1. **J Clin Endocrinol Metab. 2022 Jan 1;107(1):e95-e105. doi: 10.1210/clinem/dgab623.**

Interrelationships Between Sclerostin, Secondary Hyperparathyroidism, and Bone Metabolism in Patients on Hemodialysis.

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CONTEXT: Sclerostin is an osteocyte-derived inhibitor of bone formation and is increased in kidney failure, but its role in the pathogenesis of renal bone disease remains unknown.

OBJECTIVE: We aimed to explore the association of serum sclerostin with bone metabolism in patients undergoing hemodialysis, with a particular focus on parathyroid hormone (PTH)-dependent and PTH-independent pathways.

METHODS: This cross-sectional and prospective cohort study included 654 patients undergoing hemodialysis at 10 facilities in Japan. We employed multivariable linear regression to explore whether sclerostin levels were associated with metacarpal bone mineral density (BMD), intact PTH, bone alkaline phosphatase (BAP), and tartrate-resistant acid phosphatase-5b (TRACP-5b). We employed mediation analyses to explore whether and to what extent the association of PTH with bone turnover markers is mediated by sclerostin. We also compared sclerostin levels between patients with and without previous or incident fractures.

RESULTS: The median sclerostin level in hemodialysis patients was 3- to 4-fold higher than that in healthy individuals. Higher sclerostin levels were associated with higher metacarpal BMD and lower levels of intact PTH, BAP, and TRACP-5b. However, the relationships of sclerostin with bone turnover markers were substantially attenuated after adjustment for PTH. Mediation analysis suggested that the effects of PTH on bone turnover markers were mainly direct rather than mediated by sclerostin. Sclerostin levels were not associated with previous or incident fractures.

CONCLUSION: These findings suggest that in patients undergoing dialysis, sclerostin has only a limited role in bone metabolism and may not mediate the effect of PTH on bone turnover.

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2. **Ann Surg. 2021 Oct 1;274(4):674-679. doi: 10.1097/SLA.0000000000005059.**
Outcomes of Subtotal Parathyroidectomy Versus Total Parathyroidectomy With Autotransplantation for Tertiary Hyperparathyroidism: Multi-institutional Study.
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OBJECTIVES: Due to the paucity of data and controversy regarding the preferred surgical approach for managing tertiary HPT, we sought to investigate the outcomes of different surgical approaches in managing this challenging disease.
METHODS: We performed a multi-center retrospective study to include patients with tertiary HPT who underwent STPX or total parathyroidectomy with autotransplantation (TPX-A).
RESULTS: One hundred five patients had kidney transplant, and 43 were on dialysis. In the kidney transplant group, 61 patients underwent STPX, and 44 for TPX-A. Patients' demographics were not significantly different (48.61 ± 9.31 vs 47.95 ± 12.73 years, P = 0.759. The postoperative follow-up showed that the TPX-A cohort had a higher rate of hypoparathyroidism (N = 20, 45.45%) versus (N = 14, 22.95%) with the STPX cohort (P = 0.013). The cure among the TPX-A cohorts (84.09%) over the STPX cohort (73.77%) (P = 0.153). The long-term follow-up showed that the rate of developing temporary (N = 16, 41.03%) or permanent (N = 8, 20.51%) hypoparathyroidism was significantly higher among patients who underwent TPX-A over the patients who underwent STPX (N = 7, 17.95%), and (N = 4, 10.26%), respectively (P = 0.012). There was no statistical difference between the persistence (N = 3, 7.69%) or the recurrence (N = 2, 5.13%) of the HPT in the TPX-A cohort and the STPX cohort (N = 2, 5.13%). (N = 4, 10.26%), respectively, P = 0.644.
CONCLUSIONS: To our knowledge, this is the largest multi-center study that compared different approaches for managing tertiary HPT. Showing that STPX is the better modality in patients diagnosed with tertiary HPT and had kidney transplants avoiding the risk of hypoparathyroidism.

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Conflict of interest statement: The authors report no conflicts of interest.

3. **J Clin Endocrinol Metab. 2022 Jan 1;107(1):e165-e177. doi: 10.1210/clinem/dgab622.**

Age, American Thyroid Association Risk Group, and Response to Therapy Are Prognostic Factors in Children With Differentiated Thyroid Cancer.

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Comment in
J Clin Endocrinol Metab. 2021 Oct 05;:

CONTEXT: Against the background of increasing incidence, pediatric differentiated thyroid carcinoma (DTC) frequently presents with advanced disease and high recurrence rates while prognosis remains excellent.
BACKGROUND: We investigated the use of a pediatric classification and an adult response to therapy risk stratification for pediatric DTC patients and their implications for adaptation of treatment and follow-up.
METHODS: Data from patients aged <18 years with a diagnosis of primary DTC, registered with the German Pediatric Oncology Hematology-Malignant Endocrine Tumor registry since 1995, were analyzed. For risk prediction, patients were retrospectively assigned to the American Thyroid Association (ATA) risk groups and evaluated for response to therapy.
RESULTS: By October 2019, 354 patients with DTC had been reported (median age at diagnosis 13.7 years, range 3.6-17.9) with lymph node and distant metastases in 74.3% and 24.5%. Mean follow-up was 4.1 years (range 0-20.6). Ten-year overall and event-free survival (EFS) rates were 98.9% and 78.1%. EFS was impaired for patients with lymph node and distant metastases ($P < .001$), positive postoperative thyroglobulin ($P = .006$), incomplete resection ($P = .002$), sequential surgeries to achieve total thyroidectomy ($P = .042$), invasion of capsule ($P < .001$) and lymph vessels ($P = .005$), infiltration of surrounding soft tissues ($P < .001$), tumor multifocality ($P < .001$), ATA intermediate- and high-risk group ($P < .001$), and age <10 years ($P < .001$). Multivariate analysis revealed age <10 years at diagnosis, ATA high-risk level, and poor response to therapy as significant negative prognostic factors for EFS.
CONCLUSION: Age, ATA risk group, and response to therapy emerged as significant prognostic factors for EFS in pediatric patients with DTC, requiring risk-adapted individualized therapy and follow-up.

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PMID: 34415989

4. **J Clin Endocrinol Metab. 2022 Jan 18;107(2):e612-e618. doi: 10.1210/clinem/dgab676.**

Serum Phosphate: A Neglected Test in the Clinical Management of Primary Hyperparathyroidism.

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Comment in
J Clin Endocrinol Metab. 2021 Oct 28;:

BACKGROUND: Although the inverse correlation between serum PTH and phosphate (P) levels in patients with primary hyperparathyroidism (PHPT) is well known, the relationship between P levels and the clinical picture of the disease has not been well investigated. This was thus the aim of this paper.
PATIENTS: A total of 472 consecutive patients with PHPT attending our center were retrospectively evaluated at diagnosis.
RESULTS: P levels lower than 2.5 mg/dL (HypoP) were found in 198/472 patients (41.9%). HypoP was mild (2-2.5 mg/dL), moderate (1-1.9 mg/dL), and severe (<1 mg/dL) in 168 (84.9%), 30 (15.1%), and 0 cases, respectively. P levels were lower in males than females. Patients with more severe bone density impairment at the radial (but not the vertebral or femoral) site had P levels significantly lower than other patients. PHPT severity was worse in HypoP patients, both clinically (higher prevalence of renal stones, but not of osteoporosis) and biochemically (higher serum calcium and PTH levels). All patients in the moderate HypoP group were either symptomatic or asymptomatic reaching surgical indication according to the latest guidelines.
CONCLUSIONS: We observed a relationship between P levels and biochemical and clinical features of PHPT severity. In asymptomatic PHPT patients, even moderate HypoP is predictive of surgical indication, regardless of age and hypercalcemia severity.

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PMID: 34519347

5. **Minerva Endocrinol (Torino). 2021 Sep 16. doi: 10.23736/S2724-6507.21.03393-9. Online ahead of print.**

A predictive model and survival analysis for local recurrence in differentiated thyroid carcinoma.

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BACKGROUND: Local recurrence (LR) is associated with poor outcome in patients with differentiated thyroid carcinoma (DTC). The aim of this study was to explore potential risk factors for LR and build a predictive model.
METHODS: The medical data of patients who were diagnosed with DTC after initial surgery in three medical centers (2000-2018) were reviewed. Detailed clinicopathologic characteristics of all cases were identified.
RESULTS: Multiple factors, including extrathyroidal extension (ETE), histology, symptoms, multifocality, and tumor diameter, were significantly different between the LR and no evidence of disease groups in univariate and multivariate analysis ($P < 0.05$). Tumor diameter, symptoms, and ETE made the greatest contributions to prognosis according to decision tree analysis and random forest algorithm. The predictive model constructed from these data achieved 98.7% accuracy of classification. A five-fold cross-validation confirmed that the model has 84.7%-89.7% accuracy of classification. Additionally, symptoms and ETE were independent predictors on survival analysis ($P < 0.05$).
CONCLUSIONS: This study optimized the weight of risk factors, including tumor diameter, symptoms, ETE, and multifocality, in predicting LR in patients with DTC. Our predictive model provides a strong tool to distinguish between high-risk and low-risk DTC.
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PMID: 34528778

6. **J Clin Endocrinol Metab. 2022 Jan 18;107(2):e604-e611. doi: 10.1210/clinem/dgab691.**
Low-Iodine Diet of 4 Days Is Sufficient Preparation for 131I Therapy in Differentiated Thyroid Cancer Patients.
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CONTEXT: No consensus exists about the optimal duration of the low-iodine diet (LID) in the preparation of 131I therapy in differentiated thyroid cancer (DTC) patients.
OBJECTIVE: This work aimed to investigate if a LID of 4 days is enough to achieve adequate iodine depletion in preparation for 131I therapy. In addition, the nutritional status of the LID was evaluated.
METHODS: In this prospective study, 65 DTC patients treated at 2 university medical centers were included between 2018 and 2021. The patients collected 24-hour urine on days 4 and 7 of the LID and kept a food diary before and during the LID. The primary outcome was the difference between the 24-hour urinary iodine excretion (UIE) on both days.
RESULTS: The median 24-hour UIE on days 4 and 7 of the LID were not significantly different (36.1 mcg [interquartile range, 25.4-51.2 mcg] and 36.5 mcg [interquartile range, 23.9-47.7 mcg], respectively, P = .43). On day 4 of the LID, 72.1% of the DTC patients were adequately prepared (24-hour UIE < 50 mcg), and 82.0% of the DTC patients on day 7 (P = .18). Compared to the self-reported regular diet, DTC patients showed a significantly (P < .01) lower percentage of nutrient intake (calories, protein, calcium, iodine, and water) during the LID.
CONCLUSION: The 24-hour UIE on day 4 of the LID did not differ from day 7, and therefore shortening the LID from 7 to 4 days seems justified to prepare DTC patients for 131I therapy in areas with sufficient iodine intake and may be beneficial to maintain a sufficient nutritional intake during DTC treatment.

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PMCID: PMC8764339
PMID: 34534327

7. **J Clin Endocrinol Metab. 2022 Jan 18;107(2):474-490. doi: 10.1210/clinem/dgab480.**
METTL3-Induced miR-222-3p Upregulation Inhibits STK4 and Promotes the Malignant Behaviors of Thyroid Carcinoma Cells.
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CONTEXT: Abnormally high expression of N6-methyladenosine (m6A) methyltransferase-like 3 (METTL3) has been implied to accompany thyroid carcinoma (TC) development.
OBJECTIVE: This study aimed to explore the protumorigenic role and downstream signaling axis of METTL3 in TC.
METHODS: This study was conducted at the Sun Yat-Sen Memorial Hospital Sun Yat-Sen University. METTL3 and miR-222-3p were overexpressed or downregulated in

TC cells. Tumor and adjacent normal tissues were collected from 80 patients (19 men and 60 women, aged 30-70 years) with a pathological diagnosis of TC from January 2012 to January 2015. Cells were classified and subjected to different treatments. The expression of METTL3 was validated in TC tissues and cell lines. In functional studies, METTL3 and miR-222-3p were overexpressed or downregulated in TC cells to evaluate their effects on malignant behaviors, which were subsequently verified by xenografts in nude mice.
RESULTS: The expression of METTL3 was elevated in TC, correlating with poor prognosis of TC patients. Heightened METTL3 expression accelerated malignant behaviors of TC cells. Mechanistically, METTL3 stimulated miR-222-3p expression by mediating the m6A modification of pri-miR-222-3p. miR-222-3p targeted and inversely regulated serine/threonine stress kinase 4 (STK4). Knockdown of METTL3 augmented STK4 expression by downregulating miR-222-3p, thereby suppressing the malignant behaviors of TC cells as well as tumor growth and lung metastasis in nude mice.
CONCLUSION: Silencing METTL3 suppresses miR-222-3p expression and thus stimulates STK4 expression, thereby repressing the malignancy and metastasis of TC.

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PMID: 34562008

8. **J Clin Endocrinol Metab. 2021 Oct 5:dgab711. doi: 10.1210/clinem/dgab711. Online ahead of print.**
"Young children are not the same as adolescents when it comes to treating thyroid cancer".
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Comment on
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PMID: 34610121

9. **World J Surg. 2022 Jan;46(1):104-111. doi: 10.1007/s00268-021-06337-4. Epub 2021 Oct 11.**
Impact of Extent of Surgery on Long-Term Prognosis of Follicular Thyroid Carcinoma Without Extrathyroidal Extension and Distant Metastasis.
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AIM: To analyze the effect of total thyroidectomy (TT) and thyroid lobectomy (LT) on the long-term prognosis of follicular thyroid carcinoma (FTC) without extrathyroidal extension and distant metastasis and to clarify whether the tumor size (≤ 40 mm vs. > 40 mm) has an important impact on the extent of surgery.
METHODS: Data on FTC patients without extrathyroidal extension and distant metastasis treated with either TT or LT between 1998 and 2016 were extracted from the Surveillance, Epidemiology, and End Results Database. Propensity score matching was performed to minimize impact of selection bias and potential confounding. Kaplan-Meier curves and Cox regression analysis were conducted to assess the impact of the extent of surgery on disease-specific survival (DSS).
RESULTS: A total of 8435 patients were identified. The DSS after LT were 100%, 98.3%, and 97.6% at 5, 10, and 15 years, respectively, compared with those seen after TT of 99.3%, 97.9%, and 96.6%. The difference between the two groups is not statistically significant (p = 0.083). Similar results were observed in cohorts after adjusting for baseline covariates. There was also similar prognosis between LT and TT in patients with tumors size ≤ 40 mm or > 40 mm.
CONCLUSIONS: For patients with FTC of any size without extrathyroidal extension and distant metastases at diagnosis, TT and LT confer equivalent DSS. Completion thyroidectomy after LT may be not necessary unless patients relapse; however, recurrence rates and development of metastases are not evaluated in this study.

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10. **J Clin Endocrinol Metab. 2021 Oct 19:dgab731. doi: 10.1210/clinem/dgab731. Online ahead of print.**
A Randomized Study of Lenvatinib 18 mg Vs 24 mg in Patients With Radioiodine-Refractory Differentiated Thyroid Cancer.
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BACKGROUND: Lenvatinib is a multikinase inhibitor approved to treat radioiodine-refractory differentiated thyroid cancer (RR-DTC) at a starting dose of 24 mg/day. This study explored, in a double-blinded fashion, whether a starting dose of 18 mg/day would provide comparable efficacy with reduced toxicity.
METHODS: Patients with RR-DTC were randomized to lenvatinib 24 mg/day or 18 mg/day. The primary efficacy endpoint was objective response rate as of Week 24 (ORRwk24); odds ratio noninferiority margin: 0.4. The primary safety endpoint was frequency of grade ≥3 treatment-emergent adverse events (TEAEs) as of Week 24. Tumors were assessed using RECIST v1.1. TEAEs were monitored and recorded.
RESULTS: The ORRwk24 was 57.3% (95% confidence interval [CI] 46.1-68.5) in the lenvatinib 24-mg arm and 40.3% (95% CI 29.3-51.2) in the lenvatinib 18-mg arm, with an odds ratio [18/24 mg] of 0.50 (95% CI 0.26-0.96). As of Week 24, the rates of TEAEs grade ≥3 were 61.3% in the lenvatinib 24-mg arm and 57.1% in the lenvatinib 18-mg arm, a difference of -4.2% (95% CI -19.8-11.4).
CONCLUSION: A starting dose of lenvatinib 18 mg/day did not demonstrate noninferiority compared with a starting dose of 24 mg/day as assessed by ORRwk24 in patients with RR-DTC. The results represent a clinically meaningful difference in ORRwk24. The safety profile was comparable, with no clinically relevant difference between arms. These results support the continued use of the approved starting dose of lenvatinib 24 mg/day in patients with RR-DTC and adjusting the dose as necessary.

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PMID: 34664662

11. **J Clin Endocrinol Metab. 2021 Oct 20:dgab685. doi: 10.1210/clinem/dgab685. Online ahead of print.**
"Cutting the Support" to improve treatment efficacy in thyroid cancer by targeting tumor microenvironment.
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Comment on
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PMID: 34668970

12. **J Clin Endocrinol Metab. 2021 Oct 28:dgab768. doi: 10.1210/clinem/dgab768. Online ahead of print.**
Is Moderate Hypophosphatemia a New Indication for Surgery in Asymptomatic Primary Hyperparathyroidism?
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Comment on
J Clin Endocrinol Metab. 2021 Sep 14;:
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PMID: 34718624

13. **J Clin Endocrinol Metab. 2021 Oct 28:dgab776. doi: 10.1210/clinem/dgab776. Online ahead of print.**
Increased risk of type 2 diabetes in patients with thyroid cancer after thyroidectomy: A nationwide cohort study.
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CONTEXT: Abnormal thyroid function after thyroidectomy and subsequent thyroid-stimulating hormone suppression can have detrimental effects on glucose homeostasis in thyroid cancer patients.
OBJECTIVE: To investigate whether thyroidectomy increases the risk of type 2 diabetes in thyroid cancer patients and to explore the association between levothyroxine dosage and type 2 diabetes risk.
DESIGN: A retrospective population-based cohort study.
SETTING: The Korean National Health Insurance database.
PARTICIPANTS: We included 36,377 thyroid cancer patients without known diabetes who underwent thyroidectomy between 2004 and 2013. Matched non-thyroid cancer subjects were selected using 1:1 propensity score matching.
MAIN OUTCOME MEASURE: Newly developed type 2 diabetes mellitus.
RESULTS: Thyroid cancer patients who underwent thyroidectomy had a higher risk

of developing type 2 diabetes mellitus than the matched controls (hazard ratio [HR]: 1.43, 95% confidence interval [CI]: 1.39-1.47). Among thyroid cancer patients, when the second quartile group (in terms of the mean levothyroxine dosage; 101-127 μg/day) was considered the reference group, the risk of type 2 diabetes mellitus increased in the first quartile (<101 μg/day; HR: 1.45, 95% CI: 1.36-1.54) and fourth quartile groups (≥150 μg/day; HR: 1.37, 95% CI: 1.29-1.45); meanwhile, the risk decreased in the third quartile group (128-149 μg/day; HR: 0.91, 95% CI: 0.85-0.97).
CONCLUSION: Thyroid cancer patients who underwent thyroidectomy were more likely to develop type 2 diabetes mellitus than the matched controls. There was a U-shaped dose-dependent relationship between the levothyroxine dosage and type 2 diabetes mellitus risk.

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PMID: 34718625

14. **J Clin Endocrinol Metab. 2021 Oct 26:dgab781. doi: 10.1210/clinem/dgab781. Online ahead of print.**
Physician specialties involved in thyroid cancer diagnosis and treatment: Implications for improving healthcare disparities.
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CONTEXT: Little is known about provider specialties involved in thyroid cancer diagnosis and management.
OBJECTIVE: Characterize providers involved in diagnosing and treating thyroid cancer.
DESIGN/SETTING/PARTICIPANTS: We surveyed patients with differentiated thyroid cancer from the Georgia and Los Angeles County SEER registries (N=2632, 63% response rate). Patients identified their primary care physicians (PCP), who were also surveyed (N=162, 56% response rate).
MAIN OUTCOME MEASURES: 1) patient-reported provider involvement (endocrinologist, surgeon, PCP) at diagnosis and treatment; 2) PCP-reported involvement (more vs. less) and comfort (more vs. less) with discussing diagnosis and treatment.
RESULTS: Among thyroid cancer patients, 40.6% reported being informed of their diagnosis by their surgeon, 37.9% by their endocrinologist, and 13.5% by their PCP. Patients reported discussing their treatment with their surgeon (71.7%), endocrinologist (69.6%), and PCP (33.3%). Physician specialty involvement in diagnosis and treatment varied by patient race/ethnicity and age. For example,

Hispanic patients (vs. non-Hispanic White) were more likely to report their PCP informed them of their diagnosis (OR: 1.68, 95%CI: 1.24-2.27). Patients ≥65years (vs. <45years) were more likely to discuss treatment with their PCP (OR: 1.59; 95%CI 1.22-2.08). Although 74% of PCPs reported discussing their patients' diagnosis and 62% their treatment, only 66% and 48% respectively were comfortable doing so.
CONCLUSIONS: PCPs were involved in thyroid cancer diagnosis and treatment and their involvement was greater among older patients and patients of minority race/ethnicity . This suggests an opportunity to leverage PCP involvement in thyroid cancer management to improve health and quality of care outcomes for vulnerable patients.

DOI: 10.1210/clinem/dgab781
PMID: 34718629

15. **J Clin Endocrinol Metab. 2021 Nov 9:dgab819. doi: 10.1210/clinem/dgab819. Online ahead of print.**
CAR-T cells Targeting TSHR Demonstrate Safety and Potent Preclinical Activity Against Differentiated Thyroid Cancer.
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BACKGROUND: Chimeric antigen receptor T cells （CAR-T） have been demonstrated remarkable efficacy in hematological cancers but have not yet translated in treating solid tumors. The significant hurdles limiting CAR-T therapy were due to a paucity of differentially expressed cell surface molecules on solid tumors that can be safely targeted. Here, we present thyroid-stimulating hormone receptor (TSHR) as a putative target for CAR-T therapy of differentiated thyroid cancer (DTC).

METHODS: We undertook a large-scale screen on thyroid cancer tissues and multiple internal organs through bioinformatical analysis and immunohistochemistry to date TSHR expression. Using three previously described mAb, we generate three third-generation CAR-Ts. We tested anti-TSHR CAR-T in vitro activity by T-cell function and killing assay. Then we tested pre-clinical therapeutical efficacy in a xenograft mouse model of DTC and analyzed mice's physical conditions and histological abnormalities to evaluate anti-TSHR CAR-T's safety.
RESULTS: TSHR is highly and homogeneously expressed on 90.8% (138/152) of papillary thyroid cancer, 89.2% (33/37) of follicular thyroid cancer, 78.2% (18/23) of the cervical lymph node metastases, and 86.7% of RAI-R diseases. We developed three novel anti-TSHR CAR-T from mAb M22, K1-18, and K1-70; all three CAR-Ts mediate significant anti-tumor activity in vitro. Among these, we demonstrate that K1-70 CAR-T can have therapeutical efficacy in vivo, and no apparent toxicity has been observed.
CONCLUSION: TSHR is a latent target antigen of CAR-T therapy for DTC. Anti-TSHR CAR-T could represent a therapeutic option for patients with local-regional relapsed or distant metastases of thyroid cancer and should be tested in carefully designed clinical trials.

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PMID: 34751400

16. **J Clin Endocrinol Metab. 2021 Nov 9:dgab820. doi: 10.1210/clinem/dgab820. Online ahead of print.**

Primary Hyperparathyroidism is Associated with Shorter QTc Intervals, but not Arrhythmia.

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CONTEXT: Primary hyperparathyroidism (PHPT) is associated with subclinical cardiovascular disease, but data regarding cardiac conduction abnormalities are limited.
OBJECTIVE AND DESIGN: Retrospective cross-sectional comparison of cardiac conduction in patients with PHPT or thyroid disease (TD).
PARTICIPANTS AND SETTING: Patients ≥40 years old who underwent parathyroidectomy or thyroidectomy at a single tertiary institution from 2013-2018.
METHODS AND OUTCOMES: Demographics and pre-operative electrocardiogram (EKG) parameters were compared using the Mann-Whitney U, Chi Square tests, and linear regression.
RESULTS: A total of 1,242 patients were included: 49.8% PHPT (n=619) and 50.2% TD (n=623). Median age was 60.5 years (IQR 53.6-67.9). Compared to controls,

PHPT patients had higher median serum calcium [10.7 mg/dL (IQR 10.4-11.1) vs 9.5 mg/dL (IQR 9.3-9.8), p<0.001] as expected, as well as, a higher prevalence of hyperlipidemia (49% vs 36%, p<0.001) and hypertension (50.1% vs 42.2%, p<0.01). Based on EKG, there was no difference in PR interval or the prevalence of arrhythmia, atrioventricular block, ST segment/T wave changes, premature ventricular complexes, right bundle branch block or left bundle branch block after adjusting for covariates. The PHPT group had a lower mean corrected QT interval (414ms (+/- 24) vs 422ms (+/- 24), p<0.01), adjusted for covariates. Serum calcium predicted QTc independently of age, sex, and other covariates. CONCLUSIONS: In the largest study to date, PHPT patients had shorter QTc intervals compared to TD controls, but no increased prevalence of arrhythmia based on pre-operative EKG.

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PMID: 34752632

17. **J Clin Endocrinol Metab. 2021 Nov 14:dgab833. doi: 10.1210/clinem/dgab833. Online ahead of print.**
Letter to the Editor from [Shijie Yang]: (Efficacy and Safety of Thermal Ablation for Solitary T1bN0M0 Papillary Thyroid Carcinoma: A Multicenter Study).
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DOI: 10.1210/clinem/dgab833
PMID: 34791303

18. **J Clin Endocrinol Metab. 2021 Nov 16:dgab836. doi: 10.1210/clinem/dgab836. Online ahead of print.**
Recurrence of Papillary Thyroid Cancer: A Systematic Appraisal of Risk Factors.
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BACKGROUND: Thyroid cancer recurrence is associated with increased mortality and adverse outcomes. Recurrence risk is currently predicted using clinical tools, often restaging patients after treatment. Detailed understanding of recurrence risk at disease-onset could lead to personalised and improved patient care.

OBJECTIVE: To perform a comprehensive bioinformatic and experimental analysis of 3 levels of genetic change (mRNA, microRNA, and somatic mutation) apparent in recurrent tumours and construct a new combinatorial prognostic risk model.
METHODS: We analysed The Cancer Genome Atlas data (TCGA) to identify differentially expressed genes (mRNA/microRNA) in 46 recurrent versus 455 non-recurrent thyroid tumours. Two exonic mutational pipelines were used to identify somatic mutations. Functional gene analysis was performed in cell-based assays in multiple thyroid cell lines. The prognostic value of genes was evaluated with TCGA datasets.
RESULTS: We identified a total of 128 new potential biomarkers associated with recurrence, including 40 mRNAs, 39 miRNAs and 59 genetic variants. Among differentially expressed genes, modulation of FN1, ITGα3 and MET had a significant impact on thyroid cancer cell migration. Similarly, ablation of miR-486 and miR-1179 significantly increased migration of TPC-1 and SW1736 cells. We further utilised genes with a validated functional role and identified a 5 gene risk score classifier as an independent predictor of thyroid cancer recurrence.
CONCLUSIONS: Our newly proposed risk model based on combinatorial mRNA and microRNA expression has potential clinical utility as a prognostic indicator of recurrence. These findings should facilitate earlier prediction of recurrence with implications for improving patient outcome by tailoring treatment to disease risk and increasing post-treatment surveillance.

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PMID: 34791326

19. **J Clin Endocrinol Metab. 2021 Nov 14:dgab835. doi: 10.1210/clinem/dgab835. Online ahead of print.**

Response to Letter to the Editor from [Shijie Yang]: (Efficacy and Safety of Thermal Ablation for Solitary T1bN0M0 Papillary Thyroid Carcinoma: A Multicenter Study).

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PMID: 34791335

20. **J Clin Endocrinol Metab. 2021 Dec 6:dgab875. doi: 10.1210/clinem/dgab875. Online ahead of print.**

Identifying and addressing Health disparities in Thyroid Cancer Care.

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DOI: 10.1210/clinem/dgab875

PMID: 34871424

21. **J Clin Endocrinol Metab. 2021 Nov 23:dgab851. doi: 10.1210/clinem/dgab851. Online ahead of print.**
Characterization of Subtypes of BRAF-Mutant Papillary Thyroid Cancer Defined by Their Thyroid Differentiation Score.
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CONTEXT: The BRAFV600E mutation has been associated with more advanced clinical stage in papillary thyroid cancer (PTC) and decreased responsiveness to radioiodine (RAI). However, some BRAF mutant PTCs respond to RAI and have an indolent clinical behavior suggesting the presence of different subtypes of BRAF mutant tumors with distinct prognosis.
OBJECTIVE: To characterize the molecular and clinical features of 2 subtypes of BRAF-mutant PTCs defined by their degree of expression of iodine metabolism genes.
DESIGN: 227 BRAF-mutant PTCs from the Cancer Genome Atlas Thyroid Cancer study were divided into 2 subgroups based on their thyroid differentiation score (TDS): BRAF-TDShi and BRAF-TDSlo. Demographic, clinico-pathological, and molecular characteristics of the 2 subgroups were compared.
RESULTS: Compared to BRAF-TDShi tumors (17%), BRAF-TDSlo tumors (83%) were more frequent in blacks and Hispanics (6% vs 0%, P = 0.035 and 12% vs 0%, P = 0.05, respectively), they were larger (2.95 ± 1.7 vs 2.03 ± 1.5, P = 0.002), with more tumor-involved lymph nodes (3.9 ± 5.8 vs 2.0 ± 4.2, P = 0.042), and a higher frequency of distant metastases (3% vs 0%, P = 0.043). Gene set enrichment analysis showed positive enrichment for RAS signatures in the BRAF-TDShi cohort, with corresponding reciprocal changes in the BRAF-TDSlo group. Several microRNAs (miRs) targeting nodes in the transforming growth factor β (TGFβ)-SMAD pathway, miR-204, miR-205, and miR-144, were overexpressed in the BRAF-TDShi group. In the subset with follow-up data, BRAF-TDShi tumors had higher complete responses to therapy (94% vs 57%, P < 0.01) than BRAF-TDSlo tumors.
CONCLUSION: Enrichment for RAS signatures, key genes involved in cell polarity and specific miRs targeting the TGFβ-SMAD pathway define 2 subtypes of BRAF-mutant PTCs with distinct clinical characteristics and prognosis.

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PMID: 34897468

22. **J Clin Endocrinol Metab. 2021 Dec 18:dgab907. doi: 10.1210/clinem/dgab907. Online ahead of print.**

Long-Term Efficacy of Ethanol Ablation as Treatment of Metastatic Lymph Nodes from Papillary Thyroid Carcinoma.

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CONTEXT: Ethanol ablation (EA) is considered an alternative to surgery for metastatic lymph nodes from papillary thyroid carcinoma (PTC) in selected patients.
OBJECTIVE: The aim of this study was to evaluate the long-term efficacy and safety of this particular treatment.
DESIGN AND SETTING: Adult patients with PTC who had received EA in lymph node metastasis at a tertiary referral center, and were included in a published study from 2011, were invited to participate in this follow-up study.
METHODS: Radiologic- and medical history were reviewed. Ultrasound examination of the neck was performed by radiologists, and clinical examination was performed by an endocrine surgeon. Response was reported according to predefined criteria for satisfactory EA-treatment. Adverse events associated with EA were evaluated. Cause of death was reported for deceased patients.
RESULTS: From the 2011-study 51 of 63 patients were included. Forty-four patients were reexamined (67/109 lesions) and 7 patients were deceased. Median follow-up time from primary surgery was 14.5 years. Median follow-up from the latest performed EA in the 2011 study was 11.3 years. Local control was permanently achieved in most patients (80 %). Recurrence within an ablated node was registered in 13 metastases in 10 patients. Seven of these patients also had recurrent disease elsewhere in the neck. No major side effects were reported.
CONCLUSION: EA is a minimally invasive procedure with a low risk of complications. Our data suggest that EA is a safe and efficient treatment, providing excellent results for a large group of patients also in the long term.

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PMID: 34922379

23. **J Clin Endocrinol Metab. 2021 Dec 20:dgab906. doi: 10.1210/clinem/dgab906. Online ahead of print.**

Pre-existing or concomitant thyroiditis in papillary thyroid cancer: Something more than a mere issue of timing?

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Comment on
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24. **J Clin Endocrinol Metab. 2021 Dec 30:dgab929. doi: 10.1210/clinem/dgab929. Online ahead of print.**

GCM2 Variants in Familial and Multiglandular Primary Hyperparathyroidism.

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CONTEXT: Multiglandular and familial parathyroid disease constitute important fractions of primary hyperparathyroidism (PHPT). Germline missense variants of GCM2, a regulator of parathyroid development, were observed in familial isolated hyperparathyroidism (FIHP) and sporadic PHPT. However, as these previously-reported GCM2 variants occur at relatively high frequencies in the population, understanding their potential clinical utility will require both additional penetrance data and functional evidence relevant to tumorigenicity.
OBJECTIVE: Determine the frequency of GCM2 variants-of-interest among patients with sporadic multigland or familial parathyroid disease, and assess their penetrance.

DESIGN AND PATIENTS: DNA encoding PHPT-associated GCM2 germline-variants were PCR-amplified and sequenced from 107 patients with either sporadic multigland or suspected/confirmed familial parathyroid tumors.
RESULTS: GCM2 variants were observed in 9 of 107 cases (8.4%): Y282D in 4 patients (6.3%) with sporadic multigland disease; Y394S in 2 patients (11.1%) with familial PHPT and three (4.8%) with sporadic multigland disease. Compared with the general population, Y282D was enriched 5.9-fold in multigland disease but its penetrance was very low (0.02%). Y394S was enriched 79-fold in sporadic multigland disease and 93-fold in familial PHPT, but its penetrance was low (1.33%, 1.04% respectively).
CONCLUSIONS: Observed in vitro activating GCM2 variant alleles are significantly overrepresented in PHPT patients with multiglandular or familial disease compared with the general population, yet penetrance values are very low i.e. most individuals with these variants in the population have a very low risk of developing PHPT. The potential clinical utility of detecting these GCM2 variants requires further investigation, including assessing their possible role as pathogenic/low-penetrance alleles.

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PMID: 34967908

25. **World J Surg. 2022 Jan 10. doi: 10.1007/s00268-021-06422-8. Online ahead of print.**
Comparison of Parathyroid Autofluorescence Signals in Different Types of Hyperparathyroidism.
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BACKGROUND: There are scant data in the literature regarding whether parathyroid autofluorescence (AF) signal patterns vary based on the etiology of hyperparathyroidism. The aim of this study was to compare AF signals of parathyroid glands across different etiologies of hyperparathyroidism.
METHODS: As a prospective institutional review board-approved study between 2016 and 2019, AF intensities and heterogeneity indexes (HIs) of parathyroid glands in patients who underwent parathyroidectomy using AF were calculated and compared using Chi-square, Kruskal Wallis, Mann Whitney U, and logistic regression tests.
RESULTS: Of the total of 183 patients, 127 patients had sporadic classic primary hyperparathyroidism, 30 patients had sporadic normohormonal primary hyperparathyroidism, 10 patients had sporadic normocalcemic primary hyperparathyroidism, 12 patients had tertiary hyperparathyroidism, and 4 patients had familial primary hyperparathyroidism related to multiple endocrine neoplasia (MEN) 2A. There were no statistical differences in AF signals of abnormal parathyroid glands in classic, normohormonal or normocalcemic sporadic

hyperparathyroidism. Parathyroid glands in patients with tertiary hyperparathyroidism were similar in intensity, but more homogenous compared to those in sporadic primary hyperparathyroidism.
CONCLUSIONS: The pattern of AF exhibited by abnormal parathyroid glands was similar across different spectrums of primary hyperparathyroidism, in accordance with observations in the literature. However, parathyroid glands in tertiary hyperparathyroidism were more homogeneous, despite exhibiting a similar intensity of AF compared to those in sporadic primary hyperparathyroidism. These differences should be kept in mind when using the AF pattern as an adjunct to visual assessment in parathyroid exploration.

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PMID: 35006327

26. **J Clin Endocrinol Metab. 2022 Jan 11:dgac009. doi: 10.1210/clinem/dgac009. Online ahead of print.**
Circulating MicroRNA Profiles as Potential Biomarkers for differentiated thyroid cancer recurrence.
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CONTEXT: Circulating microRNAs (miRNAs) are emerging biomarkers of thyroid cancer.
OBJECTIVE: This study sought to identify the profile of circulating miRNAs and its response to human recombinant TSH (rhTSH) in thyroid cancer patients with recurrent/persistent disease.
METHODS: We obtained serum samples from 30 patients with differentiated thyroid cancer, 14 with recurrent/persistent disease and 16 with complete remission. We used next generation sequencing to define the miRnomes along with a comprehensive qPCR validation using two different platforms. We made a transversal study by comparing serum miRNA profiles of patients with or without recurrent/persistent disease and a longitudinal study looking at differences before and after rhTSH stimulation. Selected miRNAs were then studied in human thyroid cancer cell lines TPC-1, FTC-133 and OCUT-2 in response to TSH

stimulation.
RESULTS: We could not demonstrate any consistent differences in serum profiles of known miRNAs between patients with and without recurrent/persistent disease or before and after rhTSH stimulation. However, our sequencing data revealed two putative novel miRNAs that rise with rhTSH stimulation in the serums of patients with recurrent/persistent disease. We further confirmed by qPCR the upregulation of these putative miRNAs both in serums and in TSH-stimulated cells. We also show miRNAs that are good candidates for housekeeping genes in the serum of patients independently of the levels of TSH.
CONCLUSIONS: The present study does not provide evidence that known miRNAs can be used as circulating markers for recurrence of thyroid cancer. However, we suggest that novel miRNA molecules may be related to thyroid cancer pathogenesis.

DOI: 10.1210/clinem/dgac009
PMID: 35022762

27. **J Clin Endocrinol Metab. 2022 Jan 14:dgac018. doi: 10.1210/clinem/dgac018. Online ahead of print.**
Efficacy of ethanol ablation in long-term local control of neck nodal metastases in adult papillary thyroid carcinoma.
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PMID: 35030635

28. **World J Surg. 2022 Jan 12. doi: 10.1007/s00268-022-06439-7. Online ahead of print.**
Parathyroidectomy Versus Cinacalcet for the Treatment of Secondary Hyperparathyroidism in Hemodialysis Patients.
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BACKGROUND: Secondary hyperparathyroidism in patients with end stage renal disease on dialysis is associated with bone pain and fractures in addition to cardiovascular morbidity. Cinacalcet is the most commonly used drug to treat such patients, but it has never been compared to surgery. The goal of this study is to compare the long-term outcomes and survival between cinacalcet and parathyroidectomy in the treatment of secondary hyperparathyroidism in

hemodialysis patients.
METHODS: Adult patients on hemodialysis who were treated with cinacalcet or parathyroidectomy in the United States Renal Data System were included. Patients treated with surgery (n = 2023) were compared using 1:1 propensity score matching ratio to a cohort of patients treated with cinacalcet. A Cox regression analysis was conducted to compare the overall mortality.
RESULTS: The propensity score matching successfully created two groups with similar demographics. Patients in the surgery group had a higher mean peak PTH level prior to therapy (2066.8 vs 1425.4, P < 0.001). No difference was observed in the development of new-onset coronary artery disease (7.7% vs 7.9%, P = 0.8) or cerebrovascular disease (7% vs 6.7%, P = 0.8). Surgical patients had a higher rate of pathologic fractures (27.8% vs 24.9%, P = 0.04). Survival analysis showed that patients undergoing surgery had a better 5-year survival (65.6% vs 57.8%) and were less likely to die within the study period (HR 0.77, 95% CI 0.7-0.85, P < 0.0001).
CONCLUSIONS: Patients on dialysis undergoing parathyroidectomy for the treatment of secondary hyperparathyroidism have a better overall survival than those treated with cinacalcet.

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