important contributor to morbidity and mortality.(2-9) Historically, renal bone disease has been considered primarily to be a manifestation of secondary hyperparathyroidism (SHPT), reflecting both the severity and overall duration of the disorder. The extent of the pathological changes of SHPT in bone among patients with ESRD thus corresponds generally to the prevailing concentration of parathyroid hormone (PTH) in blood. Persistently high PTH levels cause osteitis fibrosa cystica, high rates of bone remodeling and turnover, increases in the numbers of osteoblasts and osteoclasts in bone, and either peri-trabecular or bone marrow fibrosis. In contrast, patients with persistently low PTH concentrations in blood more often display pathological features of adynamic bone. Unlike the bone disease of hyperparathyroidism, adynamic renal osteodystrophy is characterized by low rates of bone remodeling and turnover and by reduced numbers of osteoblasts and osteoclasts. Evidence of fibrous tissue deposition adjacent to individual trabecular structures or within the bone marrow is distinctly absent.(2-9)

Over the past 15 to 20 years, the prevalence of adynamic bone has increased substantially among patients receiving dialysis to manage ESRD. Some reports indicate that adynamic renal osteodystrophy is now the predominant skeletal lesion both among adults managed with hemodialysis and in those treated with peritoneal dialysis.(3-9) The likelihood of developing dynamic bone increases substantially when PTH levels are consistently below 150pg/mL, and the disorder affects most patients with PTH levels below 65pg/mL.(3-10)

Adynamic bone is quite common among diabetic patients, who now comprise approximately 38% of the ESRD population.(1) The prevalence of adynamic renal osteodystrophy in ESRD patients with diabetes approaches 70%.(3,6,9-14) Such individuals often have PTH levels that are substantially lower than those among persons with ESRD from other causes. Apart from low PTH levels, insulin deficiency and/or resistance to the biological actions of insulin in bone may also contribute to the high prevalence of adynamic renal osteodystrophy among diabetic patients undergoing dialysis.(3,6,9-14)

Separately, therapeutic interventions that lower plasma PTH levels excessively for sustained periods among patients with SHPT represent an additional cause of adynamic renal osteodystrophy among patients with ESRD. Vitamin D analogs and calcimimetic compounds both can reduce plasma PTH levels substantially and result in adynamic bone if treatment is not monitored regularly and adjusted appropriately.(15,16)

Although limited information is available about the long-term consequences of adynamic renal osteodystrophy, two reports suggest that adynamic bone is associated with a greater risk of skeletal fracture among patients undergoing dialysis,(17,18) but robust studies addressing this issue have yet to be published. Nevertheless, soft-tissue and vascular calcification represent additional causes for concern. Using ultrasound methods to detect arterial calcification, both the prevalence and severity of vascular calcification was reported to be greater among hemodialysis patients with adynamic bone as documented by bone biopsy

compared with other types of renal bone disease.19 Because bone turnover is reduced substantially among persons with adynamic renal osteodystrophy, the capacity of bone to buffer calcium and phosphorus entering the blood after absorption from the intestine or after exposure to high concentrations of calcium in dialysis solutions is diminished. This may lead to episodes of hypercalcemia and/or hyperphosphatemia and promote the deposition of mineral in soft-tissues including the vasculature, myocardium and cardiac valves. The risk of hypercalcemia among patients with adynamic bone is aggravated further by the use of large doses of calcium-containing, phosphate-binding agents and vitamin D analogs, either alone or together. Both interventions increase net intestinal calcium absorption.(19-24)

Cardiovascular calcification is common among patients with ESRD, and the process is thought to contribute substantially to the development of cardiovascular disease and to mortality in the dialysis population.(19-24) Because adynamic bone represents a recently recognized, but potentially important risk, factor for cardiovascular calcification among those with ESRD, there is need to identify patients with adynamic renal osteodystrophy and to implement measures designed to avoid clinical management practices that inappropriately suppress parathyroid gland function and lower PTH concentrations excessively for extended periods.

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

1. U.S. Renal Dialysis System, USRDS 2010 Annual Data Report: Atlas of Chronic Kidney Disease and End-Stage Renal Disease in the United States. 2010.

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

3. 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.

4. 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.

5. Hutchison A, Moore P. Low turnover bone disease. Periton Dial Int. 1996;16(Suppl 1):295–9.

6. Monier-Faugere M, Malluche H. Trends in renal osteodystrophy: a survey from 1983 to 1995 in a total of 2248 patients. Nephrol Dial Transplant. 1996;11(Suppl 3):111–20.

7. Mucsi I, Hercz G. Adynamic bone disease: pathogenesis, diagnosis and clinical relevance. Curr Opin Nephrol Hypertens. 1997;7:356–61.

8. Spasovski G, Bervoets 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.

9. 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.

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

11. 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.

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

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

14. 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.

15. 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.

16. 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.

17. Atsumi K, Kushida K, Yamazaki K et al. Risk factors for vertebral fractures in renal osteodystrophy. Am J Kidney Dis. 1999;33(2):287-93.

18. Coco M and Rush H. Increased incidence of hip fractures in dialysis patients with low serum parathyroid hormone. Am J Kidney Dis. 2000;36(6):1115-21.

19. London G, Pannier B, Marchais S, Guerin A. Calcifications of the aortic valve in the dialysed patient. J Am Soc Nephrol. 2000;11:778–83.

20. Avram M, Mittman N, Myint M et al. Importance of low serum intact parathyroid hormone as a predictor of mortality in hemodialysis and peritoneal dialysis patients: 14 years of prospective observation. Am J Kidney Dis. 2001;38:1351-7.

21. Ganesh S, Stack A, Levin N et al. Association of elevated serum PO(4), Ca × PO(4) product, and parathyroid hormone with cardiac mortality risk in chronic hemodialysis patients. J Am Soc Nephrol. 2001;12:2131-8.

22. Guh J, Chen H, Chuang H et al. Risk factors and risk for mortality of mild hypoparathyroidism in hemodialysis patients. Am J Kidney Dis. 2002;39:1245-54.

23. Stevens L, Djurdjev O, Cardew S et al. Calcium, phosphate, and parathyroid hormone levels in combination and as a function of dialysis duration predict mortality: evidence for the complexity of the association between mineral metabolism and outcomes. J Am Soc Nephrol. 2004;15:770-9.

24. 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.

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:
Low serum intact PTH levels in dialysis patients resulting from the use of vitamin D analogs or calcimimetic agents to treat SHPT is a risk factor for the development of adynamic bone disease and its sequellae—fractures, hypercalcemia, vascular calcifications, and increased mortality. As reflected in the current KDOQI and KDIGO practice guidelines, it is thus recommended that providers reduce or discontinue these medications as necessary to maintain intact PTH levels above a lower limit to increase bone turnover, minimize hypercalcemia, and improve outcomes for patients with chronic renal disease. There is no definitive consensus as to what PTH value should trigger such action on the part of the physician (i.e., 130 versus 150pg/mL) or as to what that action should be (i.e., dosage reduction versus discontinuation of the medication[s]). Thus, to identify only those cases of inappropriate care that are clearly inconsistent with existing guidelines, the measure has been specified to capture patients with the lower of the two candidate PTH levels—i.e., 130pg/mL. Since the risk is not disputed in these more severely hypoparathyroid patients, and given the gravity of the adverse events in question, the measure does not allow for dosage adjustments, but rather requires discontinuation of the responsible medication(s).

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 60% of patients in LDO facilities and 46% of patients in DOPPS with serum PTH values <130pg/mL were still being treated with a vitamin D analog or a calcimimetic agent, behaviors inconsistent with recommendations provided in current clinical practice guidelines. (See Tables 1A and B [Prevalence of PTH <130 and Selected Lab Parameters by Treatment Status] in the accompanying Attachment A.)

The same sets of data were used to assess performance variability among facilities. The results indicated that more than 59% of LDO facilities and 58% of DOPPS facilities had patients with documented PTH values <130pg/mL who were still being treated with a vitamin D analog and/or calcimimetic agent. (See Table 2 [Percent of Facilities with Patients with PTH <130 Still Being Treated with a Vitamin D Analog and/or Calcimimetic Agent] in Attachment A.)

Such findings demonstrate that a substantial proportion of hemodialysis patients with PTH concentrations in a range below currently recommended values continue to be treated inappropriately for SHPT. Failure to withdraw treatment when medically indicated occurs in a substantial proportion of dialysis facilities. The results identify an important gap in clinical performance that requires attention. Nevertheless, such a 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 discrete surveillance intervals and noted substantial variations 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 PTH levels in chronic renal disease are 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 (95% confidence interval) for adynamic bone disease (maximum PTH <150pg/mL) was 0.26 (0.17 to 0.41), whereas the odds ratio for hyperparathyroid bone disease (mean PTH >500pg/mL) was 4.4 (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). (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: ESRD patients diagnosed with secondary hyperparathyroidism (SHPT); Patients with SHPT treated with vitamin D analog and/or calcimimetic >> PROCESS: Measure PTH >> Identify patients with PTH <130pg/mL >> Choose/plan intervention >> Discontinue vitamin D analogs and calcimimetics >> OUTCOME: Normalization of PTH and related biomarkers >> Bone turnover increased and hypercalcemia minimized >> Reversal of adynamic bone disease and lower fracture and mortality rates.

With the expanded and widespread use of calcitriol and other synthetic vitamin D analogs to treat SHPT during the past 15 to 20 years, adynamic bone has become increasingly common among patients with ESRD. It is now considered by some to be predominant type of renal osteodystrophy both in adults managed with hemodialysis and in those undergoing peritoneal dialysis.(1-12) The likelihood of adynamic bone increases when PTH levels are below 150pg/mL, and the disease is highly prevalent among dialysis patients with PTH levels below 65pg/mL.(1-12) Several large observational studies and reviews published within the past decade have linked adynamic bone disease with a number of adverse outcomes—specifically, fractures, hypercalcemia, vascular and myocardial calcifications, and increased mortality.(14-20) This relationship between adynamic bone disease and vascular disease may at least in part explain why intact PTH levels less than 150pg/mL were associated with a 1.4-fold increase in mortality in a study of 58,000 ESRD patients after extensive multivariate adjustments,(20) and why patients with very low (<32pg/mL) intact PTH levels were found to be at increased risk for sudden death in a two-year follow-up study of 12,800 dialysis patients by Ganesh et al.(16) Smaller studies(17,18) have reported similar findings—specifically, that the combination of low intact PTH and high serum calcium and phosphate levels (a combination typical for adynamic bone disease) was associated with substantial mortality.

As reflected in the current KDOQI and KDIGO practice guidelines, it is thus recommended that providers reduce or discontinue

calcitriol, vitamin D analogs, and calcimimetics as necessary to maintain intact PTH levels above a lower limit to increase bone turnover and minimize hypercalcemia. There is no definitive consensus in the guidelines as to what PTH value should trigger such action on the part of the physician (i.e., 130 versus 150pg/mL) or as to what that action should be (i.e., dosage reduction versus discontinuation of the medication[s]). Thus to identify only those cases of inappropriate care that are clearly inconsistent with existing guidelines, the measure has been specified to capture patients with the lower of the two candidate PTH levels—i.e., 130pg/mL. As the risk is not disputed in these more severely hypoparathyroid patients and given the gravity of the adverse events in question—adynamic bone disease, fractures, increased mortality—the measure does not allow for dosage adjustments, but rather requires discontinuation of the responsible medication(s).

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: Renal bone disease, 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 consists of 12 peer-reviewed publications encompassing 13 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 twelve studies address the etiology, clinical course, and sequellae of parathyroid oversuppression in renal disease. The strengths and weaknesses of each study are presented below; the consistency of the evidence across these twelve studies is discussed in Section 1c.7. (Numbered according to Citations sequence in Section 1c.14.)

Rodriguez-Perez J, Plaza C, Torres A et al. Low turnover bone disease is the more common form of bone disease in CAPD patients. Adv Perit Dial. 1992;8:376-80. (Citation 1.)
The authors evaluated biochemical and histomorphometric parameters of 26 patients maintained on continuous ambulatory peritoneal dialysis (CAPD) for 12-14 months to assess for low turnover bone disease (LTBD). Three (11.5%) showed mild hyperparathyroidism, five (19.2%) osteitis fibrosa, three (11.5%) mixed forms, four (15%) osteomalacia, and eleven (42.3%) adynamic bone disease. Intact PTH serum levels were lower in LTBD (133.2 +/- 128 versus 468.2 +/- 451pg/mL; $p < 0.05$). Eleven patients who underwent a bone biopsy at start of dialysis and after 12 months of CAPD treatment were also prospectively evaluated. Bone biopsies pre-CAPD demonstrated normal-high bone turnover disease in eight of eleven (72.7%) and LTBD in three of eleven (27%). In the follow-up biopsies, LTBD was found in seven patients (three osteomalacia and four adynamic bone disease), making it the predominant bone lesion in study patients, predominantly adynamic forms. The authors concluded that low intact PTH serum levels may be a predictor of low turnover bone disease.

Hercz G, Pei Y, Greenwood C et al. Aplastic osteodystrophy without aluminum: the role of "suppressed" parathyroid function. Kidney Int. 1993;44:860-6. (Citation 2.)
The authors evaluated 259 dialysis patients using serum PTH (normal range 10 to 55pg/mL), the deferoxamine infusion test, and iliac crest bone biopsy to determine the various forms of renal osteodystrophy and their risk factors. Although half of the biopsied patients had low turnover osteodystrophy, evidence of aluminum toxicity was present in only one third. Additional risk factors for this bone lesion included treatment with peritoneal dialysis, ingestion of calcium carbonate, diabetes mellitus, and advanced age. The PTH levels in patients with the aplastic lesion were significantly lower than in patients with normal or high bone turnover lesions

(77 +/- 61 versus 369 +/- 32pg/mL, P <0.0001). Aside from hypercalcemia, these patients were relatively asymptomatic. In a second study, ten patients on peritoneal dialysis with the aplastic lesion had their dialysate calcium lowered from 1.62 to 1.0mM. This resulted in a significant increase in PTH levels, from 37 +/- 8 to 106 +/- 19pg/mL (P <0.001), which persisted over the nine-month observation period. The authors concluded that the aplastic lesion is the most common form of renal osteodystrophy, with aluminum intoxication implicated in only a third of the cases. In the remainder, identified factors include therapy with peritoneal dialysis using supraphysiological dialysate calcium, oral calcium carbonate intake, and diabetes mellitus.

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. (Citation 3.)
The authors assessed the bone histology in 259 chronic dialysis patients, all of whom were in the same dialysis program. All patients had bone biopsies with quantitative histomorphometry, intact PTH measurements, and basal and deferoxamine stimulated serum aluminum levels. Results demonstrate the increased incidence of aplastic bone lesions, particularly in patients treated with peritoneal dialysis. A different pattern of bone lesions was seen in peritoneal dialysis as compared with hemodialysis, with low turnover disorders comprising 66% of the lesions seen in peritoneal dialysis and high turnover lesions accounting for 62% of the bone histologic findings in hemodialysis. The difference in these patterns may relate to alterations in PTH levels, as mean PTH levels in hemodialysis patients were 2.5 times the levels found in peritoneal dialysis patients (P <0.0005).

Couttenye M, D'Haese P, Van Hoof V et al. Low serum levels of alkaline phosphatase of bone origin: a good marker of adynamic bone disease in haemodialysis patients. Nephrol Dial Transplant. 1996;11:1065–72. (Citation 5.)
The authors demonstrated the diagnostic performance of intact PTH in the non-invasive diagnosis of adynamic bone disease. Based on 103 bone biopsies, including all types of renal osteodystrophy, an optimal cut-off value for intact PTH in the diagnosis of adynamic bone disease was de?ned by ROC analysis. At a level <150pg/mL, intact PTH has a sensitivity of 80.6% and a speci?city of 76.2% for diagnosing adynamic bone disease. Applying Bayes' theorem, it was calculated that in the current hemodialysis population in which a prevalence of adynamic bone disease up to 35% has been described, the positive and negative predictive values for the proposed cut-off levels are 65 and 88% for intact PTH.

Couttenye M, D'Haese P, Deng J et al. High prevalence of adynamic bone disease diagnosed by biochemical markers in a wide sample of the European CAPD population. Nephrol Dial Transplant. 1997;12(10):2144-50. (Citation 8.)
In this study (n = 212), the prevalence of adynamic bone disease in the European continuous ambulatory peritoneal dialysis (CAPD) population was evaluated by means of biochemical markers, including intact PTH. In this population with a low exposure to aluminium, the prevalence of adynamic bone disease as indicated by either a low level of bone alkaline phosphatase (BAP) or PTH was 43%. The following risk factors were identified: advanced age, shorter time on renal replacement therapy, male gender, and high calcium content of peritoneal dialysate fluid. The index of calcium exposure was significantly higher in patients with low intact PTH levels compared to those with intact PTH >150pg/mL, giving further support to the hypothesis that a high calcium load administered to renal failure patients may lead to ´oversuppressed´ parathyroids in adynamic bone disease.

Ureña P, Malergue M, Goldfarb B et al. Evolutive aortic stenosis in hemodialysis patients: analysis of risk factors. Nephrologie. 1999;20:217-25. (Citation 14.)
The authors retrospectively investigated the incidence rate of aortic stenosis (AS) from 1991 to 1996 in 110 hemodialysis patients followed by Doppler echocardiography. Progressive AS was diagnosed in 16 patients who had a decrease in their indexed aortic valve area from 1.24 to 0.66cm2/m2 in 17 months. The mean incidence of AS per year was 3.3%, ranging from 1.5 to 8.0%. Eight patients died in less than three years after the diagnosis of AS with a mean survival time of 23.0 +/- 9.5 months. Survival curves using Kaplan-Meier estimates showed a statistically significant decrease in the survival rate of patients with AS compared with patients without valvulopathy (p <0.001); the AS patients were older than patients with normal valves (68.6 versus 56.7 years, respectively), and men were four times more affected and showed a significantly more rapid progression to AS than women. The calcium-phosphorus product was higher in AS patients (5.43mM) than in patients without AS (3.95mM), mainly due to hyperphosphatemia without hypercalcemia. The hyperphosphatemia was associated with biological signs of hypoparathyroidism or adynamic bone disease in 62% of the cases. Plasma vitamin D3 was also higher in patients with AS (20.5ng/mL) than in those with normal valves (9.6ng/mL). Logistic regression showed that age, vitamin D3 and hyperphosphatemia correctly predicted 56% of the AS cases. The authors concluded that AS is frequent and of poor outcome in hemodialysis patients. Age, relatively high plasma vitamin D3 levels, and hyperphosphatemia due to hypoparathyroidism are risk factors.

Avram M, Mittman N, Myint M et al. Importance of low serum intact parathyroid hormone as a predictor of mortality in hemodialysis and peritoneal dialysis patients: 14 years of prospective observation. Am J Kidney Dis. 2001;38:1351-7. (Citation 15.)

The authors studied prospectively the relationship of enrollment serum intact PTH and various demographic characteristics and other biochemical parameters to all-cause mortality in 345 hemodialysis and 277 peritoneal dialysis patients. Patients were monitored for 14 years. Observed survival and survival after adjustment for age, race, gender, months on dialysis at enrollment, diabetic status, and nutritional markers were significantly better for patients with enrollment PTH greater than 200pg/mL than for patients with PTH 65-199pg/mL and patients with PTH < 65pg/mL. Enrollment serum PTH was an independent predictor of survival in hemodialysis and peritoneal dialysis patients. For hemodialysis patients, age and months on dialysis at enrollment were associated inversely with PTH level, whereas black race, creatinine, and phosphorus were associated directly with PTH. For peritoneal dialysis patients, age, diabetes, and months on dialysis at enrollment were inverse predictors, whereas black race, albumin, creatinine, and phosphorus were associated positively with PTH. Lower than expected levels of PTH in uremic patients is associated with increased mortality. The authors hypothesize that inadequate protein and/or phosphorous intake result in impaired development of the expected SHPT and in the excess mortality risk inherent with malnutrition.

Ganesh S, Stack A, Levin N et al. Association of elevated serum PO(4), Ca × PO(4) product, and parathyroid hormone with cardiac mortality risk in chronic hemodialysis patients. J Am Soc Nephrol. 2001;12:2131-8. (Citation 16.)
Data from two national random samples of hemodialysis patients (n = 12,833) were used to test the hypothesis that elevated serum contributes mainly to cardiac causes of death. During a two-year follow-up, the cause-specific relative risk (RR) of death for patients was analyzed separately for several categories of cause of death, including coronary artery disease (CAD), sudden death and other cardiac causes, cerebrovascular death, and infection. Cox regression models were fit for each of the eight cause of death categories, adjusting for patient demographics and non-cardiovascular comorbid conditions. Higher mortality risk was seen for patients in the high phosphorus (PO4) group (>6.5mg/dL) compared with the lower PO4 group (<6.5mg/dL) for death resulting from CAD (RR 1.41; P <0.0005), sudden death (RR 1.20; P <0.01), infection (RR 1.20; P <0.05), and unknown causes (RR 1.25; P <0.05). Patients in the high PO4 group also had non-significantly increased RR of death from other cardiac and cerebrovascular causes of death. The RR of sudden death was also strongly associated with elevated Ca x PO4 product (RR 1.07 per 10 mg2/dL2; P <0.005) and serum PTH levels greater than 495pg/mL (RR 1.25; P <0.05). Patients with very low (<32pg/mL) intact PTH levels were found to be at increased risk for sudden death.

Guh J, Chen H, Chuang H et al. Risk factors and risk for mortality of mild hypoparathyroidism in hemodialysis patients. Am J Kidney Dis. 2002;39:1245-54. (Citation 17.)
To clarify risk factors and prognosis of time-dependent relative hypoparathyroidism in hemodialysis patients (PTH <200pg/mL), a retrospective cohort study was performed for 126 hemodialysis patients with four or more PTH determinations and no previous total or subtotal parathyroidectomy. Values for intact PTH, ionized calcium, phosphate, magnesium, albumin, creatinine, urea reduction ratio (URR), glucose, hemoglobin A1c (HbA1c), aluminum, and 1,25(OH)2D were obtained at enrollment and at some time during follow-up. The prevalence of relative hypoparathyroidism at entry was 76 of 126 patients (60.3%). Univariate analysis showed that patients with hypoparathyroidism were older, more likely to have diabetes, and had greater ionized calcium levels and lower phosphate, albumin, blood urea nitrogen (BUN), and creatinine levels. Patients with diabetes were older and had a shorter duration of dialysis therapy and lower PTH, phosphate, albumin, BUN, and creatinine levels and URRs. Conversely, multivariate analysis showed that PTH levels at entry were associated directly with creatinine levels and inversely with age and ionized calcium levels, but not diabetes. During follow-up, PTH levels fluctuated concomitantly with ionized calcium and phosphate levels over time in all patients. Time-dependent PTH levels were associated directly with duration of dialysis therapy and use of vitamin D and phosphate and albumin levels, but inversely with age and ionized calcium and magnesium levels, but not glucose or HbA1c levels. Interestingly, time-dependent PTH levels were independently associated with survival after adjusting for traditional risk factors (diabetes, age, albumin and creatinine levels, and URR) and duration of dialysis therapy. The authors concluded that in hemodialysis patients, time-dependent PTH levels were associated with age, duration of dialysis, and levels of ionized calcium, phosphate, albumin, and magnesium. Moreover, relative hypoparathyroidism at entry and lower time-dependent PTH levels predicted mortality.

Stevens L, Djurdjev O, Cardew S et al. Calcium, phosphate, and parathyroid hormone levels in combination and as a function of dialysis duration predict mortality: evidence for the complexity of the association between mineral metabolism and outcomes. J Am Soc Nephrol. 2004;15:770-9. (Citation 19.) Prevalent dialysis patients in British Columbia, Canada, who had measurements of calcium, phosphate, and intact PTH between January-March 2000 were followed prospectively until December 2002. Statistical analysis included Cox proportional hazard models with calcium, phosphate, and intact PTH alone and in combination as explanatory variables; analyses were stratified by duration of dialysis. The 515 patients included in this analysis are representative of British Columbia and Canadian dialysis populations: 69% were on hemodialysis, mean age was 60 +/- 17 years, 40% were female, and 34% had diabetes. Mean calcium and phosphate values were 2.32 +/- 0.22mmol/L and 1.68 +/- 0.59mmol/L,

respectively, and median intact PTH was 15.8pmol/L (25th to 75th percentile: 6.9 to 37.3pmol/L). Serum phosphate, after adjusting for demographic, dialysis type and adequacy, hemoglobin, and albumin, independently predicted mortality (risk ratio [RR], 1.56 per 1 mmol/L; 95% confidence interval [CI], 1.15 to 2.12; P = 0.004). When combinations of parameters were modeled (overall P = 0.003), the combinations of high serum phosphate and calcium with high intact PTH (RR, 3.71; 95% CI, 1.53 to 9.03; P = 0.004) and low intact PTH (RR, 4.30; 95% CI, 2.01 to 9.22; P <0.001) had highest risks for mortality as compared with the combination of high intact PTH with normal serum calcium and phosphate that had the lowest mortality and was used as index category. These effects varied across different strata of dialysis duration.

Kalantar-Zadeh K, Kuwae N, Regidor DL et al. Survival predictability of time-varying indicators of bone disease in maintenance hemodialysis patients. Kidney Int. 2006;70:771-80. (Citation 20.)
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 that lower levels of serum PTH, especially below the KDOQI recommended lower threshold (<150pg/mL), are associated with increased risk of death.

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. (Citation 22.)
The authors followed 14 children and adolescents with biopsy-proven SHPT who were treated with intermittent oral or intraperitoneal doses of calcitriol for 12 months. Biochemical indices of mineral metabolism, including serum intact PTH levels, were measured monthly throughout the study, and bone biopsies were repeated at the end of treatment. Before treatment, 11 patients had osteitis fibrosa and three had mild lesions of SHPT. Histologic improvement was seen in 12 of 14 patients, and osteitis fibrosa resolved in 10 of 11 cases. Bone formation decreased in all patients during intermittent calcitriol therapy, falling from 861 +/- 380 to 150 +/- 170microns2/mm2/day, P <0.001. Bone formation decreased to normal in six patients, but six patients developed adynamic lesions of bone with subnormal bone formation rates. Serum PTH and alkaline phosphatase levels declined in those who developed adynamic bone, but values remained elevated in patients with normal rates of bone formation at follow-up evaluation. Neither the mean dose of calcitriol nor the average dose per kilogram body weight differed in patients with adynamic lesions. Thus, adynamic renal osteodystrophy develops in a substantial number of patients during intermittent calcitriol therapy. Calcitriol may directly suppress osteoblastic activity in patients with SHPT when given in large doses to patients undergoing peritoneal dialysis.

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 a relationship between hypersuppression of PTH, adynamic bone disease, hypercalcemia, and increased mortality.(1-20) As noted in the KDOQI Clinical Practice Guidelines for Bone Metabolism and Disease in Chronic Kidney Disease, recommendations on therapy can be based only on the current understanding of the pathogenetic mechanisms of the bone abnormalities.

1c.7 Consistency of Results across Studies *(Summarize the consistency of the magnitude and direction of the effect):* The studies described consistently demonstrate a relationship between hypersuppression of PTH, adynamic bone disease, hypercalcemia, and increased mortality.(1-20)

1c.8 Net Benefit *(Provide estimates of effect for benefit/outcome; identify harms addressed and estimates of effect; and net benefit - benefit over harms)*:
The focus of this measure is to encourage discontinuation of calcitriol, synthetic vitamin D analogs, and calcimimetic agents in ESRD patients being treated for secondary hyperparathyroidism (SHPT) when PTH levels fall below 150pg/mL so as to prevent adynamic bone disease and its sequellae. However, upon discontinuation of these medications, clinicians must continue to monitor PTH values regularly and resume treatment as clinically appropriate. 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.(1-12) SHPT of ESRD is associated with an increased risk of high turnover bone lesions, fracture-related hospitalization, and all-cause and cardiovascular mortality.(14-20) 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.(20) 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.(18)

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. To ensure that PTH values are monitored regularly and medications are adjusted as clinically appropriate, two measures are thus recommended to address performance across the range of renal parathyroid disease:

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

• ESRD patients with PTH >400pg/mL and not treated 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: The Kidney Disease Improving Global Outcomes (KDIGO) utilizes a structured approach to grading the quality of evidence for outcomes, 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 5 [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 con?icts 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 con?icts 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 Mineral and Bone Disorder (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: KDIGO Recommendation 4.2.4 = C

1c.14 Summary of Controversy/Contradictory Evidence: We note that there are no RCTs showing that treatment to achieve a speci?c 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), the studies described in the body of evidence clearly indicate a relationship between hypersuppression of PTH, adynamic bone disease, hypercalcemia, and increased mortality.(1-20)

Additionally, Palmer et al. (26) 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.(27)

Lastly, no ratings of the individual studies cited in the body of evidence were included in the KDIGO guideline document. However, the overall quality of the evidence supporting the relevant guideline—that calcitriol, vitamin D analogs, and/or calcimimetics should be reduced or stopped if the intact PTH levels fall below two times the upper limit of normal for the assay (i.e., approximately 130pg/mL)—was rated as "low," indicating that the true effect may be substantially different from the estimate of the effect. The KDIGO document indicates that this rating was chosen because no RCTs have speci?cally evaluated the effect of vitamin D, calcitriol, or vitamin D analogs on patient-level outcomes (mortality, fracture, quality of life, hospital admission, and cardiovascular outcomes), and observational data are inconclusive. Likewise, the KDOQI Guideline Document on Bone Metabolism and Disease in Chronic Kidney Disease notes that there are no controlled studies on this topic and that recommendations on therapy can be based only on the current understanding of the pathogenetic mechanisms of the bone abnormalities.

While the current KDOQI and KDIGO practice guidelines both recommended that providers reduce or discontinue calcitriol, vitamin D analogs, and calcimimetics as necessary to maintain intact PTH levels above a lower limit to increase bone turnover and minimize hypercalcemia, there is no definitive consensus as to what PTH value should trigger such action on the part of the physician (e.g., 100pg/mL, 130pg/mL, 150pg/mL) or as to what that action should be (i.e., dosage reduction versus discontinuation of the medication[s]). To identify only those cases of inappropriate care that are clearly inconsistent with existing guidelines, the measure has been specified to capture patients with the lower of the two candidate PTH levels—i.e., 130pg/mL. As the risk is not

disputed in these more severely hypoparathyroid patients and given the gravity of the adverse events in question—adynamic bone disease, fractures, increased mortality—the measure does not allow for dosage adjustments, but rather requires discontinuation of the responsible medication(s).

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

1. Rodriguez-Perez J, Plaza C, Torres A et al. Low turnover bone disease is the more common form of bone disease in CAPD patients. Adv Perit Dial. 1992;8:376-80.

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

3. 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.

4. 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.

5. Couttenye M, D'Haese P, Van Hoof V et al. Low serum levels of alkaline phosphatase of bone origin: a good marker of adynamic bone disease in haemodialysis patients. Nephrol Dial Transplant. 1996;11:1065–72.

6. Hutchison A, Moore P. Low turnover bone disease. Periton Dial Int. 1996;16(Suppl 1):295–9.

7. Monier-Faugere M, Malluche H. Trends in renal osteodystrophy: a survey from 1983 to 1995 in a total of 2248 patients. Nephrol Dial Transplant. 1996;11(Suppl 3):111–20.

8. Couttenye M, D'Haese P, Deng J et al. High prevalence of adynamic bone disease diagnosed by biochemical markers in a wide sample of the European CAPD population. Nephrol Dial Transplant. 1997;12(10):2144-50.

9. 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.

10. Mucsi I, Hercz G. Adynamic bone disease: pathogenesis, diagnosis and clinical relevance. Curr Opin Nephrol Hypertens. 1997;7:356–61.

11. Spasovski G, Bervoets 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.

12. 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.

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

14. Ureña P, Malergue M, Goldfarb B et al. Evolutive aortic stenosis in hemodialysis patients: analysis of risk factors. Nephrologie. 1999;20:217-25.

15. Avram M, Mittman N, Myint M et al. Importance of low serum intact parathyroid hormone as a predictor of mortality in hemodialysis and peritoneal dialysis patients: 14 years of prospective observation. Am J Kidney Dis. 2001;38:1351-7.

16. Ganesh S, Stack A, Levin N et al. Association of elevated serum PO(4), Ca × PO(4) product, and parathyroid hormone with cardiac mortality risk in chronic hemodialysis patients. J Am Soc Nephrol. 2001;12:2131-8.

17. Guh J, Chen H, Chuang H et al. Risk factors and risk for mortality of mild hypoparathyroidism in hemodialysis patients. Am J Kidney Dis. 2002;39:1245-54.

18. 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.

19. Stevens L, Djurdjev O, Cardew S et al. Calcium, phosphate, and parathyroid hormone levels in combination and as a function of dialysis duration predict mortality: evidence for the complexity of the association between mineral metabolism and outcomes. J Am Soc Nephrol. 2004;15:770-9.

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

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

22. 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.

23. 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.

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

25. 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.

26. 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.

27. 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 13C.1: Adynamic bone disease in Stage 5 CKD (as determined either by bone biopsy or intact PTH <100pg/mL) should be treated by allowing plasma levels of intact PTH to rise in order to increase bone turnover. (OPINION)

• Guideline 13C.1a: This can be accomplished by decreasing doses of calcium-based phosphate binders and vitamin D or eliminating such therapy. (OPINION)

KDIGO Clinical Practice Guideline 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). We suggest that, if the intact PTH levels fall below two times the upper limit of normal for the assay (i.e., 130pg/mL), calcitriol, vitamin D analogs, and/or calcimimetics be reduced or stopped (2C).

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 13C.1 = Opinion; KDOQI Guideline 13C.1a = Opinion; 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 developer's assessment of the quantity, quality, and consistency of the body of evidence?
1c.25 Quantity: High 1c.26 Quality: Moderate1c.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 <130pg/mL who continue to be treated with a calcimimetic agent or vitamin D analog.

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 <130pg/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 'Yes' in any of the three months of the reporting period during which the serum intact PTH <130pg/mL.

2a1.21-23 Calculation Algorithm/Measure Logic Diagram URL or attachment:
Attachment
HypoPTH_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 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 renal bone disease, 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 was compared to Dialysis Outcomes and Practice Patterns Study (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 large dialysis organization (LDO) database can be viewed as valid representations of the U.S. ESRD population, Table 8 (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 9A and B [Prevalence of PTH <130pg/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 suppressed serum intact PTH level—a modifiable risk factor in ESRD patients that is associated with adverse patient outcomes, including adynamic bone disease, bone fractures, hypercalcemia, vascular and myocardial calcification, and increased 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 >9 mg/dL" (NQF Measure 0059), which also is 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 <130pg/mL and treated with a calcimimetic 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 <130pg/mL and treated with a calcimimetic or vitamin D analog) / (Total ESRD patients aged 18 years and older)
= 2,272 / 3,796 = 59.9%

Table 10 (see Attachment A) displays the 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_TablesandGraphsHypo.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 the 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 in?ection point at which PTH becomes signi?cantly 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 adynamic bone disease are of equal

concern. To balance the methodological issues of PTH measurement with the known risks and bene?ts of hypoparathyroidism 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:
1655 : ESRD patients with PTH >400pg/mL and not treated 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 <130pg/mL AND CONTINUED TREATMENT WITH A CALCIMIMETIC OR VITAMIN D ANALOG

ATTACHMENT A: TABLES AND GRAPHS

Table 1A and B: Prevalence of PTH ≤130pg/mL and selected lab parameters by treatment status.

A. LDO (Total N=24,485)

Variable	N (%)	PTH (Mean ± SD)	PTH (Median)
All ≤130pg/mL (16% of total)	3,796 (100)	78 ± 28	83 (51;108)
Vitamin D + Cinacalcet	268 (7)	83 ± 16	87 (59;111)
Vitamin D or Cinacalcet	2,272 (60)	81 ± 26	87 (56;110)
No Vitamin D or Cinacalcet	1,524 (40)	73 ± 31	76 (44;103)

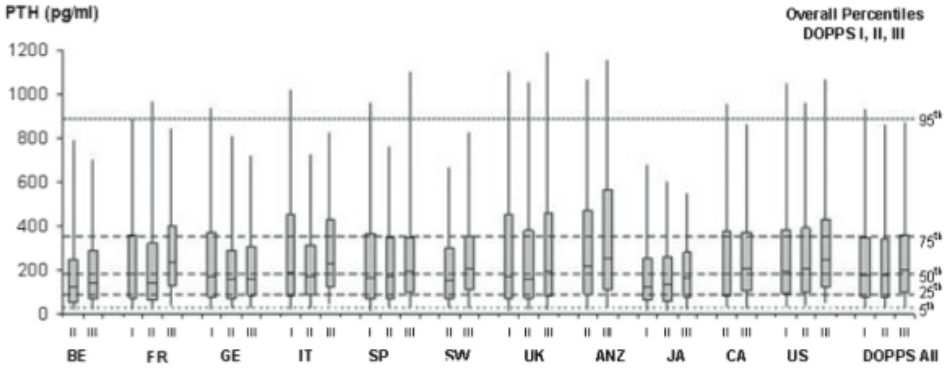
B. DOPPS III (Total N=6,927)

Variable	N (%)	PTH (Mean ± SD)	PTH (Median)
All ≤130pg/mL (34% of total)	2,369 (100)	65.9 ± 37.1	66.4 (34.2;99)
Vitamin D + Cinacalcet	41(1.7)	74.6 ± 33	75 (50.6;98)
Vitamin D or Cinacalcet	1,097 (46)	68 ± 37.5	69.5 (36.1;102)
No Vitamin D or Cinacalcet	1,264 (53)	64 ± 36.8	63.1 (33;95)

Table 2: Percent of facilities with patients with PTH ≤130pg/mL still being treated with a vitamin D analog and/or calcimimetic agent

	Total Patients	Patients with PTH ≤130pg/mL	% Facilities with Patients with PTH ≤130pg/mL Receiving Vitamin D Analog and/or Calcimimetic
LDO	24,495	9,425	59.1
DOPPS III	6,927	1,449	58.0

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 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 6: 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 7: 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 8: 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 9A and B: Prevalence of PTH ≤130pg/mL and selected lab parameters by treatment status.

A. LDO (Total N=24,485)

Variable	N (%)	PTH (Mean ± SD)	PTH (Median)
All ≤130pg/mL (16% of total)	3,796 (100)	78 ± 28	83 (51;108)
Vitamin D + Cinacalcet	268 (7)	83 ± 16	87 (59;111)
Vitamin D or Cinacalcet	2,272 (60)	81 ± 26	87 (56;110)
No Vitamin D or Cinacalcet	1,524 (40)	73 ± 31	76 (44;103)

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

Variable	N (%)	PTH (Mean ± SD)	PTH (Median)
All ≤130pg/mL (34% of total)	2,369 (100)	65.9 ± 37.1	66.4 (34.2;99)
Vitamin D + Cinacalcet	41(1.7)	74.6 ± 33	75 (50.6;98)
Vitamin D or Cinacalcet	1,097 (46)	68 ± 37.5	69.5 (36.1;102)
No Vitamin D or Cinacalcet	1,264 (53)	64 ± 36.8	63.1 (33;95)

Table 10: Prevalence of PTH ≤130pg/mL by treatment status.

Variable	N (%)	PTH (Mean ± SD)	PTH (Median)
All ≤130pg/mL (16% of total)	3,796 (100)	78 ± 28	83 (51;108)
Vitamin D + Cinacalcet	268 (7)	83 ± 16	87 (59;111)
Vitamin D or Cinacalcet	2,272 (60)	81 ± 26	87 (56;110)
No Vitamin D or Cinacalcet	1,524 (40)	73 ± 31	76 (44;103)

AMGEN INC.
ESRD PATIENTS WITH PTH <130pg/mL AND CONTINUED TREATMENT 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* = <130pg/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* = 'Yes' in any of the three months of the study period during which the serum intact PTH <130pg/mL.

MEASURE SCORE CALCULATION

Performance Rate = (Patients with serum iPTH <130pg/mL and 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)