

conflict about youths' gender identity was reported by 40.1%, but was not associated with age of accessing care, types of providers seen, length of time accessing care, or age at first appointment. This research will help fill gaps in knowledge for health care providers about youth accessing gender affirming medical care, enhancing gender-affirming care and support for these youth and their parents/families.

Tumor Biology

TUMOR BIOLOGY: GENERAL, TUMORIGENESIS, PROGRESSION, AND METASTASIS

A Multi-Omics Analysis of Advanced Papillary Thyroid Cancer

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SAT-LB25

Molecular profiling of papillary thyroid carcinoma has largely been confined to exome sequencing of non-aggressive cancer.^{1,2} Canonical mutations in BRAF and RAS are significantly represented in thyroid tumors, but these mutations have not resulted in diagnostics and therapeutics for advanced disease. To broadly examine the molecular landscape of advanced disease, we conducted a multi-omic analysis of 34 cases of advanced papillary thyroid carcinoma, including patient-matched lymph node metastases, primary tumor, adjacent-normal thyroid and germline. Our genome-wide multi-omic analysis links the regions of activated chromatin with expressed transcripts and proteins, identifying regulatory elements at primary tumor and nodal metastases stages of thyroid cancer progression. Distal regulatory elements putatively upregulate expression of MAPK-pathway genes in both tumors and metastases (36 genes ($p=0.0057$) in tumors and 76 genes ($p=0.0011$) in metastases). Furthermore, tumors and metastases harbor accessible chromatin regions that appear to be bound by MAPK transcription factors, FOS and JUN (p -value $<10^{-150}$ for tumors and metastases). This study identifies regulatory elements that mediate MAPK activity in tumors and metastases of advanced papillary thyroid carcinoma and may ultimately lead to diagnostics and therapeutics that utilize advanced-thyroid-cancer-specific epigenetic targets. *References*

- Cancer Genome Atlas Research Network. Integrated genomic characterization of papillary thyroid carcinoma. *Cell*. 2014
- Masoodi T, et al. Whole-Exome Sequencing of Matched Primary and Metastatic Papillary Thyroid Cancer. *Thyroid*. 2020

Diabetes Mellitus and Glucose Metabolism

DIABETES COMPLICATIONS II

Euglycemic Diabetic Ketoacidosis in a Patient on Canagliflozin Presenting With Hypoglycemia

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MON-LB119

Background: Sodium glucose co-transporter 2 (SGLT-2) inhibitors are newer class of antihyperglycemics that cause reversible inhibition of the sodium-glucose cotransporters in the renal proximal tubules resulting in increased urinary glucose. Common side effects include yeast and urinary tract infections. The US Food and Drug Administration issued a safety warning pertaining to the development of diabetic ketoacidosis (DKA) with the use of SGLT2 inhibitors. The mechanisms by which SGLT2 inhibitors cause euglycemic DKA are unclear. SGLT2 inhibitors may lead to a decrease in either endogenous or exogenous insulin and an increase in glucagon production.¹ This insulin deficiency or resistance may be mild in Type 2 diabetics, however, preventing the profound spike in blood glucose seen in traditional DKA. Here, we report a case of euglycemic DKA in a patient on Canagliflozin who presented initially with hypoglycemia.

Clinical case: A 70 year old female presented with altered mental status for 1 day duration. Her past medical history is significant for type 2 Diabetes Mellitus, being managed on Canagliflozin, Glimepiride and Janumet. One week prior to admission she had lumbar spinal fusion surgery. Since then she has been feeling weak and tired with poor oral intake, but continued to use her medications. Initial laboratory findings showed blood glucose of 68 (70-100 mg/dl) without any acidosis. Her altered mental status was attributed to higher opioid doses which she received prior. Oral hypoglycemic agents have been held. On 2nd day of hospitalization, patient became more lethargic and complained of nausea. Laboratory testing revealed a serum glucose of 250 mg/dL, serum bicarbonate of 13 (21–31 mmol/L), and Anion gap of 25 (3.6–11.0 mmol/L). With the suspicion of DKA, a beta-hydroxy butyrate level was obtained which was elevated at 90.10 (0 – 4.16 mg/dL). Venous blood gas analysis was significant for pH 7.23 (7.31-7.41) and pCO₂ – 28 (41-51 mmHg). Urinalysis showed ketosis and glucosuria. Patient was diagnosed as euglycemic diabetic ketoacidosis from Canagliflozin in presence of precipitating factors - stress and poor intake. Patient was treated with insulin drip and intravenous fluids with reduction in anion gap and correction of acidosis within 24hrs. There was a gradual improvement in her mental status. She was discharged on subcutaneous insulin, and all other diabetic medications were stopped.

Conclusion: Our case highlights the importance of being vigilant in a patient on Canagliflozin, euglycemic DKA can occur even if they present initially with hypoglycemia and no acidosis.

Reference: 1. Ogawa W, Sakaguchi K. Euglycemic diabetic ketoacidosis induced by SGLT2 inhibitors: possible mechanism and contributing factors. *J Diabetes Investig*. 2016;7(2):135-138.

Thyroid

THYROID NEOPLASIA AND CANCER

Validation of TI-RADS (Thyroid Imaging, Reporting and Data System) Follow-Up Recommendations

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MON-LB84

Background: Thyroid nodules are exceedingly common, leading to costly interventions for many lesions that ultimately prove benign. Therefore, a reliable, noninvasive method to identify which nodules warrant fine needle aspiration and/or follow-up on the basis of a reasonable likelihood of malignancy is highly desirable. American College of Radiology (ACR) created a standard terminology (lexicon) to describe all thyroid nodules on sonography and standardized TI-RADS risk-stratification system to identify nodules that warrant biopsy and/or follow-up. Many healthcare institutions including UPMC adapted the TI-RADS scoring system in order to identify most clinically significant malignancies while reducing the number of biopsies and follow-up ultrasounds performed on benign nodules. According to ACR, TI-RADS category 3 nodules <1.5 cm and TI-RADS category 4 nodules <1 cm do not warrant follow-up imaging. There are no validation studies on TI-RADS follow-up recommendations.

Methods: We completed a retrospective chart review from UPMC endocrine surgery thyroid nodule database from 2002 to 2012. We identified 57 nodules that showed a change in size during follow-up and had surgical data. Patient demographics, nodule baseline TI-RADS category, size, follow-up volume change and histopathological data were recorded. We reviewed ultrasound images and calculated TI-RADS category at baseline and during follow-up.

Results: TI-RADS category 1-2 (TR1 and TR2) nodules (n=4) did not show any change in size over an average of 6.5 years confirming the recommendations that TR1 and TR2 nodules do not need follow-up. TI-RADS category (TR3) nodules (n=22) showed an average 225% change in volume over 4 years of follow-up. TR3 nodules <1.5 cm showed 397% volume change; 3 out of 15 (20%) nodules that showed a change in size proved to have thyroid cancer >1cm.

TI-RADS category (TR4) nodules (n=31) showed a 786% volume change over 2.6 years of follow-up. TR4 nodules <1 cm, 5/14(35%) proved to have thyroid cancer >1 cm in follow up.

Conclusions: TR1 and TR2 nodules did not show thyroid cancer during follow-up validating ACR recommendations not to follow these nodules. 3/15(26.5%) TR3 nodules <1.5 cm that showed a change in volume proved to have thyroid cancer. 5/14(35%) TR4 nodules <1cm that changed in volume were found to have thyroid cancer. Further studies are needed to identify nodules that require follow-up in order to decrease the misdiagnosis of thyroid cancer.

Neuroendocrinology and Pituitary**ADVANCES IN NEUROENDOCRINOLOGY****Increased In Vivo Pulsatile LH Secretion and Hypothalamic Kisspeptin, NKB, and Dynorphin RNA Levels in a PCOS-Like Mouse Model**

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SUN-LB50

Polycystic ovary syndrome (PCOS) is a reproductive disorder in women characterized by hyperandrogenemia, anovulation, cystic ovaries, and LH hyper-pulsatility, but

the mechanisms causing the pathophysiology remain incompletely understood. We recently reported a novel mouse model that recapitulates the majority of PCOS phenotypes in adulthood. Females given constant, long-term letrozole to reduce aromatase activity demonstrate PCOS-like phenotypes, including polycystic ovaries, anovulation, elevated circulating testosterone, and increased LH. *In vivo* LH pulsatile secretion, which is greatly elevated in PCOS women, was not previously studied, nor were possible changes in reproductive neurons known to control GnRH/LH secretion. Here, we used recent technical advances in the field to examine *in vivo* LH pulse dynamics of freely-moving LET female mice versus control and ovariectomized (OVX) mice. We also studied whether hypothalamic gene expression of several important reproductive regulators, kisspeptin, neurokinin B (NKB), and dynorphin, is altered in LET females. Compared to controls, LET females exhibited very rapid, elevated *in vivo* LH pulsatility, with increased pulse frequency, amplitude, and basal levels, similar to PCOS women. LET mice also had markedly elevated *Kiss1*, *Tac2*, and *Pdyn* expression along with increased *Kiss1* neuron activation in the hypothalamic arcuate nucleus. Although elevated, most hyperactive LH pulse parameters and increased arcuate mRNA measures of LET mice were significantly lower than in OVX littermates. Our findings demonstrate that LET mice, like PCOS women, have markedly elevated LH pulsatility which likely drives increased ovarian androgen secretion. Increased arcuate kisspeptin and NKB levels may be fundamental contributors to the enhanced stimulation of LH pulse secretion in this PCOS-like condition, and perhaps, in some PCOS women.

Healthcare Delivery and Education**EXPANDING CLINICAL CONSIDERATIONS FOR PATIENT TESTING AND CARE****Evaluating the Impact of a New Intake Process for British Columbia Children's Hospital Gender Clinic**

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MON-LB302

Our pediatric Gender Clinic is receiving a growing number of referrals, yet continues to operate with limited resources. To try to address this issue, a new clinical pathway was developed in 2017, which included an inter-professional assessment clinic run by nurses and social workers as the entry point for new referrals (known as 'intake appointments'). These visits help to identify those youth who require urgent access to care (i.e. for imminent puberty), wayfinding to community supports and providers who can complete GnRH analog and hormone-readiness assessments, and information about potential medical interventions. The goals of this study were to (1) map out current processes, (2) evaluate wait times for patients referred in 2015-2016 (pre-intake) and 2018-2019 (post-intake), and (3) describe referral patterns and outcomes. Patients referred in 2017 were excluded, as this was a transitional year. In 2015-2016, 222 referrals were received, compared to 407 referrals in 2018-2019. Of the post-intake cohort, to date, 202/407