Appendix D: Clinical evidence tables

Reference	**Christensen, 2008** [13]
Study type	Cross-sectional study
Study methodology	Data source: database Recruitment: From August 2003 to April 2007, 54 hypercalcaemic (mean of up to three measurements of albumin-adjusted calcium) patients with familiar hypocalciuric hypercalcaemia (FHH), a clinically significant mutation in the CASR gene and no clinical signs of parathyroid adenoma as judged by combined single photo emission computed tomography (SPECT) and planar parathyroid (Tc-sestamibi) and thyroid (Tc) scintigraphy and ultrasonography were included. In 21 FHH kindreds, 14 participants were index patients and 40 were diagnosed by subsequent family screening. In 3 of the 14 index patients it was not possible to identify hypercalcaemic family members. To minimise the exposure to radiation, the family members were not subjected to radionuclear scintigraphy. FHH patients were compared with 97 patients with PHPT. All PHPT patients were hypercalcaemic (mean of up to 3 measurements of albumin-adjusted calcium) with elevated or high normal plasma PTH. The upper 1/3 of the normal reference range was included because plasma PTH depends on the vitamin D status in the reference population. Only 3.7% of the FHH patients (n=54, median=57 nmol/L; range=18–154) and only 6.1% of the PHPT patients (n=66, median=61nmol/L, range 12–169 nmol/L) had a 25 OHD level below 25 nmol/L, that is vitamin D deficiency. The PHPT patients all underwent parathyroid surgery, leading to normocalcaemia 2 months after surgery. Histopathological examination revealed adenomas in 84 of the patients, hyperplasia in 11 and combined adenoma and hyperplasia in 2 of the patients.
Number of patients	n=54 FHH; n=97 PHPT
Patient characteristics	Age: FHH: 18–75 years; PHPT: 19–86 years Gender (male to female ratio): FHH: 17 males and 37 females ; PHPT: 17 males and 80 females Ethnicity: not stated Country: Denmark Among the FHH patients 13/54=24% [95% CI 12.7–35.5%] had elevated plasma PTH (average of up to 3 measurements) compared with 86/97=89% (95% CI 82.4–95%) of the patients with PHPT. The FHH patients had significantly lower median values for plasma creatinine, plasma PTH and all 3 indices of renal calcium handling and higher plasma phosphate levels than the PHPT patients.

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	Inclusion criteria: Patients with PHPT; patients with FHH Exclusion criteria: for both patient groups were reduced renal function (plasma creatinine>140 µmol/l), other calcium metabolic or bone diseases, lithium treatment, systemic glucocorticoid treatment for more than 6 months, malignant disease, uncontrolled or newly diagnosed chronic disease, and hospital admission due to drug or alcohol abuse.
Target condition(s)	PHPT; FHH
Index test(s) and reference standard	Index test(s) 1. 24-hour renal calcium excretion (CE, mmol, measured directly in the urine) 2. 24-hour renal calcium/creatinine excretion ratio (CR, mmol/mmol) calculated as: CR= 24-hour renal calcium/24-hour renal creatinine excretion 3. Calcium /creatinine clearance ratio (CCCR) calculated as: CCCR= (24-hour U-calcium/P-calcium, total)/ (24-hour U-creatinine/P-creatinine) with variables entered as mmol or mmol/L. Reference standard Histopathological findings at neck exploration leading to normocalcaemia in all PHPT cases. The gold standard for FHH – genetic studies confirming a clinically significant mutation in all FHH patients.
Statistical measures	Index texts Receiver operating characteristic (ROC) curve analysis for discrimination between patients with FHH and patients with PHPT. Cut-off points are for the diagnosis of FHH AUC SE Cut-off point Sensitivity Specificity 2P CE 0.867 0.029 <5.45 0.870 0.722 0.50* CR 0.903 0.027 <0.52 0.889 0.814 0.56** CCCR 0.923 0.021 <0.0115 0.796 0.876 0.19*** 2P denotes significance of differences between area under the curves (AUCs): * CE vs CR, ** CR vs CCCR, *** CCCR vs CE From the AUC's it appears that CCCR gives a marginally better discrimination between FHH and PHPT than CR and CE. However the AUCs were not significantly different, with p-values of 0.50 (CE vs CR), 0.56 (CR vs CCCR), and 0.19 (CCCR vs CE). The optimal cut-off point for diagnosing FHH patients suing CCCR in a one-step diagnostic procedure was <0.0115. This value returns a

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diagnostic specificity of 0.88 and a sensitivity of 0.80. The optimal cut-off values for 24-hour CE and 24-hour CR were 5.45 mmol and 0.52 mmol/mmol, respectively.

Overlap analysis: (Post-hoc)

Sampling	≤ 85% FHH	Sampling ≤ 90% FHH	Sampling ≤ 95% FHH	Sampling 100% FHH
CE				
Cut-off	< 5.4	< 6.6	< 8.0	< 9.7
Sensitivity	0.833	0.889	0.944	1
Specificity	1–0.268 = 0.732	732 1–0.412 = 0.588	1–0.546 = 0.454	1–0.680 = 0.320
PHPT sample	26/97 = 26.8%	40/97 = 41.2%	53/97 = 54.6%	66/97 = 68.0%
CR				
Cut-off	< 0.52	< 0.57	< 0.75	< 1.84
Sensitivity	0.833	0.889	0.944	1
Specificity	1–0.186 = 0.814	1–0.268 = 0.732	1–0.443 = 0.557	1–0.979 = 0.021
PHPT sample	18/97 = 18.6%	26/97 = 26.8%	43/97 = 44.3%	95/97 = 97.9%
CCCR				
Cut-off	< 0.014	< 0.018	< 0.019	< 0.027
Sensitivity	0.833	0.889	0.944	1
Specificity	1–0.175 = 0.825	1–0.309 = 0.691	1–0.309 = 0.691	1–0.649 = 0.351

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	PHPT sample 17/97 = 17.5% 30/97 = 30.9% 30/97 = 30.9% 63/97 = 64.9% Overlap performance analysis disclosed that the CCCR included fewer patients with PHPT together with the FHH patients than the other two variables at different cut-off points. The overlap performance analyses for the three variables of renal calcium handling using fixed FHH sample sizes showed that to sample 100% of all patients with FHH (diagnostic sensitivity = 1), a cut-off point of < 0.027 should be used for CCCR, < 1.84 mmol/mmol for CR and < 9.7 mmol/24-hour for CE. The resulting diagnostic specificities would be 0.351, 0.021 and 0.320, respectively. This means that 64.9%, 97.9% and 68.0%, respectively, of the PHPT patients would be sampled together with the FHH patients. The co-sampling of PHPT patients is significantly lower when using the CCCR or the CE compared to the CR, with 2 P-values of < 0.01 (CCCR vs. CR) and < 0.01 (CE vs. CR). However, the co-sampling of PHPT patients did not differ significantly between the CCCR and the CE, 2P= 0.64 (CCCR vs. CE). Results showed that a decrease in the percentage of effectively sampled FHH patients would result in a lower diagnostic sensitivity and fewer co-sampled PHPT patients. In the case of 95% efficacy for FHH, the CCCR did not sample significantly fewer PHPT patients than the CE (2P = 0.051, CCCR vs. CE) or the CR (2P= 0.053, CCCR vs.CR). When CR and the CE compared with each other (2P = 0.989), there was no significant difference. At nearly all fixed FHH sample sizes, CCCR performed better than CR and CE in co-sampling fewer PHPT patients. However, a cut-off point of CCCR < 0.01 for FHH without subsequent CASR gene analysis would sample only 65% of the FHH patients and misclassify 4% of the PHPT patients as having FHH. It would leave 33% of the PHPT patients with CCCR between 0.010 and 0.020, and 35% of the FHH patients undiagnosed due to a CCCR ≥0.010.
Source of funding	Not stated
Limitations	Indirectness: the included population was with a confirmed diagnosis of PHPT
Comments	Most of the patients in the study had adenoma, not hyperplasia, as seen in some cases of FHH.