in adults and may lead to increased fracture risk. Little is known in pediatrics about the risks for impaired BMD and fragility (low trauma) fractures after HSCT. Factors that may influence the risk of bone disease include underlying diagnosis, glucocorticoid exposure, and HSCT complications (e.g. graft versus host disease (GVHD)). Our study aims to describe the incidence of fragility fractures in a large diverse pediatric HSCT population and to identify risk factors of both fracture and impaired BMD.

Methods: We reviewed the records of 237 patients (age ≤ 21 years at time of transplant) who underwent HSCT at our institution between January 2015 and March 2018. The primary endpoint was incidence of fragility fractures and the secondary endpoint was assessment of BMD on dual-energy X-ray absorptiometry (DXA). We analyzed DXA results at one-year post-HSCT in 72 out of 206 patients alive at 1 year.

Results: There were 25/237 (10.5%) patients with evidence of fragility fracture on x-ray. Of those, 18/25 (72%) were spine fractures. For patients who had fractures, median time to fracture was 5.9 months after BMT. Mortality at one-year was proportionally higher, though not significant (p=0.11) in patients who had at least one fragility fracture (24%; 6/25) compared to patients without fragility fracture (12%; 25/212). Vitamin D status at one-year post transplant was sufficient (>20ng/mL) in 94% (160/171) of patients measured. There was no difference in incidence of fracture between vitamin D sufficient and insufficient patients. The median height-for-age adjusted Z-score (HAZ) for spine BMD at one-year post transplant was 0.13 in all patients. The median HAZ spine BMD Z-score in patients with fragility fracture was -1.64, though data was available for only 5 patients.

Conclusions: The incidence of fragility fractures, especially vertebral compression fractures, after pediatric HSCT is striking and is higher than in adult populations. Furthermore, there are likely additional asymptomatic patients with occult fractures not detected in our cohort. Additional analysis will assess the associations between underlying medical diagnosis, GVHD, and chronic glucocorticoid exposure on fragility fracture risk. The high incidence of fragility fractures seen in this study advocates for establishing bone health screening protocols with attention toward spinal imaging in pediatric patients undergoing HSCT.

Thyroid

THYROID NEOPLASIA AND CANCER

**ATA and ACR TIRADS Classification Systems as Additional Predictors of Malignancy in Afirma GSC Suspicious Thyroid Nodules**

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MON-525

**Objective:** Evaluation and management of thyroid nodules with cytologically indeterminate results remain challenging in clinical practice. Despite the implementation of molecular testing in an attempt to avoid surgical intervention, diagnostic thyroidectomy still occurs due to the relatively low positive predictive value of these molecular testing. We conducted a study to analyze whether combining US characteristics and results of molecular testing would better elucidate predicting true positive results.

**Methods:** We retrospectively reviewed thyroid ultrasound images of 172 nodules in 162 patients (mean age, 55 years +/- 14) with indeterminate cytology results (Bethesda III and IV) that underwent Afirma Gene Sequencing Classifier (GSC) testing at a single academic medical center between 2017–2019. All nodules were classified according to 2015 American Thyroid Association (ATA) and 2017 American College of Radiology Thyroid Imaging Reporting and Data System (ACR-TIRADS).

**Results:** A total of 172 with subsequent Afirma GSC molecular testing were included in the study. There were 127 nodules with Bethesda III (AUS/FLUS) (73.8%), and 45 nodules with Bethesda IV (FN/SFN) (26.2%) results. The mean nodule volume was 5.4 +/- 10 cm³. Afirma GSC identified 129 nodules (75%) as benign and 43 nodules (25%) as suspicious. Per ATA classification, 10.4% (19) of nodules were classified as very low risk, 40.7% (70) as low risk, 36.5% (62) as intermediate and 12.8% (22) as high risk for malignancy. There was a significant association between ATA classification and Afirma benign nodules (P=0.002). All nodules were also classified per TIRADS system with the following distribution: 5 (1.16%) TIRADS 1, 7 (4%) TIRADS 2, 54 (31%) TIRADS 3, 90 (52%) TIRADS 4, and 16 (9.3%) TIRADS 5. We did not observe the similar association between TIRADS system and benign nodules as we did with ATA classification (P=0.4).

35 patients (79.5%) with Afirma suspicious results underwent surgery, of which 18 (51.4%) surgical pathology were malignant. 8 patients with Afirma suspicious results decided to proceed with ultrasound surveillance. The malignancy rates of nodules with low, intermediate and high suspicion for malignancy classified by the ATA guidelines were 44% (9 of 18), 33% (56 of 18) and 22% (4 of 18). The malignancy rates of TIRADS category 3, 4 and 5 nodules were 44% (8 of 18 nodules), 44% (8 of 18 nodules) and 11% (2 of 18 nodules). Subset analysis of surgical pathology benign and cancerous nodules did not show significant association between ATA (P=0.5) or TIRADS (P=0.4) classification systems.

**Conclusion:** Our study showed that Afirma benign nodules were associated with a lower risk of malignancy per ATA classification but not with TIRADS system. We did not find a significant association between pathology proven cancer cases and high-risk ATA or TIRADS ultrasound classification systems.

Steroid Hormones and Receptors

STEROID BIOLOGY AND ACTION

**Common Genetic Variants Associated with SERPINA6 Expression in Liver Influence Cortisol-Responsive Transcriptional Networks in Human Adipose Tissue**

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A genome wide meta-analysis by the CORtisol NETwork (CORNET) consortium(1) has identified genetic variants spanning the SERPINA6/SERPINA1 locus on chromosome 14, associated with morning plasma cortisol and predictive of cardiovascular disease (Crawford et al, Unpublished). SERPINA6 encodes Corticosteroid Binding Globulin (CBG), responsible for binding most cortisol in blood and putatively mediating delivery of cortisol to target tissues. We hypothesised that genetic variants in SERPINA6 influence CBG expression in liver and cortisol delivery to extra-hepatic tissues, influencing cortisol-regulated gene expression. The Stockholm Tartu Atherosclerosis Reverse Networks Engineering Task study (STARNET)(2) provides RNA sequencing data in 9 vascular and metabolic tissues from 600 genotyped individuals (mean age 65.8, 70.3% male) undergoing coronary artery bypass grafting. We used STARNET to identify SNPs associated with plasma cortisol at genome wide significance in CORNET as cis-eQTLs for SERPINA6 in liver and as trans-eQTLs for the expression of genes across STARNET tissues. Causal inference methodologies(3,4) were then employed for the network reconstruction of these trans-genes and their downstream targets. We identified 21 SNPs that both were associated with cortisol at genome wide significance in CORNET (p ≤ 5x10^{-8}) and were cis-eQTLs for SERPINA6 expression in liver (q ≤ 0.05). Moreover, these SNPs were trans-eQTLs for sets of genes in liver, subcutaneous and visceral abdominal adipose tissue, with over-representation of known glucocorticoid-regulated genes in adipose. The highest confidence gene network identified was specific to subcutaneous adipose, with the interferon regulatory trans-gene, IRF2, controlling a putative glucocorticoid-regulated network. Targets in this network include LDB2 and LIPA, both associated with coronary artery disease.

We conclude that variants in the SERPINA6/SERPINA1 locus mediate their effect on plasma cortisol through variation in SERPINA6 expression in liver, and in turn affect gene expression in extra-hepatic tissues through modulating cortisol delivery. This supports a dynamic role for CBG in modulating cortisol delivery to tissues. The cortisol-responsive gene networks identified here represent candidate pathways to mediate cardiovascular risk attributable to elevated cortisol.

(1) Bolton, et al. (2014) PLOS Genet. 10:e1004474., (2) Franzén et al. (2016). Science 353:827., (3) Wang and Michael. (2017). PLOS Comput. Biol. 13:e1005703.

SUN-173
Introduction
Patients with untreated congenital adrenal hyperplasia (CAH) can present early with severe symptoms of salt wasting, adrenal insufficiency and hyperandrogenism. Late consequences as a result of long term untreated CAH are rarely seen nowadays. We present a patient who presented with a massive uterine leiomyoma and bilateral adrenal myelolipomas due to longstanding treatment noncompliance.  

Clinical Case
A female was born with ambiguous genitalia and diagnosed with CAH at birth. She was raised as a female and received steroids until age 29 when she stopped taking steroids on her own with the intention of identifying as a male. At age 37, she presented with abdominal distension, vomiting, and hypotension. Physical exam was notable for hypotension, significantly distended abdomen, hirsutism, gynecomastia and clitoromegaly. Labs revealed sodium 136 meq/L (136–145) cortisol 78.5 ug/dL (3.7–19.4), ACTH 166 pg/mL (6–50), 17-hydroxyprogesterone 4356 ng/dL (≤285), androstenedione 7188 ng/dL (35–250), total testosterone 737 ng/dL (2–45), estradiol 414 pg/mL (48–440), aldosterone <1 ng/dL (3–16), renin 0.45 ng/mL/hr (0.25–5.82), metanephrines 56 pg/mL (≤205), normetanephrines 56 pg/mL (≤148). CT abdomen and pelvis revealed a large 31 x 35 x 31 cm pelvic mass, a 5.9 x 2.4 cm right adrenal mass and an 11.8 x 8.8 cm left adrenal mass. The patient underwent total abdominal hysterectomy and bilateral adrenalectomy. Pathology of the pelvic mass was consistent with uterine leiomyoma (tumor was 12.4 kg) and pathology of the bilateral adrenal masses were consistent with bilateral adrenal myelolipomas.

Discussion
Glucocorticoids and mineralocorticoids are the mainstays of treatment in CAH, with the goal of providing adequate replacement while reducing levels of ACTH and adrenal androgens. Persistently elevated levels of ACTH and androgens can lead to many serious sequelae, even outside of adrenal insufficiency and virilization. Due to the conversion of androgens to estrogens, untreated females with CAH have significantly elevated levels of both hormones. These high levels of androgens and estrogen can then stimulate growth of estrogen-dependent organs as exemplified by our patient. Chronic ACTH stimulation can cause adrenal hyperplasia, but has also been associated with the development of other adrenal masses including adrenal myelolipomas. Adrenal myelolipomas can become hormonally functional or cause mass effect, hemorrhage, necrosis when reaching a large enough size.

Conclusion
This case demonstrates the importance of CAH treatment compliance as there are many serious sequelae outside of the expected adrenal insufficiency and virilization. Even when the desired effect is virilization with physical male features, other means of hormonal therapy should be considered as there remains the risks of abnormal growth of certain organs sensitive to the excessive hormones.

Adrenal
ADRENAL CASE REPORTS II
A Gigantic Uterine Leiomyoma and Big Bilateral Adrenal Myelolipomas as a Result of Untreated Congenital Adrenal Hyperplasia
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