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DIVISION OF ENDOCRINOLOGY AND METABOLISM

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Dear Colleagues,

We are pleased to share our latest edition of *Update in Endocrinology*. Even amid the global pandemic, we are closing out 2020 strong and are looking forward to many exciting endeavors in 2021. In this issue, we continue to highlight our contributions to the research, educational, clinical, and quality missions.

To highlight our research excellence, basic scientist **Alison B. Kohan, PhD**, discusses intestinal lipoproteins in normal metabolism and disease and the ongoing research the Kohan Lab is conducting on this topic. Dr. Kohan has been awarded a Kenneth Rainin Foundation Synergy Award in collaboration with Gwendolyn Randolph, PhD, to further the research on intestinal lipoproteins and their relation to Crohn's disease.

On the clinical front, **Jagdeesh Ullal, MD, MS, FACE, FACP, ECNU,** and **Kara S. Hughan, MD**, directors of the UPMC Adult and Pediatric Endocrinology Cystic Fibrosis Centers, respectively, discuss the multidisciplinary aspects of the Centers and how the care of patients with cystic fibrosis has evolved over the last 70 years. Drs. Ullal and Hughan were both awarded a grant through the Cystic Fibrosis Foundation EnVision CF: Emerging Leaders in CF Endocrinology II Program as mentee and mentor.

Complex cases continue to challenge our expertise and provide fellows with transformative lessons in clinical care. Clinical fellow **Divya Sistla, MD**, and her mentor, **Hussain Mahmud, MD**, present a clinical case discussing an unusual case of medullary thyroid cancer.

Lauren Willard, DO, and **Archana Bandi, MD**, discuss how the Endocrinology Divisions at UPMC and the VA Pittsburgh Healthcare System expanded their current telemedicine practices to create continuity of care for patients during the global COVID-19 pandemic.

Our division continues to grow as we welcome **Stephanie Hakimian, MD**, and **Andrey Parkhitko, PhD**, to our faculty. Dr. Hakimian's clinical interests include diabetes care and complications prevention in underserved populations, as well as diabetes technology and artificial pancreases. Dr. Parkhitko's research interests include the use of tumor models in *Drosophila* for the search of new modulators of tumorigenesis, as well as metabolic alterations and their potential targeting during aging.

In addition, we also celebrate many accomplishments of our faculty and trainees. **Helena Levitt, MD**, was chosen as one of the 2020 Best Doctors in America. **Anjana Murali**, a Physician Scientist Training Program student in the University of Pittsburgh School of Medicine, was awarded a NIDDK T32 supplement under the mentorship of **Michael Jurczak, PhD**.

Finally, we want to send a heartfelt message of gratitude and encouragement to all of our health care colleagues and essential workers for their dedication to our collective well-being during these challenging times. We are all in this together, and we will overcome. Please stay safe and well, and have a happy holiday season.

Best wishes,

Erin E. Kershaw, MD
Chief, Division of Endocrinology and Metabolism

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UPMC LIFE CHANGING MEDICINE

Intestinal Lipoproteins in Normal Metabolism and Disease

Alison B. Kohan, PhD

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Critical Importance of Plasma Triglycerides in Disease

Cardiovascular disease (CVD) is the leading cause of mortality in the United States[1]. In the past 40+ years, research and epidemiology has largely focused on the role of cholesterol in the blood as a major modifiable risk. As a result, we now have a variety of clinical approaches to lowering plasma cholesterol (most notably statin therapies)[2]. Despite the widespread and successful use of statins in patients to reduce blood cholesterol (by lowering concentrations of low-density lipoprotein, LDL), patients who present at the emergency room with myocardial infarction are almost all already prescribed statins[3,4]. This highlights the fact that lowering blood cholesterol level, and successful statin therapy, does not fully reduce the risk of cardiovascular disease. There are additional residual risk factors that we must find and treat in order to reduce CVD mortality.

In recent years, there has been significant progress in identifying and defining these residual risk factors. Elevated plasma triglycerides, especially after a meal, has long been identified as an independent CVD risk factor[5–7]. In addition, post-meal plasma triglyceride concentrations are strongly predictive of ischemic events in both sexes, even considering differences in protective high-density lipoprotein (HDL) concentration[6]. Despite this known relationship between plasma triglycerides and CVD risk, approximately 30% of the U.S. population still have moderate-to-high plasma triglyceride levels (greater than 150 mg/dL)[8,9]. Pharmaceutical and lifestyle interventions that reduce plasma triglycerides are clearly critical. The anti-PCSK-9 drugs (Repatha®) and anti-apoC-III drugs (by both Staten Biotechnology and Ionis Pharmaceuticals[10,11]) are an example of pharmaceutical targets of plasma triglycerides.

Chylomicrons are the Intestinal Lipoprotein Responsible for Dietary Fat Absorption and Metabolism

Physiologically, chylomicrons and very-low-density lipoprotein (VLDL), two types of triglyceride-rich lipoproteins, make up the largest pool of extracellular lipid substrates *in vivo*. Immediately following a meal containing fat, there is a transient rise in circulating plasma triglyceride. The triglyceride comes largely from the intestinal enterocyte, where lipids from the diet are taken up and packaged into chylomicrons. This process occurs predominantly in the duodenum and jejunum[12,13]. Two hours after a fatty meal, the small intestine reaches its peak chylomicron synthesis and secretion rate, though chylomicrons are secreted as early as 13 minutes from fat absorption and for as long as ~6 hours[14].

Chylomicrons deliver dietary-derived lipids from the intestine while hepatic-derived lipids are packaged into VLDL and secreted into circulation primarily during fasting. Triglycerides from these lipoproteins are delivered to tissues for energy through uptake via the low-density lipoprotein receptor (LDLr). In addition, these lipoproteins are hydrolyzed by lipoprotein lipase (LPL) and release free fatty acids which can be taken up by cells through fatty acid transporters or passive diffusion. Because of this delivery, chylomicrons can provide a source of lipid fuel for almost all cells in the body. Chylomicrons are unique from VLDL because they also carry antigens from diet, intestinal microbiota, and intestine cells to the gut immune system, and thus interact extensively with mucosal immune cells. Since chylomicrons have a dual role in immune modulation, factors that can regulate the digestion and absorption of dietary lipid, as well as the secretion of chylomicrons, can also regulate the exposure of the immune system to potential antigen and lipid fuel.

Chylomicrons contain triglyceride and cholesterol in their core, surrounded by phospholipids, and contain apolipoproteins B-48, A-I, A-IV, and C-III. Apolipoproteins are biologically active in metabolic processes (including lipid clearance and glucose homeostasis). ApoB-48 is essential to the structure of the chylomicron, but interestingly, the other apolipoprotein components serve as signaling molecules and enzymatic modulators that are essential for chylomicron metabolism and clearance from the blood. Moderating post-prandial lipids and the apolipoproteins associated with them is an important part of moderating cardiovascular disease risk.

Apolipoprotein C-III (apoC-III) is another apolipoprotein that is a potent cardiovascular risk factor. It is an exchangeable apolipoprotein produced by both the intestine and liver, found on both chylomicrons and very low-density lipoproteins[15]. In humans, plasma apoC-III levels are elevated during both hyperlipidemia and diabetes[16–18]. In plasma, apoC-III delays chylomicron and VLDL clearance, and in the liver it stimulates VLDL secretion. Through both of these actions, apoC-III stimulates plasma hyperlipidemia[19,20]. In addition to its role in the maintenance of the hyperlipidemic state, apoC-III levels are themselves an independent predictor of cardiovascular disease risk[21,22]. Recent large-scale epidemiological studies have revealed that

mutations in apoC-III result in a striking decrease in ischemic cardiovascular disease and coronary heart disease risk in humans[23,24]. This finding has generated significant new interest in apoC-III.

ApoC-III has also recently been shown to act in the intestine as an inhibitor of dietary lipid absorption[25]. This new intestinal role for apoC-III is likely important in understanding the mechanism by which apoC-III mediates cardiovascular disease risk given that fat absorption and intestinal lipoprotein secretion contribute to cardiovascular disease progression[6,26,27]. How intestinal apoC-III is regulated is unknown and may be quite different from hepatic apoC-III regulation since the hepatic and intestinal lipoprotein synthesis and pathways are unique and regulated at different steps[28–30]. There may be a valuable difference in the regulation and function of apoC-III in these tissues and it is likely that dietary nutrients moderate this effect.

Hurdles to Studying Chylomicron Secretion and Small Intestinal Physiology

Despite the importance of studying the intestine and its lipoprotein secretion in metabolism and disease, it has been notoriously difficult to study because the tissue rapidly degrades during isolation, as well as due to the lack of cell culture models[31,32]. Primary enterocytes are short-lived (~24h); everted gut sacs cannot be transfected; and Caco-2 cells are a monolayer colon cancer cell line that lacks essential biology of the small intestine. Overall, the lack of a culture model has been a significant roadblock to gaining mechanistic insights into the function of the small intestine as a metabolic organ.

Intact intestine is a complex tissue comprised of multiple cell types, including enterocytes (the absorptive cells of the intestine), enteroendocrine cells (which secrete incretin hormones), goblet cells (which secrete mucus), and mast cells (which secrete immune modulators). There are two primary structures in the intestinal epithelium: the villus and crypt. The crypt is found at the base of the villus, and these structures contain the multi-potent intestinal stem cells (ISCs), which express the transcription factor LGR5 and give rise to all of the cells lining the intestinal epithelium[33,34]. *In vivo*, the intestinal epithelium is in a constant state of differentiation, renewal, and replacement driven by these ISCs within the crypt niche.

The isolation and propagation of these stem cells was first established by Sato and Clevers in 2009 and has had a major impact on the field[34]. They showed that the crypt, when plated into 3D Matrigel and treated with growth factors, will differentiate into a 3D enteroid. In the enteroid culture, the LGR5+ stem cells within those crypts grow and differentiate into all the cell types normally found in the intestinal epithelium, including new stem cells.

As the primary stem cell within an isolated crypt differentiates in response to growth factors, it forms a three-dimensional enteroid. Mature enteroids (by convention "enteroid" refers to mouse-derived cultures, whereas "organoids" refer to human-derived cultures) form at approximately day 10 in growth media and retain intestinal barrier function, express amino acid transporters, and intestine-specific stem cell markers[31,35,36]. These cells maintain their physiological orientation around a central lumen (the apical surface) and a basolateral surface facing media.

The stem cells differentiate in culture by sloughing off cells into the luminal compartment followed by regeneration of crypt epithelium. Enteroids are therefore not only powerful models of intestinal function, but also represent a significant advance in our ability to determine intestinal mechanisms for dietary fat absorption and lipoprotein synthesis and secretion.

Beyond Cardiovascular Disease: The Role of Intestinal Lipoproteins in Other Diseases

Short-bowel syndrome is an extreme example of what happens without small intestinal lipid absorption processes. Patient energy needs cannot be met through carbohydrate feeding, nor through parenteral nutrition. In addition, the liver cannot handle the increased burden of clearing portal nutrients while also secreting VLDL to keep up with energy demands. Ultimately, patients die of liver failure. This brutal disease illustrates key physiological processes of the small intestine: ability to absorb dietary triglycerides and present these triglycerides to the rest of the body in easily metabolizable form (chylomicrons), the importance of the lymphatic route of lipid absorption (because otherwise all nutrients are shunted to the liver via portal circulation), and finally the inability to sustain energy homeostasis without dietary lipids.

Diseases where these lipases are absent or reduced also cause a significant defect in dietary fat absorption, including cystic fibrosis (CF), where stricture of the pancreas seriously reduces the secretion of lipases and bicarbonate during fat ingestion. Thus, deficiency in pancreatic enzyme secretion leads to an inability to hydrolyze dietary lipids in the intestinal lumen. Cystic fibrosis transmembrane conductance regulator (CFTR) is also critical in bile acid secretion from the liver to the intestinal lumen. Therefore, luminal conditions in the CF intestine are antagonistic to lipid absorption, which requires hydrolysis of dietary lipid with pancreatic lipase and emulsification with bile salts. These are relatively well-understood physio-chemical defects in the CF intestine, and CF patients are prescribed Pancreatic Enzyme Replacement Therapy (PERT) to bring total fat absorption to normal levels. Despite PERT, when human intestinal explants are cultured, they secrete reduced numbers of intestinal triglyceride-rich lipoproteins, as well as exhibit reduced apoB synthesis[37]. With the advent of CFTR tri-modulator Trikafta, it will be interesting to see whether the small intestinal manifestations of CF become a larger focus.

Conclusion and Future Directions

Lipid absorption by the small intestine is absolutely critical for whole-body metabolism and overall triglyceride concentrations, both of which are risk factors for cardiovascular disease. Chylomicron metabolism also plays a critical role in determining plasma levels of triglyceride and dietary antigens. The rates of chylomicron secretion and remnant clearance are controlled by intracellular and extracellular factors including apoC-III. Functionally, therefore, humans are almost always in the post-prandial state. Understanding

chylomicron synthesis and secretion, metabolism, and interaction with immune cells is a critical frontier for understanding inflammatory disease.

The Kohan Lab has been using primary intestinal organoids to dissect these chylomicron-driven effects on human disease. Dr. Kohan's team was the first to show that organoids recapitulate intestinal fat absorption by taking up 3H-FFA and secreting 3H-TAG along with apoB-48 in a chylomicron particle[31,36].

Chylomicrons are difficult to isolate, and the intestine is notoriously finicky to study. Dr. Kohan's team uses primary intestinal organoids to get around these issues and discover new metabolic processes that are chylomicron driven. Researchers in the Kohan Lab have recently discovered a mechanism of regulatory T cell (Treg) regulation by intestinal chylomicrons. Specifically, they discovered that mice overexpressing human apoC-III are protected from dextran-sulfate sodium (DSS)-induced colitis and its associated symptoms. Conversely, apoC-III knockout mice are susceptible to severe colitis and have fewer colonic Tregs than their wild-type counterparts.

The canonical role of apoC-III is to inhibit lipid uptake from triglyceride-rich lipoproteins like chylomicrons, by inhibiting lipoprotein lipase (LPL) and low-density lipoprotein receptor (LDLr). Building upon their team's expertise in intestinal lipid metabolism and lipoprotein clearance, Dr. Kohan's team found that intestinal Tregs and T cells express high levels of LDLr and, in response to apoC-III, T cells take up less triglyceride. These data suggest that inhibiting lipid uptake from chylomicrons into Tregs stimulates intestinal Tregs and protects against colitis. Dr. Kohan's team is now dissecting the molecular mechanisms in the hopes that this pathway might be a therapeutic target for inflammatory bowel diseases.

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Heralding a New Era in Cystic Fibrosis Care

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Cystic Fibrosis Endocrinopathies

Cystic fibrosis (CF) is a multisystem disorder that results from pathogenic variants of the CF transmembrane conductance regulator (CFTR) gene on chromosome 7. The most common endocrinopathies that result from CF are manyfold, including diabetes, bone disease, hypogonadism, infertility, growth disorders, and malnutrition, in addition to multiple fat-soluble vitamin deficiencies. While the most common pathology is a progressive lung disease, which is often the cause of death, poor glycemic control and malnutrition greatly contribute to the worsening of lung disease. Individuals with CF have been known to develop a distinct form of diabetes referred to as type 3c diabetes mellitus (DM), which is distinct from type 1 and type 2 DM.

Type 3c DM is characterized by exocrine pancreatic insufficiency and consequent beta-cell dysfunction in the absence of autoantibodies[1]. This CF-related diabetes (CFRD) was previously referred to as pancreatogenous diabetes; however, the American Diabetes Association and the World Health Organization changed the terminology to type 3c diabetes in 2012-2013. Individuals with CFRD are subject to the DM-related risks of microvascular disease such as retinopathy, nephropathy, and neuropathy, but have a relatively low risk of macrovascular disease[2].

The Cystic Fibrosis Center at the University of Pittsburgh and UPMC

In 1955, a group of volunteers in Philadelphia established the Cystic Fibrosis Foundation (CFF). In 1961, the CFF subsequently created an accredited care center network beginning with the formation of two centers devoted to treating CF. Following the formation of the CFF, yet long before the concept of multidisciplinary care for CF was recognized, the Cystic Fibrosis (CF) Center at the University of Pittsburgh was established by pediatrician Dr. Joan B. Rodman and pediatric radiologist Dr. Murray Sachs. This CF Center became the second center to receive CFF accreditation in the nation.

Due in large part to the concerted efforts of the national network of CF centers and the CFF, the median predicted survival increased from 16 years in the 1970s, to 29 years, in the late 1980s. This generated the need to recruit an adult pulmonologist for adult CF care, leading to the hire of Dr. Joel Weinberg in 1983 to build the adult CF Center at the University of Pittsburgh and UPMC. Pediatric pulmonologist Dr. David Orenstein was recruited in the mid-1980s to lead what became the Antonio J. and Janet Palumbo Cystic Fibrosis Center. Adult pulmonologist Dr. Joseph Pilewski was recruited in the mid-1990s and is currently the Co-Director of the CF Center and Director of the Adult CF Program in Pittsburgh.

At the program's inception, adult patients with CF were scheduled in conjunction with the pediatric pulmonary clinic at UPMC Children's Hospital of Pittsburgh. As the program evolved, adult patients with CF were cared for at the Comprehensive Lung Center at UPMC Presbyterian-Shadyside Hospital.

The Lung Transplant Program at UPMC draws patients regionally and nationally due to the expertise and excellent outcomes in lung transplants in CF, patients with Burkholderia cepacia colonization, and other resistant pathogens or risk factors for poor outcomes. The program treats patients with CF not only from western Pennsylvania, but also from Ohio, West Virginia, upstate New York, northwestern Maryland, and across the country.

The CF Center at UPMC is a stellar example of multidisciplinary care that is offered through the combined efforts of pulmonologists, dieticians, nurses, social workers, respiratory therapists, and pharmacists who collectively have decades of CF care experience. In addition, other subspecialties with interest and experience in CF, such as Gastroenterology, Otolaryngology, Hepatology, and Endocrinology are routinely incorporated for longitudinal care of extra-pulmonary manifestations of CF. The endocrinology efforts in CF care are spearheaded by Dr. Kara Hughan at the Pediatric CF Center and Dr. Jagdeesh Ullal at the Adult CF Center.

The CF center also supports basic and clinical research in CF. Via its role as a longstanding site in the CF Therapeutics Development Network, the UPMC CF Center has contributed to pre-clinical development and Phase 2 and 3 clinical trials of modulators of the CF transmembrane conductance regulator (CFTR). CFTR modulator treatment is a new class of small molecular therapies that represent a major development in the therapeutics of CF. With the approval and use of CFTR modulators and other pulmonary therapies over the last three decades, the median predicted survival for CF patients now approaches 50 years.

Both Drs. Hughan and Ullal are funded through the CFF "EnVision CF: Emerging

Leaders in CF Endocrinology II Program" as mentor and mentee, respectively. This award program provides training in developing expertise in the endocrinologic care of patients with CF by developing and maintaining a CF Endocrine clinic, a series of monthly webinars, and lectures and participation in local and national meetings. The program encourages the development of a research track in CF and promotes scholarly activity in CF Endocrine care. Drs. Hughan and Ullal have CF-dedicated Endocrine clinics that are conducted in conjunction with CF Pulmonary clinics and are actively engaged in their own clinical research projects. Continuity of care is established through a smooth transition from the pediatric CF Endocrine clinic to the adult CF Endocrine clinic. This multidisciplinary care model, along with ongoing research projects and the continuously growing literature on clinical care for patients with CF, enables the team at the CF Center to provide the most up-to-date evidenced-based care for our patients.

A Groundbreaking Change in Cystic Fibrosis Care

The CFTR gene regulates the chloride channel, and the lack of function of the chloride channels causes decreased transport of chloride and sodium. This leads to dehydration and desiccation of epithelial cells and mucous membranes. CFTR is highly expressed in the pancreatic ducts and is essential for proper duct function. Its loss from ductal epithelium may contribute to islet dysfunction in CF via paracrine mechanisms[3]. It is also possible that CFTR may have direct actions in β-cells, although this issue remains controversial[4].

CFTR modulators are a class of drugs that improve synthesis and intracellular processing of CFTR protein resulting in expression of chloride channels, thus addressing the primary defect in CF[5]. CF gating mutations are characterized by a defect in the passage of chloride ions through the CFTR. Ivacaftor is a medication that potentiates the chloride flux by activating CFTR protein without ATP. This drug was FDA approved in 2012. Ivacaftor and Lumacaftor are drugs that act as chaperones during protein folding and increase the number of CFTR channels that are trafficked to the plasma membrane. This combination was FDA-approved in 2015. Elexacaftor is a CFTR corrector that substantially increases the amount of mature CFTR protein and CFTR activity when added to the combination of tezacaftor plus ivacaftor.

This triple drug combination, when given to individuals with at least one CF F508del mutation, has been shown to cause a profound improvement in lung function (FEV1), sweat chloride concentration, and quality of life[6]. The combination medication elexacaftor-tezacaftor-ivacaftor (Trikafta®) with respective ratios of 100:50:75 mg with doses delivered in two tablets taken in the morning and ivacaftor 150 mg tablet taken in the evening. Trikafta® received FDA approval in October 2019 for patients with at least one F508del mutation. This represents a significant milestone in the development of therapeutics for CF[7].

CFTR modulator drugs may help to treat and/or prevent CFRD by recovering CFTR-dependent islet-associated ductal function, by improving gut incretin function, and reducing the inflammation and insulin resistance of systemic illness[8]. The therapeutic effects of this drug class on endocrine pancreatic function and other organs remain to be ascertained. A two-year observational study, in which UPMC Children's Hospital of Pittsburgh is participating, (PROMISE; ClinicalTrials.gov: NCT04038047) has been designed to address longer-term, multi-system outcomes.

Case Reports of Individuals with CF Treated with Triple Combination Therapy

Case 1: A 48-year-old female with pancreatic insufficient CF (delF508/delF508) was diagnosed with CFRD at age 19 while hospitalized for pneumonia and on glucocorticoid treatment when her blood glucose concentrations were as high as 600mg/dl. She had been treated with insulin over the subsequent three decades. In 2012, insulin pump therapy was initiated with a basal rate of 0.4 units/hour (9.6 units/day), carbohydrate ratio of 1:20, and correction factor of 1 unit for every 60 above 120mg/dl. Her HbA1c was estimated at 6.7% while her post-prandial glucoses were reported to be as high as 300mg/dl. The patient was seen by the CF pulmonary nutritionist to optimize calorie intake and the endocrinology diabetes educator to estimate carbohydrate ratios for mealtime insulin and to educate the patient on pump and continuous glucose monitor (CGM) use.

Over the following six years, the same basal rate was maintained, but her carbohydrate ratios varied from meal to meal: Breakfast 1:16; Lunch 1:20, and Dinner 1:25. While her HbA1c remained below 7% in 2018, her average sensor glucose reading, as recorded on a professional CGM, was 191±105mg/dl. In May 2019, she was changed to a personal CGM that helped her to improve her average glucose to 150±58 mg/dl, with only three episodes of hypoglycemia every two weeks. Two weeks after initiating Trikafta® (January 2020), hypoglycemia became more frequent (up to six episodes every two weeks). The rapid, uncontrolled descent of her blood glucose levels required her to suspend her pump insulin delivery several times a day to minimize hypoglycemia. Subsequent reduction of total basal insulin doses from 7.8 to 3.9 units/day and relaxation of carbohydrate ratios to 1:25 were recommended to address the recurrent hypoglycemia. No other medications had been introduced to explain the drastic decline in insulin requirements. Kidney function remained stable and no signs of adrenal insufficiency (hypotension or anorexia) were present. The patient felt drastically better on Trikafta® and her glucoses remain reasonably controlled at this time with a HbA1c of 5.7%.

Case 2: A 24-year-old male with homozygous delta F508 mutation deletion CF was first identified to have CFRD in 2011 and was started on insulin therapy in early 2013. His HbA1c was 6.2% with insulin therapy. His CFRD had progressed to uncontrolled CFRD by mid-2015 with worsening glycemic control, an HbA1c of 9.2%, and a 4.7 kg weight loss noted.

The worsening control of his blood glucose levels accompanied increased CF exacerbations. This required the use of steroids, which further worsened blood glucose control. Eventually, mealtime Lispro

insulin was added with a carbohydrate ratio of 1:10 grams and correction factor of 1 unit for every 25 mg/dl above 150 mg/dl.

The patient had a fear of needles, which may have contributed to his poor adherence to the prescribed insulin regimen. A team-based approach helped to identify his fear of needles. The problem was ameliorated by introducing him to Autoshield Duo needles that keep the needle shaft hidden from view at the time of the injection. The patient worked closely with his psychologist and the social worker from his CF team to help overcome his anxiety and improve his willingness to take his injections, which yielded in improved weight gain. Unfortunately, the patient was unable to maintain self-management tasks, self-monitoring, and insulin adherence, which resulted in a subsequent rise of HbA1c levels to the 10-11% range. Insulin Degludec was prescribed to support basal coverage, which helped to lower his HbA1c to 8.7%. His total daily Lispro doses remained constant at 60 units in divided doses. A professional CGM revealed an average sensor glucose of 220 +/- 108 mg/dl.

In 2019, the patient's HbA1c again increased to 11.8%. Following this the patient was placed on the triple combination CFTR modulator, which led to rapid improvement in his HbA1c to 7.9%. His weight improved from 73 kg to 81 kg. Insulin doses were reduced by 20% in order to prevent low blood glucose.

While both patients above demonstrated a change in their insulin requirements and improvements in glycemic control, these are not universal results with triple combination therapy. Many of our CF endocrine colleagues, both adult and pediatric, across the country have reported varying effects of triple combination therapy on glycemic control. Until data from long-term studies are available, we recommend close monitoring of patients' glycemic control in the weeks and months following initiation of modulator therapy. The care of CF is entering a new age where drug therapy is dramatically improving the pathophysiologic defect caused by the delF508 genetic mutation. This advance has been due to a concerted effort by the CFF, basic scientists, clinicians, industry, patients, and their families. The future holds great promise for bettering the lives of individuals with cystic fibrosis.

Conclusion

CF is a complex disease that requires a team of professionals to deliver specialized and comprehensive care. Over the years, the natural evolution of CF care and best practices have grown and developed into one that is best delivered through the combined effort of a multidisciplinary team. The figure below represents members of a typical interdisciplinary CF care team. A group of trained and experienced CF specialist health care professionals can offer care that improves morbidity and mortality and face the challenge of addressing complex issues such as treatment of CFRD, pregnancy, renal disease, metabolic bone disease, malnutrition, and transplantation. Indeed, at CF centers, we embody a slogan from the Cystic Fibrosis Foundation – "Together is the way forward."

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An Unusual Case of Medullary Thyroid Cancer

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Case Presentation

An 18-year-old Caucasian male presented to the UPMC Ear, Nose, and Throat Center with recent onset of painful neck nodules. He denied any swallowing difficulty, hoarseness, or other neck symptoms. He also denied fever, chills, night sweats, or weight loss. There was no history of head and neck radiation exposure.

His past medical history included von Willebrand disease and asthma. His father had passed away from cholangiocarcinoma. There was no family history of thyroid disease, including thyroid cancer. Physical examination showed left sided level III/IV diffuse enlargement of lymph nodes that were nontender and firm to palpation.

Ultrasound imaging of the neck revealed a 1.8 x 1.4 x 1.4 cm heterogenous hypoechoic thyroid nodule and a 2.5 cm left level IV cervical lymph node (see Figure 1). This thyroid nodule met criteria for FNA biopsy according to the American Thyroid Association (ATA) guidelines. Cytology from FNA of the thyroid nodule and lymph node was consistent with medullary thyroid cancer (MTC). Molecular testing with ThyroseqV3 was positive for calcitonin expression and BRAF K601E mutation. Serum calcitonin was significantly elevated at 8268 pg./ml (normal 0-8 pg./ml), supporting the diagnosis of MTC.

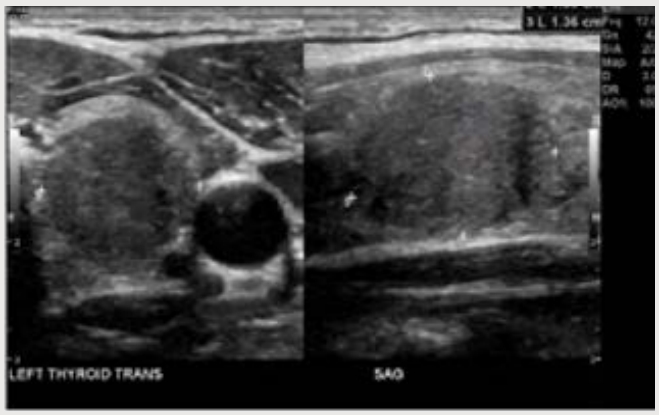
The patient underwent total thyroidectomy with extensive lymph node dissection. Surgical pathology revealed a 2.1 cm primary tumor and 39 out of 41 lymph nodes positive for metastatic MTC with extrathyroidal and extra nodal extension. The margins were uninvolved by carcinoma. C-cell hyperplasia was also noted in background thyroid parenchyma. Pathological stage was pT3N1.

Genetics

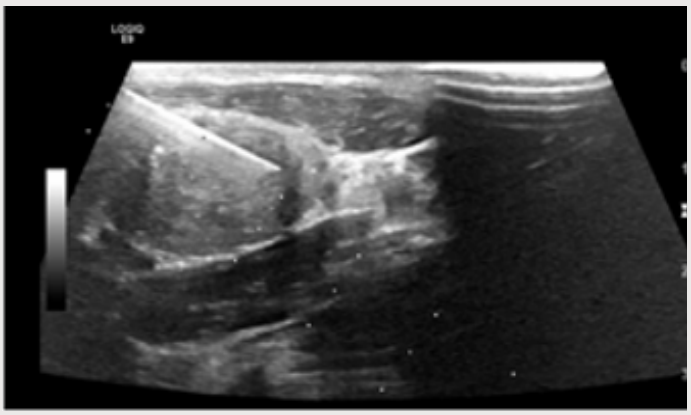
Due to the patient's young age, presence of an aggressive tumor, C-cell hyperplasia, and unusual molecular findings on cytology aspirate, further testing to evaluate driver mutations and rule out heritable causes was performed. ThyroSeq V3 testing was performed both on the tumor sample and surrounding tissue. BRAF K601E mutation was only noted in the tumor, thus proving that this was a somatic mutation. Interestingly, RET mutation, which is the most common genetic mutation associated with hereditary MTC, was tested negative. The patient did not meet criteria for Familial Medullary Thyroid Cancer (FMTC) or Multiple Endocrine Neoplasia Type 2 (MEN2A).

Post Op Surveillance

The patient is continuing his care in the Endocrine Clinic with calcitonin monitoring



1.8 x 1.4 x 1.4 cm heterogeneous hypoechoic left thyroid nodule.



2.5 cm left cervical level IV lymph node.

Figure 1: Ultrasound of neck. Left panel showing a 1.8 x 1.4 x 1.4 cm heterogeneous hypoechoic left thyroid nodule. Right panel showing a 2.5 cm left cervical level IV lymph node.

and serial imaging. Eight months post thyroidectomy he was noted to have an increasing calcitonin level (1,295 pg/mL) and malignant appearing lymphadenopathy on imaging. He underwent selective bilateral neck dissection. Pathology confirmed the presence of metastatic MTC in 13/66 resected lymph nodes. Twenty-two months from initial diagnosis, a doubling of calcitonin (3,622 pg/mL) was observed (see Figure 2). A neck ultrasound at this time showed metastatic appearing lymphadenopathy increasing in size. Due to significant elevation in calcitonin level, and in order to rule out distant metastases, a Ga68-dotatate PET/CT scan was performed. Results did not show distant spread.

At the patient's latest follow up visit (27 months after initial diagnosis), the calcitonin spontaneously decreased to 1538 pg/mL. Neck ultrasound showed marginal increase in size of a heterogeneous isoechoic and vascular right supraclavicular level 4/7 nodule when compared to the previous study six months prior (see Figure 3). Bilateral nonenlarged and nonspecific cervical lymph nodes were also noted.

Component	Calcitonin
Latest Ref Rng & Units	0-8 pg/mL
5/4/20	1,538 (H)
12/13/2019	3,622 (H)
6/10/2019	1,374 (H)
3/8/2019	1,069 (H)
11/23/2018	1,295 (H)
8/9/2018	924 (H)
6/16/2018	993 (H)
32/10/2018	8,268 (H)

Figure 2: Patient's serum Calcitonin levels over time

The impression is that he has persistent but stable locoregional disease. Following extensive discussion with the patient and family, a third surgery was deferred due to high risk of local complications, which possibly include recurrent laryngeal nerve damage, hypoparathyroidism, and low probability of attaining a surgical cure.

Discussion

Medullary thyroid cancer (MTC) is a neuroendocrine tumor that originates from neural crest derived parafollicular C-cells of thyroid gland, accounting for one to two percent of thyroid cancers in the USA[1] (some studies report 3-5% prevalence). MTC can occur sporadically (75%) or can be hereditary (25%)[1].

RET proto oncogene (rearranged during transfection) located on chromosome 10q 11[2] transmembrane receptor of tyrosine kinase family is the most common gene associated with MTC 2. Most patients with MEN2A, 2B and Familial MTC have RET germline mutation and ~ 50% of sporadic MTCs have somatic RET mutation.[1,2] Somatic RET codon M918T mutation in sporadic MTC often has an aggressive clinical course.

RET was the first MTC-causing gene to be defined, but several other genes associated with MTC have now also been identified. In one study[3], 84 cases of MTC were evaluated with whole-exome sequencing and fluorescence in situ hybridization. The analysis confirmed that mutations in the RET gene are the most common (~50%), followed by mutations in the HRAS and KRAS genes (combined incidence of 20% of MTCs in this study). Furthermore, RAS mutations were only found in sporadic tumors. In addition, a BRAF mutation leading to Lys601Asn (K601N) substitution was identified in one tumor.

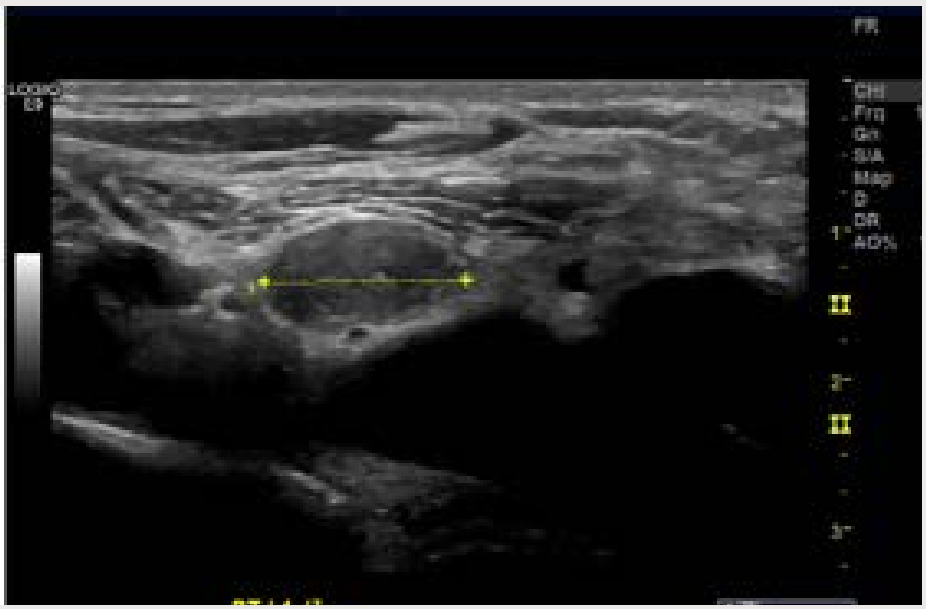


Figure 3: Latest ultrasound imaging of neck showed metastatic appearing lymphadenopathy

BRAF V600E mutations are the most common mutational events in papillary thyroid cancer[4,5]. BRAF K601E mutations have also been previously described in well-differentiated thyroid cancer but lead to different biological behavior compared to BRAF V600E mutations, causing follicular patterned lesions. The presented case is particularly unique and challenging due to the lack of literature regarding BRAF K601E mutation in MTC. A Greek study[6] reported the presence of KRAS [18 of 44 MTC cases- 40.9%] and BRAF V600E [30 of 44 MTC cases- 68.2%], but the MTC related findings have not been replicated in other studies.

In another study[3], ALK fusions, including EML4–ALK and GFPT1–ALK, were found in 2% of MTCs [2 out of 98 cases]. EML4–ALK has previously been reported in a variety of cancers but GFPT1–ALK seems to be a novel type of ALK fusion.

With the advent of targeted therapeutics, identification of genetic drivers of cancer has become very important. ALK fusions represent good therapeutic targets and a number of effective ALK inhibitors (such as Crizotinib and Ceritinib) are approved for use in lung cancers that are positive for ALK fusions. One of the patients in this earlier study presented with a metastatic MTC carrying EML4–ALK, which was treated with Crizotinib and showed a clinically significant response. Unfortunately, none of the approved targeted therapeutics for MTC show activity against BRAF. Furthermore, the BRAF V600E targeting drug vemurafenib was not effective in a melanoma patient with BRAF K601 mutation, which potentially limits the targeted therapeutic options for our patient.[7]

Role of Calcitonin

Secretory products of C-cells [Calcitonin and CEA] are valuable tumor markers in MTC[8]. The serum concentrations of these markers are directly related to C-cell mass. New immunochemiluminometric assays (ICMAs) are highly sensitive and specific for monomeric calcitonin. With ICMAs, cross-reactivity with procalcitonin or other calcitonin-related peptides is largely eliminated, which reduces the need to perform stimulated testing. Calcitonin doubling time of less than six months has been correlated with an adverse prognosis[8].

Role of Imaging in Follow Up

Several imaging modalities are available for ongoing surveillance. Ultrasound examination of the neck is recommended in all patients with MTC[1]. Contrast-enhanced CT of the neck and chest, three-phase contrast-enhanced multi-detector liver CT or contrast-enhanced MRI of the liver, and axial MRI and bone scintigraphy are recommended in patients with extensive neck disease and signs of regional or distant metastases, and in all patients with a serum Calcitonin > 500 pg/mL[1]. F-DOPA PET/CT has been shown to have a higher sensitivity in detecting tumor load and extent of disease while FDG-PET/CT is more accurate in identifying disease progression[9]. Ga68-dotatate PET/CT has been noted to be superior at detecting bone metastatic lesions[10]. After a prior negative contrast enhanced CT scan of the chest, abdomen, and pelvis in the setting of rapidly rising calcitonin levels, the Ga68-dotatate PET/CT was performed to rule out bone metastases and distant metastatic disease as described above.

Conclusion

This challenging case and literature review are aimed to bring attention to the molecular landscape of MTC and new diagnostic and therapeutic approaches for this frequently aggressive type of thyroid cancer. This case adds information regarding a new genetic mutation associated with MTC.

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A Telehealth Tale of Two Organizations During the COVID-19 Pandemic

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COVID-19, a disease caused by a novel coronavirus, SARS-CoV-2, has now become a worldwide pandemic. By October 2020, this disease has claimed more than 1 million lives worldwide, and more than 210,000 lives in the USA, with over 35.8 million cases worldwide.[1] Originating as zoonotic transmission in wet markets in Wuhan, China, this disease quickly became highly transmittable in humans through aerosol droplets. The challenges of social distancing, containment, isolation, and surge capacity across hospitals, clinics, and emergency departments have led to an increase in demands for technologically-assisted care delivery strategies, such as telemedicine and web-based triage.[2] Recognizing the dire need for telemedicine, the U.S. Department of Health and Human Services modified federal privacy and billing regulations under the CARES Act Provider Relief Fund, fueling nationwide escalated adoption of telemedicine modalities.[3]

The Endocrinology Telemedicine Unit, under the leadership of Lauren Willard, DO, (Clinical Lead, Telemedicine, UPMC Endocrine Division) and Archana Bandi, MD, (Clinical Director, Telehealth Services, VA Pittsburgh Healthcare System Endocrine Division) has experienced a rapid growth of telehealth services over the last two quarters. While the global COVID-19 pandemic encouraged this growth, our division had already recognized the importance of telehealth services and were on a trajectory to more broadly and rapidly incorporate virtual visits. These services were pivotal to the Endocrine Division, assuring continued quality care and connection with our patients, particularly our most vulnerable patients living in remote communities.

UPMC Telemedicine

A diabetes team-based telemedicine glycemic management model, known as Telemedicine for Reach, Education, Access, and Treatment (TREAT) was introduced in 2010. Patients identified by their local primary care provider (PCP) are referred to TREAT, a model that includes the specialty services of an endocrinologist and diabetes educator, whose services are often unavailable to people in these outlying communities. The local diabetes educator attends the visit with the patient at the remote site and is able to help with implementation and provide ongoing follow-up and support for the treatment plan prescribed by the endocrinologist. Although TREAT was shown to improve glycemic, behavioral, and psychosocial outcomes[4-6], the program was limited by requiring the patient to travel to the local teleconsult center. Patients with impaired mobility or access to transportation still experienced unaddressed barriers to care despite local teleconsult centers.

In 2019, to address these limitations as telehealth opportunities evolved and expanded, a video model was introduced that provided direct to patient video conferencing for access to specialist care. Patients are connected to the endocrinologist via their personal cell phone or computer, which eliminated the need to travel to a teleconsult center. With positive provider and patient feedback this program was expanded pre-COVID-19 to offer direct to patient video conferencing services care to patients with diabetes.

In addition to outpatient telehealth, our inpatient services, at all sites, are using HIPAA compliant video platforms to communicate with patients and provide effective inpatient consultations. As of 2019, under the leadership of Endocrine Medical Director **Esra Karslioglu-French, MD**, provider-to-provider e-consults were launched to address clinical questions and provide expedited care for PCPs with endocrine concerns for their patients. Provider-to-provider e-consults also help to improve patient access for when face-to-face or video encounters are required.

Since diabetes visits for glycemic management are data driven encounters, the ability to download data from insulin pumps, meters, and continuous glucose monitors became apparent and imperative to assure quality care. The Endocrine Division implemented the Tidepool system, a nonprofit organization committed to providing free software for the diabetes community.[7] Tidepool software provides support to more than 50 diabetes personal devices and applications so that patients can use a single platform for data sharing with their providers. The UPMC Thrive Grants for Change allowed for the installation of Tidepool at our clinical sites, as well as hiring a liaison to help support staff and patients with creating accounts.

Although the Division was already engaging in telemedicine visits, the COVID-19 pandemic led to an increase from approximately eight outpatient

video visits a week to more than 500. We were pleased to learn that the Division of Endocrinology had the most rapid expansion of all medicine subspecialties at UPMC. Due to our existing platform for synchronous video visits and engaging our providers pre-pandemic, we were prepared to widely implement synchronous video visits and phone consults for our outpatients promptly with the onset of social distancing restrictions.

To enhance service during the pandemic, clinical staff working remotely served as liaisons to patients, connecting them to the necessary technology. This additional support allowed for approximately 75% of our visits to be completed via video. Our division was able to successfully complete 5,075 video visits from March through early June. In review of this data, the average age of patients utilizing telemedicine did not differ from those requiring face-to-face visits. Our reach was extensive, with 86% of our patient telemedicine visit volume coming from seven adjacent counties. The data to date suggests that this platform is not just for younger, more tech savvy patients, but can be widely utilized by many of our patients despite their age and/or technological ability.

UPMC dieticians and diabetes educators have also been engaging patients via telemedicine and have found this resource invaluable with gaining insight into home conditions, resources for cooking and preparing meals, and some understanding of how complex living situations could be affecting glycemic control. As patients are becoming more acclimated to this platform of online access and app-driven care, we expect that it will create broader opportunities for education and ongoing self-management support.

The expansion of the Division's telemedicine services is due to consistent support from UPMC leadership with telehealth initiatives. UPMC is one of the nation's leading integrated health systems, aiming to provide high quality and efficient health care to residents across the tri-state area. We have resumed in-office care when needed or preferred by the patient, i.e. for procedures such as thyroid imaging or biopsy. For patient safety, UPMC has expanded SARS-CoV2 testing, provided facemasks to all patients and visitors, mandated mask use in all clinical areas, provided entrance screening, and implemented visitor restrictions.

The pandemic required an immediate response and accelerated the ability of our providers, staff, and patients to adapt to telehealth approaches to care. We anticipate more than half of visits moving forward will remain virtual. Patients feel this platform has provided a beneficial alternative to in-office visits with use of supporting data-sharing applications such as Tidepool. These telehealth strategies will remain a vital means of delivering high-value ongoing care to our patients.

VA Pittsburgh Healthcare System Telemedicine

The VA Pittsburgh Healthcare System (VAPHS), an academic affiliate of the University of Pittsburgh, serves the western market of the Veterans Integrated Service Network 4 (VISN 4). Operating in a hub and spoke manner, with its two medical centers and five community-based outpatient clinics (CBOCs), VAPHS serves as the specialty care hub for remotely located spoke hospitals and CBOCs from Altoona, Erie, Butler, and Clarksburg. A majority of veterans seeking care at VAPHS reside in the mostly rural areas of Pennsylvania, New York, Ohio, and parts of West Virginia, and carry a higher burden of chronic medical conditions such as diabetes (~25%), obesity (~37%), COPD, and congestive heart failure, which instantly puts veterans at a higher risk of poorer outcomes should they contract COVID-19.

Starting in 2010, Dr. Archana Bandi led a system wide endocrine care delivery transformation at VAPHS, initially with electronic consult services, and shortly thereafter with Clinical Video Telehealth services for veterans across geographic distanced areas served by VAPHS. In a large study comprising of more than 400 veterans in each cohort, her team showed that e-consults provide expedient care for veterans with type 2 diabetes mellitus (T2DM) located in remote locations. This care was shown to be comparable to traditional face-to-face care in achieving glycemic control and allowed for better long-term control without burdening resources[8]. Furthering this approach of the telehealth model and creating collaborative pathways through Diabetes Care Network[9], her team further elucidated the importance of breaking the silo model care using the telehealth technologies to expand the access to care for patients located in remote locations.

Prior to the pandemic, VAPHS had one of the most expansive telehealth programs in the nation, namely:

a) robust utilization of home telehealth monitoring services for various biometrics thus providing vital services during the COVID-19 environment,

b) store and forward program for tele-dermatology, tele-wound, and tele-retinal exams,

c) Clinical Video Telehealth (CVT) that connected veterans from their remotely located primary care (PC) clinics to specialty care clinics located in Pittsburgh,

d) electronic consultation allowing specialists to provide consultations to patients and PC providers in an expedited manner,

e) My HealtheVet platform that allows veterans and assigned caregivers to schedule appointments, request refills on prescriptions, access their test results, and communicate with providers via secure messaging, and

f) VA Video Connect allowing video-to-home visits.

While the VAPHS was prepared to rapidly expand the majority of endocrine services to telemedicine, there were some challenges to overcome. In March 2020, based on CDC guidance and the state mandated lockdown, VAPHS initiated care delivery transition strategies to implement virtual modes to prevent the spread of COVID-19 amongst veterans and health care providers. Under the leadership of Executive in Charge Richard Stone, MD, VA central leadership created a COVID-19 response plan[10].

Encompassing four phases, this plan laid out contingencies and planning strategies in phase-1 to sustainment operations and recovery in phase-4. For each of the four phases, telehealth is set to play a pivotal role in the provision of continuity of care for scheduled and incidental outpatient care for non-infected veterans, as well as limit the spread of COVID-19 infection to veterans and staff.

Thus, the day-to-day operations at the endocrine division at VAPHS transferred all new patients and continuity of care to virtual modalities. Due to clinic closures, heavily utilized CVT programs that offered well-designed mechanisms for veterans to rely on PC to coordinate their care with endocrinologists temporarily closed. Poor bandwidth of cell signal in rural areas, tech-related illiteracy in elderly veterans, and lack of equipment needed at home posed a new set of challenges for an overnight transition to video-to-home care.

Additionally, providers who were mostly accustomed to in-person care, or telehealth modalities such as e-consults or CVT, needed training in the transition to video-to-home care (VA Video Connect). While early adaptors of VVC quickly modified their work processes, the remaining infrastructure, including educators and ancillary support staff, needed to change their prior practices. Thus, during the early weeks of COVID-19, telephonic care and electronic consultations became the mainstay. Prior to COVID-19, approximately 50% of new endocrine consultations and up to 75% of diabetes consultations were scheduled as e-consults. Starting March 17, and up to June 5, 2020, the e-consults and phone visits became the major modalities of care delivery leading to more than 1,300 telephonic encounters, 275 diabetes e-consults, and 600 endocrine e-consults.

With the continued resurgence of COVID cases, more veterans became amenable to coordinate care via assistive technology such as the use of VVC or equivalent virtual platforms. Often, these decisions are driven by the complexity of the veteran's medical condition, comfort with technology, family or caregiver's support, and availability of training staff at the medical center. Thus, between the period of June-July, VVC modality in the Endocrine division grew exponentially from less than 1% prior to March 2020 to almost 50% of care delivery by July 2020. The VA also provided funding and technical support for issuance of tablets to conduct VVC for veterans who had no access to such devices. VAPHS strategically opened the in-person clinic capacity (~25%) to continue maintaining an environment to support social distancing and limit the potential exposure to veterans and staff. VAPHS resumed CVT clinics for smaller CBOCs and spoke hospitals, thus offering virtual care to veterans who were unable to conduct VVC visits. Telephonic visits and home telehealth services have continued as additional modalities.

Conclusion

Thus, the COVID-19 pandemic has been a watershed moment in health care delivery bringing telehealth technologies to the forefront. Laggards in this field were led to quick adoption of the virtual modalities and sweeping changes in CMS payment rules and waivers of federal requirements hastened that adoption. We share two very different experiences of uniquely different organizations in terms of adoption on the part of patients and providers to show that there are challenges that are common to both and challenges that are unique to each.

Well-designed processes and organization specific infrastructure, including tech support for veterans, will be an important key for continued use of virtual care in a post-COVID environment in value-driven systems such as the VA. ACCESS the Internet Act[11] – a bipartisan bill recently proposed in the Senate – aims to provide funding of up to two billion dollars across the government for distance learning and telehealth initiatives. Continued restructuring of the billing and regulatory mechanisms in support of telehealth technologies will be key for private sectors. Well-designed studies to understand outcomes for chronic conditions are needed to better delineate the appropriateness of telehealth technology use for long-term care. One thing is certain, telehealth strategies are here to stay and likely to play an even greater role in our future, long after the pandemic ends.

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Available Faculty Positions

Outcomes and Health Services Physician Scientist

The Division of Endocrinology at the University of Pittsburgh (Pitt) and its affiliated Medical Center (UPMC) and Veterans Administration Pittsburgh Health System (VAPHS) seek an MD or MD/PhD board-certified endocrinologist for a full-time academic faculty position, primarily to conduct outcomes, health services, and/or health equity research in the field of endocrinology, diabetes, and metabolism. In addition to clinical expertise, candidates should have a strong history of externally funded research (and associated publications) in outcomes and health services research. Leadership experience is highly desired, as this position has strong potential to develop into a substantial leadership role. Interested candidates should send a cover letter, curriculum vitae, and contact information for three references to Erin E. Kershaw, MD, Chief of Endocrinology, care of Chelsea Dempsey (email: endoadm@pitt.edu). EEO/AA/M/F/ Vets/Disabled.

Academic Clinical Endocrinologist

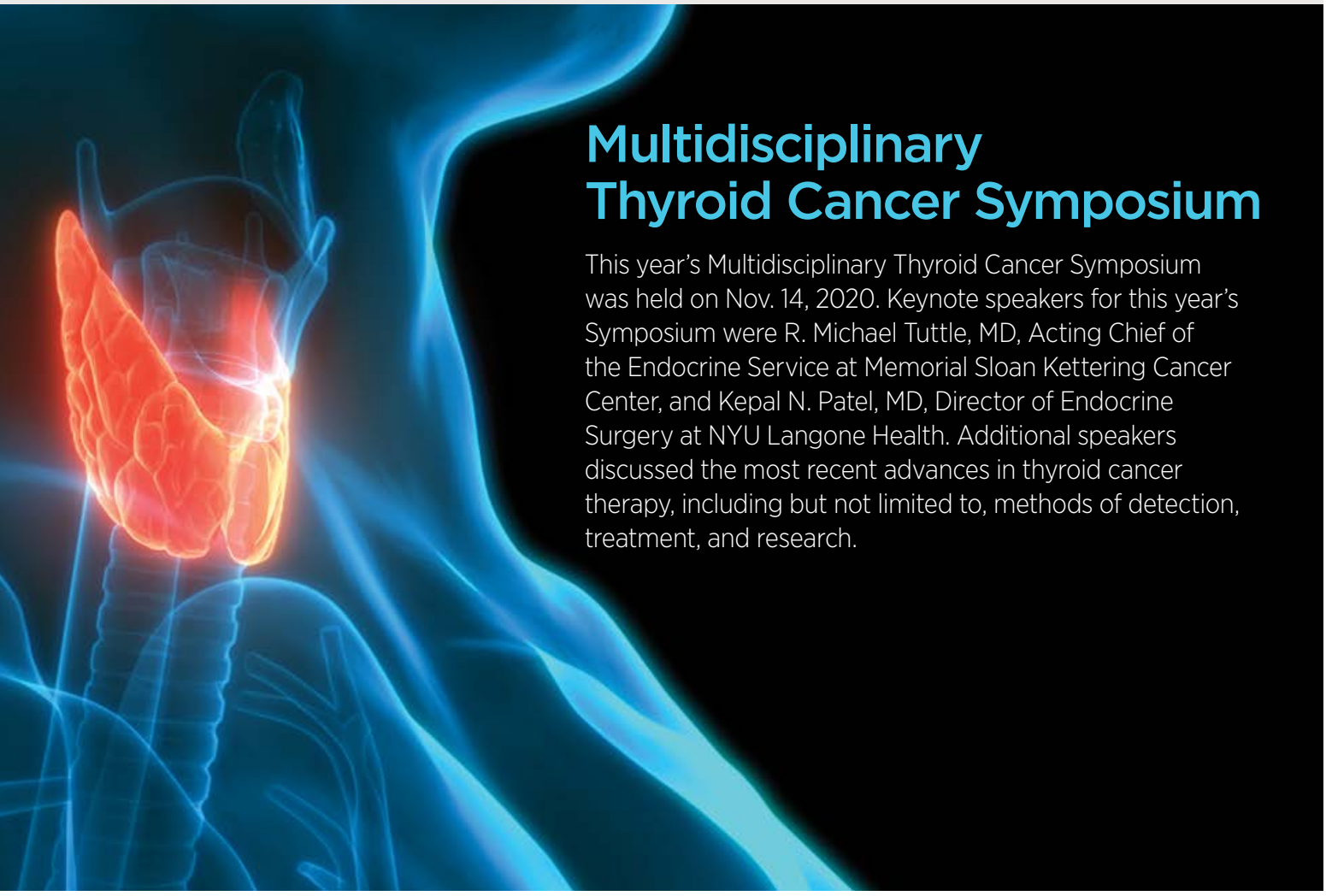
The Division of Endocrinology at the University of Pittsburgh Medical Center (UPMC) seeks full-time BC/BE Endocrinologists to join our premier, academic, high-volume outpatient and inpatient practices. Our nationally ranked Endocrinology program provides a diverse patient mix and substantial opportunity for academic and career growth. Successful candidates will have a strong foundation in endocrinology and diabetes and a desire to participate in all aspects of the academic mission (clinical care, education, and scholarly work). Candidates with an interest in telehealth are particularly desirable to help grow our expanding telehealth program. Interested candidates should send a cover letter, curriculum vitae, and contact information for three references to Erin E. Kershaw, MD, Chief of Endocrinology, care of Chelsea Dempsey (email: endoadm@pitt.edu). EEO/AA/M/F/Vets/Disabled.

Academic Clinical Neuroendocrinologist

The Division of Endocrinology at the University of Pittsburgh (Pitt) and its affiliated Medical Center (UPMC) seeks MD or MD/PhD candidates who are board-certified/eligible in Endocrinology for a position with a strong focus in neuroendocrinology. Pitt/UPMC has a well-established Multidisciplinary Neuroendocrinology Program, which includes multidisciplinary neuroendocrinology clinics, an active inpatient neuroendocrine service, a neuroendocrinology conference series, a quality improvement program, and ongoing research/scholarly work. Candidates should have a strong interest in neuroendocrinology and should be willing to contribute to all aspects of the academic mission (clinical care, education, and scholarly work). Candidates with research interests/qualifications are highly desirable. The primary appointment will be in the Division of Endocrinology within the Department of Medicine. An academic appointment at the University of Pittsburgh would be commensurate with experience, training, and achievement. Interested candidates should send a cover letter, curriculum vitae, and contact information for three references to Erin E. Kershaw, MD, Chief of Endocrinology, care of Chelsea Dempsey (email: endoadm@pitt.edu). EEO/AA/M/F/Vets/Disabled.

2020 ADA
Tour de Cure Pittsburgh

The 2020 American Diabetes Association Tour de Cure Pittsburgh was held on Oct. 3, 2020. We again teamed up with the Pediatric Division of Endocrinology at UPMC Children's Hospital of Pittsburgh and were able to donate over $6,000 to diabetes education, advocacy, and research. We look forward to this fantastic event again next year!



Multidisciplinary Thyroid Cancer Symposium

This year's Multidisciplinary Thyroid Cancer Symposium was held on Nov. 14, 2020. Keynote speakers for this year's Symposium were R. Michael Tuttle, MD, Acting Chief of the Endocrine Service at Memorial Sloan Kettering Cancer Center, and Kepal N. Patel, MD, Director of Endocrine Surgery at NYU Langone Health. Additional speakers discussed the most recent advances in thyroid cancer therapy, including but not limited to, methods of detection, treatment, and research.

Notable Publications

Tong Y, Lear TB, Evankovich J, Chen Y, Londino JD, Myerburg MM, Zhang Y, Popescu ID, McDyer JF, McVerry BJ, Lockwood KC, **Jurczak MJ**, Liu Y, Chen BB. The RNFT2/IL3Rα axis regulates IL3 signaling and innate immunity. *JCI Insight*. 2020 Jan 28. pii: 133652. PMID: 31990690.

Interleukin-3 (IL-3) receptor α (IL-3Rα) is the α subunit of the ligand-specific IL-3R and initiates intracellular signaling in response to IL-3. IL-3 amplifies proinflammatory signaling and cytokine storm in murine sepsis models. Here we found that RNFT2 (RING finger transmembrane-domain containing protein 2, also TMEM118), a previously uncharacterized RING finger ubiquitin E3 ligase, negatively regulated IL-3-dependent cellular responses through IL-3Rα ubiquitination and degradation in the proteasome. In vitro, IL-3 stimulation promoted IL-3Rα proteasomal degradation dependent on RNFT2, and we identified IL-3Rα lysine 357 as a ubiquitin acceptor site. We determined that LPS priming reduces RNFT2 abundance, extends IL-3Rα half-life, and sensitizes cells to the effects of IL-3, acting synergistically to increase proinflammatory signaling. In vivo, IL-3 synergized with LPS to exacerbate lung inflammation in LPS and Pseudomonas aeruginosa-challenged mice; conversely, IL-3 neutralization reduced LPS-induced lung injury. Further, RNFT2 overexpression reduced lung inflammation and injury, whereas Rnft2 knockdown exacerbated inflammatory responses in LPS-induced murine lung injury. Finally, we examined RNFT2 and IL-3Rα in human lung explants from patients with cystic fibrosis and also showed that IL-3 is elevated in mechanically ventilated critically ill humans at risk for acute respiratory distress syndrome. These results identify RNFT2 as a negative regulator of IL-3Rα and show a potential role for the RNFT2/IL-3Rα/IL-3 axis in regulating innate immune responses in the lung.

Weeks, O., Bosee, G.D., Oderberg, I.M., Akle, S., Houvras, Y., Wrighton, P.J., LaBella, K., Iversen, I., Tavakoli, S., Adatto, I., Schwartz, A., Kloosterman, D., Tsomides, A., Charness, M.E., Peterson, R.T., Steinhauser, M.L., **Fazeli, P.K.**, Goessling, W. Fetal alcohol spectrum disorder predisposes to metabolic abnormalities in adulthood. *J Clin Invest*. 2020 Mar 23, Epub ahead of print, PMID: 32202514.

Prenatal alcohol exposure (PAE) affects at least 10% of newborns globally and leads to the development of fetal alcohol spectrum disorders (FASDs). Despite its high incidence, there is no consensus on the implications of PAE on metabolic disease risk in adults. Here, we describe a cohort of adults with FASDs that had an increased incidence of metabolic abnormalities, including type 2 diabetes, low HDL, high triglycerides, and female-specific overweight and obesity. Using a zebrafish model for PAE, we

performed population studies to elucidate the metabolic disease seen in the clinical cohort. Embryonic alcohol exposure (EAE) in male zebrafish increased the propensity for diet-induced obesity and fasting hyperglycemia in adulthood. We identified several consequences of EAE that may contribute to these phenotypes, including a reduction in adult locomotor activity, alterations in visceral adipose tissue and hepatic development, and persistent diet-responsive transcriptional changes. Taken together, our findings define metabolic vulnerabilities due to EAE and provide evidence that behavioral changes and primary organ dysfunction contribute to resultant metabolic abnormalities.

Mady LJ, Grimes MC, Khan NI, **Rao RH**, Chiosea SI, Yip L, Ferris RL, Nikiforov YE, Carty SE, Duwuri U. Molecular Profile of Locally Aggressive Well Differentiated Thyroid Cancers. *Sci Rep*. 2020 May 15;10(1):8031. PMID: 32415114.

Knowledge of the genetic landscape of aggressive well differentiated thyroid cancers (WDTC) is lacking. Retrospective review of institutional database was performed to identify locally-invasive thyroid carcinomas and a comparison cohort of low-risk WDTC. ThyroSeq v2 next-generation sequencing was performed on available tissue. Survival time was analyzed by Kaplan-Meier methods and compared between groups via the log-rank test. Time to recurrence, treating death as a competing risk, was analyzed by cumulative incidence and compared between groups. Of 80 T4 tumors, 29 (36%) met inclusion criteria, of which 25 had genetic and clinicopathologic data. Most (24/25, 96%) harbored at least one genetic alteration, most commonly BRAF V600E (19, 76%), followed by mutations in the promoter region of TERT (14, 56%). Co-occurrence of BRAF and TERT was identified in 12 (48%) and associated with significantly higher risk of recurrence ($p < 0.05$). Conversely, co-occurrence of BRAF and TERT was present in only 5 of 102 (5%) patients presenting with early-stage WDTC. Compared to early-stage WDTC, co-occurrence of BRAF and TERT mutations are common in locally advanced (T4) thyroid cancer and are associated with an increased risk of recurrence. This knowledge may help predict aggressive behavior pretreatment and inform perioperative decision-making.

Awards and Accomplishments

Anjana Murali, Physician Scientist Training Program student in the University of Pittsburgh School of Medicine, was awarded a National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) T32 Medical Student Research Training Supplement grant under the mentorship of Michael Jurczak, PhD.

Previous T32 fellow **Brittany Durgin, PhD**, was awarded a F32 grant from the National Institutes of Health (NIH) under the mentorship of Adam Straub, PhD.

Margaret Zupa, MD; Lia Edmunds, PhD; Vrushali Shah, MD; Anju Paul, MD; and Hammam Alquadan, MD, were accepted into the American Diabetes Association Focus on Fellows program.

Charity Kwamanakweenda, MD, MBA, was promoted to medical director of UPP Endocrinology at UPMC Passavant. In her new role, Dr. Kwamanakweenda will oversee a group of UPP endocrinologists and APPs who will provide inpatient and outpatient endocrine care to UPMC Passavant patients.

Elena Morariu, MD, was named director of the Endocrine Thyroid Unit. In her new role, Dr. Morariu will lead the clinical and academic mission in thyroidology.

Mary Korytkowski, MD, was recognized as one of America's Top Doctors for 2020 and one of the 2020 Best Women in Medicine. Dr. Korytkowski also received a National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) R01 in collaboration with Daniel Rubin, MD, MSc, FACE from Temple University.

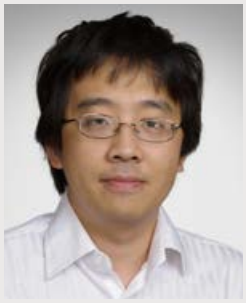
Mary Korytkowski, MD; Susan Greenspan, MD; and **Helena Levitt, MD**, were chosen as 2020 Best Doctors in America.

Alison Kohan, PhD, received a Kenneth Rainin Foundation Synergy Award in collaboration with Gwendolyn Randolph, PhD from Washington University in St. Louis. This grant will be used to expand current research on Crohn's disease.

Yusuke Sekine, PhD, received a Samuel and Emma Winters Foundation grant.

Lauren Willard, DO, was honored as one of the people throughout UPMC chosen to receive the 2019 Excellence in Patient Experience Award.

Esra Karslioglu-French, MD, was honored as an Award for Commitment and Excellence in Service (ACES) awardee. Less than 1% of UPMC employees are awarded this recognition.



Bokai Zhu, PhD has been awarded a National Institutes of Health Director's New Innovator Award from the NIH Common Fund's High Risk, High Reward Research Program. This grant supports exceptionally creative scientists pursuing highly innovative research with the potential for broad impact in biomedical, behavioral, or social sciences within the NIH mission.

Erin Kershaw, MD, was awarded a Medical Student Research Mentoring Merit Award. This is a prestigious award initiated by medical student recommendations and is presented to a Longitudinal Research Project mentor of a graduating University of Pittsburgh School of Medicine student.

Pouneh Fazeli, MD, MPH, was chosen by our fellows to receive the 2020 Dr. Frederick DeRubertis Golden Apple Teaching Award.

Sann Mon, MD, was named the UPMC McKeesport Family Medicine Teaching Attending of the Year for the sixth year in a row.

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NEW FACULTY

Stephanie Hakimian, MD, received her medical degree from the American University of Beirut in 2013. In 2018, she completed an internal medicine residency at the University of Miami/JFK Medical Palm Beach Regional GME. Dr. Hakimian completed her fellowship in endocrinology, metabolism, and molecular medicine at Northwestern University Feinberg School of Medicine in June 2020. Dr. Hakimian's clinical interests include diabetes care and complications prevention in underserved populations, diabetes technology and artificial pancreas, as well as the management of other endocrine disorders involving the thyroid, pituitary, and adrenal glands. Dr. Hakimian joined our Division as a clinical assistant professor in July 2020.

Andrey Parkhitko, PhD, received his PhD from Russian State Medical University in 2013. As part of an exchange program, he completed his graduate studies at Fox Chase Cancer Center and Brigham and Women's Hospital/Harvard Medical School. Dr. Parkhitko comes to the University of Pittsburgh following a postdoctoral fellowship in the Department of Genetics at Harvard Medical School. His research interests include the use of tumor models in *Drosophila* for the search of new modulators of tumorigenesis, as well as metabolic alterations and their potential targeting during aging. Dr. Parkhitko joined the Division of Endocrinology and the Aging Institute as an assistant professor of medicine in September 2020.

To learn more about the UPMC Division of Endocrinology and Metabolism, please visit **UPMCPhysicianResources.com/Endocrinology**.

UPMC PHYSICIAN RESOURCES

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