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ZIKA VIRUS: RELEVANCE TO THE STATE OF HAWAI‘I
William J. Lew; Wen-Yang Tsai PhD; Venkataraman Balaraman MD; Kore Kai Liow MD; Jasmine Tyson BS; and Wei-Kung Wang MD, ScD

MANAGEMENT OF SYMPTOMATIC HEPATIC “MEGA” HEMANGIOMA
William A. Ketchum MD; Kevin M. Lin-Hurtubise MD; Emily Ochmanek DO; Kelli Ishihara MD; and Robert D. Rice MD

PRIMARY CARE PHYSICIAN PERCEPTIONS OF FEMALE PELVIC FLOOR DISORDERS
Jennifer W.H. Wong MD; Bliss E. Kaneshiro MD; and Ian A. Oyama MD

A CASE REPORT OF CONGENITALLY ABSENT PERICARDIUM MASQUERADING AS RECURRENT PERICARDITIS
Tomoki Sempokuya MD; Corey J. Lum DO; Mahdi Veillet-Chowdhury MD; and Kahealani Rivera MD

MEDICAL SCHOOL HOTLINE
Girl Power: Providing Young Women with a Safe Space to Tackle the Tough Topic
Kameko M. Karasaki MS and Julie Crocker BS

HAWAI‘I JOURNAL WATCH
Karen Rowan MS

THE WEATHERVANE
Russell T. Stodd MD
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Zika Virus: Relevance to the State of Hawai‘i

William J. Lew; Wen-Yang Tsai PhD; Venkataraman Balaraman MD; Kore Kai Liow MD; Jasmine Tyson BS; and Wei-Kung Wang MD, ScD

Abstract
Zika virus (ZIKV) is spread among human populations primarily through the bite of Aedes mosquitoes. While most ZIKV infections are asymptomatic or cause self-limited symptoms, the major concerns are its association with Guillain-Barré Syndrome and fetal microcephaly together with other birth defects, known as congenital Zika syndrome (CZS). This article reviews the confirmed Zika cases in the continental United States (U.S.) and Hawai‘i thus far, as well as literature of Zika research relevant to Hawai‘i. The first case of CZS within the U.S. was reported in Hawai‘i, highlighting the unique position of Hawai‘i for emerging and re-emerging infectious diseases. Recent studies of the Zika outbreak in Florida demonstrate the key role of Ae. aegypti mosquito in transmission; continuous and proactive vector surveillance in Hawai‘i is warranted.

Additionally, an updated interim pregnancy guidance for pregnant women with possible ZIKV exposure was summarized. Due to recent decline of ZIKV transmission in the Americas, the risk of ZIKV importation to Hawai‘i has been greatly reduced. However, given the presence of Aedes mosquitoes, climate condition, and status of Hawai‘i as a travel destination and foreign import market, public health officials and healthcare providers should remain vigilant for a potential outbreak of mosquito-borne diseases in the future.

Keywords
Zika virus, microcephaly, congenital Zika syndrome, Hawai‘i

Abbreviations
CDC – Centers for Disease Control and Prevention
CHIKV – Chikungunya Virus
CZS – Congenital Zika syndrome
DENV – Dengue Virus
GBS – Guillain-Barré Syndrome
HDOH – Hawai‘i State Department of Health
NAT – Nucleic Acid Test
PRNT – Plaque Reduction Neutralization Test
ZIKV – Zika Virus

Introduction
Zika virus (ZIKV) belongs to the genus Flavivirus of the family Flaviviridae. It is spread among the human populations via the bite of Aedes mosquitoes.1 Following ZIKV infection most individuals are asymptomatic, however, approximately 20% of those infected with ZIKV exhibit symptoms such as fever, rash, joint pain or red eyes, typically lasting for 2-7 days.2 ZIKV can also be transmitted sexually and vertically from mother to fetus, resulting in microcephaly and other birth defects collectively known as congenital Zika syndrome (CZS).3,4 Microcephaly is a severe birth defect characterized by an abnormally small head and underdeveloped brain.3,4 CZS is also associated with seizures, developmental delay, intellectual disability, difficulties with movement and balance, along with other neurological issues such as dysphagia and hearing and vision problems.3,4 In addition, ZIKV infection is associated with Guillain-Barré Syndrome (GBS), a demyelination of the peripheral nerves.5

Although several candidate Zika vaccines are undergoing clinical trials, none is currently available.3 ZIKV was first isolated from a rhesus monkey in 1947 and from Aedes mosquitoes in 1948 in Uganda.1,2 In 2007, the Island of Yap reported its first outbreak of Zika.1,2 During the 2013-2014 outbreak in French-Polynesia, ZIKV infection was found to be linked to GBS.1,2 According to the Centers for Disease Control and Prevention (CDC), Zika was endemic in over 100 areas including: Africa, Asia, the Caribbean, Central America, North America, the Pacific Islands, and South America during 2015-2017.6 Limited cases have been reported since August 2017.

ZIKV transmission to humans involves primarily the anthropophilic Ae. aegypti and to a lesser extent the peridomestic Ae. Albopictus.7 In Hawai‘i, Ae. aegypti arrived in ~1890, followed by Ae. albopictus a few years later. Although previous surveys showed that the percentage of Ae. aegypti (out of Ae. aegypti and Ae. albopictus together) in Honolulu was once high (67% in 1913), it dropped to 0% in 2002.2 The decline of Ae. aegypti populations could be attributed to the regional Ae. aegypti eradication program in the 1960s. A survey in 2002 shows the dispersal of Ae. albopictus throughout the islands and the presence of Ae. aegypti in certain locations on Hawai‘i Island, mainly Hilo, Kona, Kealakekua, and the east and west coasts.7

Although all Zika cases reported in Hawai‘i thus far are travel-related, risk of an outbreak remains.8 In addition, Hawai‘i’s large number of international and domestic travelers (~8,900,000 visitors per year by air and cruise ships) together with its role as an import market, place it under continual threat of importation of mosquitoes, autochthonous infection, and potential outbreak.9,10 This article reviews the confirmed Zika cases in the continental United States (U.S.) and Hawai‘i, as well as scientific literature on Zika research relevant to Hawai‘i. The goal is to provide insights and recommendations to prevent and control a future Zika outbreak in Hawai‘i.

Methods
The authors searched and reviewed reports from government and state organizations, as well as published literature (in English) through the PubMed database. A search with the key words “Zika” and “Hawaii,” as of July 26, 2018, resulted in a total of 21 articles, of which 7 were excluded because they were non-Hawai‘i related or non-Zika. The remaining 14 articles (references 12-19, 21-22, 25-27 and 35) together with references cited in these articles were reviewed.
Results
Of the 14 peer-reviewed articles, eight are basic research on Zika transmission, serodiagnosis, animal models, and vaccine studies conducted by local researchers, indicating several active Zika research programs in Hawai‘i. Six are related to clinical medicine and public health with implications to Hawai‘i. The major findings are summarized below:

1. The first case of CZS within the U.S. and a related study:
The first case of microcephaly linked to ZIKV within the U.S. was reported on January 15, 2016 in a baby born in Hawai‘i. The Hawai‘i State Department of Health (HDOH) received a report from CDC confirming that the baby had been infected with ZIKV. The mother had resided in Brazil during the previous year, and was most likely infected by a mosquito during the first trimester of her pregnancy, potentially affecting embryonic brain development. Another retrospective study revealed higher prevalence of ZIKV antibodies in mothers from Hawai‘i (1 IgM positive and 3 IgG positive out of 6) who delivered babies with microcephaly compared with those (1 IgG positive out of 12) who delivered babies without microcephaly between 2009-2012, suggesting possible Zika cases and associated microcephaly before 2015.

2. Travel-related Zika cases in Hawai‘i:
The first confirmed case of travel-related Zika in Hawai‘i was reported in October 2015 on Hawai‘i Island. This individual became infected outside of the state. By the time of discovery, local health officials determined that no mosquito had transmitted the disease, and that the ZIKV was not locally acquired. A state vector control team was sent to survey the patient’s workplace and residence for mosquitoes. Hawai‘i’s Civil Defense Administrator informed the public that County of Hawai‘i officials together with the HDOH were, at the time, assessing affected areas for mosquito activity, educating communities, and treating mosquito breeding sites. From 2015 to 2017, there were 21 laboratory-confirmed travel-related Zika cases in Hawai‘i (4 in 2015, 11 in 2016, and 6 in 2017). Zika infection is notifiable in Hawai‘i. Healthcare providers are required to report suspect ZIKV infections to the Disease Outbreak Control Division of HDOH as soon as a provisional diagnosis is established. The Disease Investigation Branch has investigation plans for ZIKV and other arboviruses including dengue virus (DENV) and chikungunya virus (CHIKV) in place. The State Laboratory Division performs different ZIKV tests including the reverse transcriptase polymerase chain reaction and IgM test for Hawai‘i and the Pacific Islands. Any positive or equivocal IgM result will be tested by plaque-reduction neutralization test at the CDC. A recent study comparing different surveillance strategies during the 2015-2017 ZIKV epidemic in the continental U.S. revealed that testing symptomatic patients at the emergency department is a more efficient strategy for detecting transmission compared with testing blood donors or pregnant women.

3. A Zika outbreak in the continental U.S.: implications for Hawai‘i State
A study of the Zika outbreak in Florida in July 2016 showed that the primary mode of local transmission was the bite by Aedes mosquitoes. Mosquito surveillance revealed that 99.8% of the 24,351 mosquitoes collected were Aedes aegypti, and 8 pools (≤ 50 mosquitoes each pool) tested positive for ZIKV. It was estimated that about 1 of 1600 Aedes aegypti mosquitoes were infected with ZIKV, similar to the infection rates reported during the DENV and CHIKV outbreaks. Additionally, the number of ZIKV cases strongly correlated with the abundance of Aedes aegypti in each transmission zone, suggesting the importance of vector abundance to human infection rates.

Although Aedes aegypti, the principal vector of DENV, ZIKV and CHIKV, is only present in certain locations on Hawai‘i Island, its distribution correlates with the distribution of human cases during the 2015-2016 dengue outbreak, suggesting its potential contribution to future outbreaks of these three viruses. The public health response and control measures following the 2015-2016 outbreak have been described in the HDOH website and reviewed recently. The public health response and control measures following the 2015-2016 outbreak have been described in the HDOH website and reviewed recently. The public health response and control measures following the 2015-2016 outbreak have been described in the HDOH website and reviewed recently.

4. Recommendation for pregnant women
Although only 5%-6% of U.S. pregnant women with possible ZIKV infection during pregnancy gave birth to babies with CZS (9-11% if infection occurred during first trimester), it is an existing threat and must be monitored with close attention. Clinical features of CZS which includes microcephaly can be potentially identified by fetal ultrasonography but may need continued surveillance of the newborn through infancy to identify subtle abnormalities. According to the recent CDC recommendations, all pregnant women should be asked if they have possible ZIKV exposure including history of travel to or residence in areas with ZIKV transmission and possible sexual exposure to ZIKV before and during current pregnancy, or symptoms of Zika disease during current pregnancy. Before testing for ZIKV infection, the limitations and potential risks of misinterpretations of test results should be discussed. The updated interim pregnancy guidance for symptomatic and asymptomatic pregnant women with possible ZIKV exposure is summarized in Figure 1.
Figure 1. Summary of CDC’s interim guidance for pregnant women with possible ZIKV exposure. Algorithm for symptomatic (A) and asymptomatic (B) pregnant women was presented as two concise flow-charts based on the text and figures in references 37 and 38. NAT: nucleic acid test; PRNT: plaque reduction neutralization test.37,38
Discussion
Since ZIKV transmission has dramatically declined recently in the Americas, the risk of importation of Zika to Hawai‘i has been greatly reduced. However, the specter of CZS and its potential re-emergence in the tropical and subtropical regions highlight the importance of continuous effort on research, vaccine development, surveillance and vector control.

Hawai‘i’s report of the first CZS case within the U.S. on January 15, 2016, 5 months before such reports in the continental U.S., highlights the unique position of Hawai‘i for emerging and re-emerging pathogens. This is analogous to the report of the first H1N1 case in Hawai‘i during the 2009 pandemic, 21 days after the CDC reported the first cases in the continental U.S.

Based on serological tests for ZIKV antibodies, the possibility that Zika cases and CZS might have occurred in Hawai‘i between 2009-2012 is an interesting observation but remains to be verified by further studies of archived samples collected in Hawai‘i using different serological tests.

Studies of Zika outbreak in Florida indicate the critical role of *Ae. aegypti* in human transmission. Given the presence of *Aedes* mosquitoes (widespread *Ae. albopictus* and *Ae. aegypti* in some sites on Hawai‘i Island), a climate compatible with a year-round mosquito season, and the geographic location of Hawai‘i as a travel destination and foreign import market, public health officials and healthcare providers should remain vigilant for a potential outbreak of mosquito-borne diseases such as ZIKV, DENV and CHIKV.

There are several limitations. First, since the literature search on PubMed database was up to July 2018, articles published subsequently or in non-PubMed database were not covered by this review. Second, this review focused on clinical and public health related research; basic research programs on ZIKV by scientists in Hawai‘i were beyond the scope of this review. Third, the summary of guidance for pregnant women with possible ZIKV exposure was based on the most recent CDC recommendations published in July 2017. Continuous update of any revision or new guidelines from the CDC is warranted.

Conflict of Interest
None of the authors identify any conflicts of interest.

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Management of Symptomatic Hepatic “Mega” Hemangioma

William A. Ketchum MD; Kevin M. Lin-Hurtubise MD; Emily Ochmanek DO; Kelli Ishihara MD; and Robert D. Rice MD

Abstract
The majority of giant hepatic cavernous hemangiomas are asymptomatic and can safely be observed. However, when a lesion becomes symptomatic, affecting quality of life or cannot be distinguished from a malignancy, then operative therapy should be considered. We herein present a case of a symptomatic 12cm x 14cm x 17cm “mega” hemangioma (>10cm) of the left hepatic lobe. This lesion was initially refractory to transarterial embolization of the left hepatic artery, but was subsequently treated successfully with a left lateral extended hepatic segmentectomy (resection). We thus advocate a rational treatment algorithm for management of hepatic “mega” hemangiomas.

Keywords
hepatic cavernous hemangioma, transarterial embolization, liver resection

Introduction
Cavernous hemangiomas are the most prevalent (73%) benign tumors affecting the liver, with incidence up to 7.3% on autopsy series.1 They are also a common incidental finding on routine imaging, and tend to be small (<1 cm), stable, and asymptomatic. Lesions > 4 to 5 cm are considered giant hemangiomas; despite large intra-abdominal growth, giant hemangiomas generally remain asymptomatic in most cases.1-2 Hepatic hemangiomas are more prevalent in middle-aged women, can progress in size during pregnancy and can be diagnosed via multiple imaging modalities including ultrasound, MRI, and CT, but the gold standard for diagnosis remains IV contrast-enhanced abdominal CT.1-2

Management of giant hemangiomas is controversial, and prophylactic treatment via surgical resection or other means has historically been the standard of care to avert potential grave complications, such as rupture/bleeding, thrombosis, or disseminated intravascular coagulation / consumptive thrombocytopenia (Kasabach-Merritt Syndrome).2 However, prevention of rupture should not be considered a lone indication for surgical extirpation of an asymptomatic lesion.3 Conversely, treatment should be offered to patients with symptomatic lesions affecting quality of life, and the literature describes various approaches that can safely and effectively be employed.4-6

It is well established that the preponderance of giant hepatic hemangiomas are asymptomatic, in spite of their foreboding designation.1,10 Therefore, we feel it would be useful to introduce a new distinct terminology, “mega,” for hepatic hemangiomas measuring >10cm, as these lesions are far more likely to provoke symptoms with possible complications. Herein, we report a case of a symptomatic hepatic mega-hemangioma, and advocate a rational treatment algorithm for managing patients with this condition.1-12

Case Report
A 34-year-old otherwise healthy male was referred to our general surgery clinic at TAMC (Tripler Army Medical Center) for evaluation of a firm, large, non-tender abdominal mass, hepatic cavernous hemangioma, easily visible and palpable on physical exam which protruded and extended across the midline of the abdominal wall from the right upper quadrant, and also extended caudally midway between the xiphoid and umbilicus. The patient first noticed the mass approximately two months prior to evaluation, and complained of moderate abdominal discomfort and intermittent early satiety. However, his primary concerns were the rapid growth, and increasing visibility of this hepatic mass on his abdominal wall.

Of note, he was found to be near thrombocytopenic with a platelet count in the low 100,000 per microlitre (range 150,000-450,000) and anemia with a hemoglobin and hematocrit that nadired at 11.6g/dL (12-16) and 34.7% (40-50), respectively. His coagulation profile was also noted to be abnormal, with a prothrombin time of 15.5sec (10-13), a fibrinogen of 102mg/dL (200-500), and an elevated D-dimer, though he did not experience any bleeding stigmata or manifest signs of thrombocytopenia. A subsequent CT examination of his abdomen and pelvis with IV and oral contrast were performed, which revealed a 12cm x 14cm x 17cm lesion located in the left hepatic lobe, consistent with a mega-hemangioma. (Figure 1)

Due to the patient’s initial moderate symptoms of abdominal pain and early satiety after meals, we opted for conservative management and consulted our Interventional Radiology Service to perform a transarterial embolization procedure, with the goals of decreasing the size of the mass and relieving his gastrointestinal symptoms.

While undergoing radiologic interventions, pre-embolization angiography revealed a normal course of the celiac arterial axis. A selective angiography was next performed by means of a VS1 catheter, demonstrating two vessels from the left hepatic artery that were supplying the hemangioma. (Figure 2) Further subselection of the left hepatic artery demonstrated contrast pooling with a characteristic blush to the known hemangioma.

Bead Block® (Terumo Europe/ Biocompatibles) microspheres were used to embolize the left hepatic artery with an immediate result; there was decreased blood flow and no significant blush was seen in the post-embolization angiogram. (Figure 3) The patient tolerated the procedure well and there were no complications.

Post-procedure imaging at 3 months revealed that the lesion had been refractory to the transarterial embolization procedure.
of the left hepatic artery, as it effectively did not downsize, but it did help alleviate some of his abdominal symptoms. (Figure 4) This symptomatic relief was short lived however since after a few months, the patient continued to have abnormal serum laboratory tests and worsening of other baseline symptoms which include: increasing abdominal girth and new-onset shortness of breath with moderate physical exertion. The lesion had also become tender to palpation on physical examination.

The patient was offered a repeat embolization by our interventional radiologist, but he declined and opted instead for an elective surgical resection or enucleation of his hemangioma. This was completed successfully 9 months following his embolization procedure. Upon entry into the abdomen, a large liver hemangioma was readily apparent replacing the left lobe of liver. There was no blood noted or evidence of other pathology within the abdomen. The extent of the lesion was assessed and it was determined that it occupied and greatly expanded the entire left lateral segment without extension beyond the falciform ligament. The decision was made intraoperatively to perform a left lateral extended segmentectomy to include the involved segments 2 and 3 and to ensure complete resection of the mass. Hemostasis was good following the liver parenchymal dissection with a moderate amount of blood loss (500mL, estimated blood loss). The patient remained hemodynamically stable throughout the procedure and was transferred to the ICU for close postoperative monitoring.

His postoperative course was relatively uncomplicated. He required transfusion with one unit of packed red blood cells for symptomatic anemia on postoperative day #2 and one unit of cryoprecipitate due to low fibrinogen and low grade DIC (disseminated intravascular coagulation). He maintained a stable hemoglobin/hematocrit and coagulation profile following his transfusions. He was discharged home on postoperative day #6 ambulating and tolerating a regular diet with well-controlled incisional pain while on oral analgesics.

At six-month clinic follow-up, the patient was completely asymptomatic, and he had no complaints related to his surgery. A single post-procedure CT scan of the abdomen demonstrated normal post-surgical changes, along with expected hypertrophy of his right hepatic lobe. (Figure 5) There was no recurrent hemangioma evident. The patient was again seen at 18 months after surgery in our clinic and he remained asymptomatic without complications.
Figure 4. No significant change in size or appearance of mega hemangioma three months status post-embolization, measuring 12.3cm x 13.7cm x 17.2cm.

Figure 5. Six month status-post extended left lateral segmentectomy.

Discussion
With the advent of minimally invasive interventional radiology techniques, transarterial embolization has emerged as a reasonable and often effective treatment option for this benign condition given its low rate of morbidity.5-8 In our current case, while the embolization procedure did not visibly downsize the lesion, it also did not complicate or negatively impact the subsequent operative intervention of definitive hepatic resection. Additionally, it has been suggested that embolization therapy can have a positive effect on the technical aspect of the surgical procedure because it facilitates mobilization of the liver by reducing the overall volume of the hemangioma via occlusion of the main feeding vessels from the hepatic arteries. This is especially relevant for patients at high risk for bleeding during and after surgery, such as those with centrally located hemangiomas and those with hemangiomas in close proximity to vascular structures such as portal or hepatic veins.8 Embolization therapy has been successfully utilized to alleviate symptoms of mass-effect abdominal pain and discomfort in the time period prior to surgical intervention.5-7,8 Some institutions even advocate same day embolization followed by liver resection.1 Therefore, it is our recommendation that initial treatment with transarterial embolization for life-altering symptomatic mega hepatic hemangiomas (> 10 cm) be considered as either the sole therapy or as a staging (bridge) procedure prior to definitive surgery.1,5,7-8 In summary, we advocate a stepwise assessment of size, location, growth rate with IV contrast CT or MR imaging plus adding clinical symptomatology as the initial work-up of mega hepatic hemangiomas (>10 cm) leading to upfront embolization if indicated, then to definitive surgical therapy if embolization fails (Figure 6). In a similar vein the American College of Gastroenterology in their practice guideline recommends that for life-style altering symptomatic giant hemangiomas greater than 10 cm that these patients be referred for definitive surgical or non-surgical therapy by an experienced healthcare team of providers.13

This case report may be criticized for its exclusion of other treatment modalities, most notably radiofrequency (RFA) and microwave ablations (MWA). However, in general these modalities are reserved for moderate size hepatic lesions (5-10cm) with the caveat that MWA tends to work better than RFA for relatively larger hemangiomas, and MWA’s effectiveness compared to RFA is not hampered much by the “current/heat-sink” phenomenon for hemangiomas that are located adjacent to portal or major hepatic veins, nor by the local impedence of ablated (dessicated) tissue, hence these methods have been shown to be promising for definitive hepatic hemangioma treatment in some cases.14-15 The effectiveness of these ablative modalities however are limited by the “heat sink” phenomenon for hemangiomas that are
located adjacent to portal or major hepatic veins. Comparison of these ablative modalities to embolization is a potential area of further study that can help determine how ablation fits into our current proposed treatment algorithm outlined above.\textsuperscript{15} Radiation and liver transplantation are alternative treatment options; however the first is for unresectable cases and is not considered definitive and the second is generally reserved for multiple simultaneous mega hemangiomas (>10cm) in which resection of a large volume of liver parenchyma would risk post-op liver failure.\textsuperscript{6,16}

**Conclusion**

Hepatic “mega” hemangiomas (>10cm) can be safely observed when asymptomatic given their low risk for spontaneous or traumatic rupture and other complications.\textsuperscript{2} Treatment should be reserved for symptomatic patients after completing a thorough history and physical evaluation to exclude other etiologies for their complaints.\textsuperscript{7,8} When treatment is indicated based on life-quality altering symptoms, it is prudent to begin with a minimally-invasive interventional radiology procedure (embolization or ablation) given its inherently low risk of morbidity such as bleeding compared to surgery.\textsuperscript{3,14-15} If however embolization or ablative therapies are ineffective, hepatic surgical resection or enucleation remains the definitive treatment for these refractory cases.\textsuperscript{2,4,6}

The views expressed in this manuscript are those of the authors and do not reflect the official policy or position of the Department of the Army, Department of Defense, or the U.S. Government.

**Conflict of Interest**

None of the authors identify a conflict of interest.

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**References**

Primary Care Physician Perceptions of Female Pelvic Floor Disorders

Jennifer W.H. Wong MD; Bliss E. Kaneshiro MD; and Ian A. Oyama MD

Abstract
Primary care physicians (PCPs) play a major role in patient access to appropriate health care. This study examines PCPs’ perceptions and management of female pelvic floor disorders. Surveys were mailed to family medicine and internal medicine physicians associated with the Hawai‘i Medical Service Association. A total of 150 respondents were included. Only 34%, 38%, and 9% of respondents correctly identified the prevalence of urinary incontinence (UI), overactive bladder (OAB), and pelvic organ prolapse (POP), respectively. For disease-specific screening, the highest response was that PCPs “sometimes” screen for UI (36%) and OAB (45%) but “hardly ever” screen for POP (43%). With regards to management of UI and OAB, respondents would either treat (30% UI, 39% OAB) or start treatment then refer (33% UI, 49% OAB). For POP, nearly all of respondents (81%) would immediately refer. When consultation is necessary, there was a similar rate of referral to urology and urogynecology for UI (38% urology, 42% urogynecology), and a similar rate of referral to gynecology and urogynecology for POP (47% gynecology, 46% urogynecology). For OAB, PCPs would refer to urology (54.0%), then urogynecology (31%), and lastly gynecology (13%). A majority of respondents were “somewhat familiar” (56%) with urogynecology as a subspecialty, while 27% were “very familiar”, 13% were “slightly unfamiliar”, and 3% were “very unfamiliar”. This study shows that most PCPs are not comfortable managing common urogynecologic problems and would likely benefit from education on how to diagnose, treat, and refer for these conditions in order to optimize patient care.

Keywords
Health-seeking behavior, Pelvic floor disorders, Primary care, Referral and consultation, Urogynecology

Abbreviations
PCP – primary care physician
PFD – pelvic floor disorder
UI – urinary incontinence
OAB – overactive bladder
POP – pelvic organ prolapse

Introduction
Urogynecology, also known as female pelvic medicine and reconstructive medicine, is a relatively new sub-speciality, receiving accreditation in the year 2011.1 Urogynecologists are experts in treating female pelvic floor disorders (PFDs) such as female urinary incontinence, fecal incontinence, pelvic organ prolapse, and pelvic pain. Female pelvic floor disorders negatively impact the quality of life of those affected,2–4 yet over half of affected individuals fail to seek medical care due to various reasons, including embarrassment and ignorance.5–8 The healthcare burden of PFDs is expected to increase significantly over the next 30 years as the United States population ages and the rates of obesity, parity, and hysterectomies continue to rise. The prevalence of female PFDs is predicted to increase from 28.1 million Americans in the year 2010 to 43.8 million in 2050.9

Approximately 17% of women suffer from urinary incontinence (UI),10,11 30% of women suffer from overactive bladder (OAB),12 and 27% of women suffer from pelvic organ prolapse (POP).13 According to the University of Hawai‘i Division of Urogynecology, 78% of their patients are referred from gynecologists, 17% from PCPs, and 5% from self-referrals. This low referral rate from PCPs suggests a lack of knowledge about urogynecology as a subspecialty. In most healthcare systems, PCPs serve as “first-contact” care. When a new medical need arises, PCPs act as the entry point into the health care system. Thus, PCPs must be familiar with a variety of medical conditions because recognition is the first step in treatment. PCPs who feel confident managing female PFDs should proceed with treatment, but they must also know when and where referrals are appropriate, such as a case of UI that has failed conservative management or a case of POP complicated by urinary retention.

There is a current lack of knowledge regarding PCP competency with female PFDs. Only two previous studies have examined this important topic. These studies have shown that up to 75% of women with symptoms of UI fail to receive a diagnosis,14 and possibly more than half of family medicine physicians do not understand UI.15 The purpose of this study is to examine the perceptions and management of female PFDs among PCPs in Hawai‘i. This study is important because it highlights deficits in the healthcare system and identifies potential solutions to expand patient access to appropriate medical care.

Methods
This is an observational cross-sectional study. Study approval was obtained from the University of Hawai‘i institutional review board. An anonymous provider survey (Figure 1) was modeled after that created by Mazloomdoost, et al., 2017.16 The survey was designed to capture subject demographics (sex, specialty, practice type, years in practice, and number of patients daily), perceptions of female PFDs (prevalence, screening, management, and referral), and familiarity with urogynecology as a subspecialty. The survey was then piloted among 6 obstetrics/gynecology attending physicians, fellows, and residents. Suggested revisions were incorporated to enhance clarity. In August 2017, surveys were mailed to the offices of all family medicine and internal medicine physicians (N = 894) associated with the Hawai‘i Medical Service Association, the largest health insurer in the State of Hawai‘i. Surveys included an introductory letter signed by Dr. Ian Oyama, the Division Chief of Urogynecology at the University of Hawai‘i, in addition to a return envelope with a prefilled mailing address and prepaid postage stamp to facilitate participant response.
1. What is your sex?
   □ Male
   □ Female

2. What is your specialty?
   □ Family medicine
   □ Internal medicine

3. What is the nature of your practice?
   □ University/academic
   □ Private practice
   □ Hospitalist
   □ Community

4. How many years have you been in practice?
   □ 0-10 years
   □ 11-20 years
   □ > 20 years

5. On average, how many patients do you see each day?
   □ ≤ 20 patients
   □ 21-30 patients
   □ 31-40 patients
   □ > 40 patients

6. What is the PREVALENCE of the following conditions?

<table>
<thead>
<tr>
<th>Condition</th>
<th>&lt;10%</th>
<th>10%-30%</th>
<th>31%-45%</th>
<th>46%-60%</th>
<th>61%-75%</th>
<th>&gt;75%</th>
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<tbody>
<tr>
<td>Urinary incontinence</td>
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<tr>
<td>Overactive bladder</td>
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<tr>
<td>Pelvic organ prolapse</td>
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</table>

7. How often do you SCREEN female patients for the following conditions?

<table>
<thead>
<tr>
<th>Condition</th>
<th>Always</th>
<th>Very often</th>
<th>Sometimes</th>
<th>Hardly ever</th>
<th>Never</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urinary incontinence</td>
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<td>Overactive bladder</td>
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<tr>
<td>Pelvic organ prolapse</td>
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</table>

8. How would you MANAGE a female patient with the following conditions?

<table>
<thead>
<tr>
<th>Condition</th>
<th>Provide reassurance and expectant management</th>
<th>Treat the patient myself</th>
<th>Start treatment, then refer to specialist</th>
<th>Immediately refer to specialist</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urinary incontinence</td>
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<td></td>
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<tr>
<td>Overactive bladder</td>
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<tr>
<td>Pelvic organ prolapse</td>
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</table>

9. What specialty would be your FIRST CHOICE for referral?

<table>
<thead>
<tr>
<th>Condition</th>
<th>Gynecology</th>
<th>Urology</th>
<th>Urogynecology</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urinary incontinence</td>
<td></td>
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<tr>
<td>Overactive bladder</td>
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<tr>
<td>Pelvic organ prolapse</td>
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10. Are you familiar with the subspeciality of urogynecology?
    □ Very familiar
    □ Somewhat familiar
    □ Slightly unfamiliar
    □ Very unfamiliar

Figure 1. Survey Mailed to All Family Medicine and Internal Medicine Physicians on the Hawai‘i Medical Service Association Provider List.
Only fully and properly completed surveys were included in the study, and the remainder was excluded. Common mistakes included skipping questions or selecting multiple answers when asked for only one. Data were analyzed using IBM SPSS Statistics for Windows, Version 25 (IBM Corp., Armonk, NY). Descriptive statistics were reported using percentages. Associations between demographic variables and responses were analyzed using Pearson’s Chi-Square test. Statistical differences were considered significant for $P$-values less than .05.

**Results**

A total of 894 surveys were mailed out, with a response rate of 22% (n=198). However, only 150 of the surveys were completed properly and included in the study.

Respondents were evenly distributed with respect to specialty (42% family medicine, 58% internal medicine). However, the largest proportion of respondents were male (68%), private practice (81%), in practice for >20 years (53%), and caring for patients daily <20 (47%) or 21-30 (46%) (Table 1).

When asked to report the prevalence of various pelvic floor disorders, only 34%, 38%, and 9% of respondents were able to correctly identify the prevalence of UI, OAB, and POP, respectively. A majority of respondents underestimated the prevalence of these pelvic floor disorders, (Figure 2). For disease-specific screening, the highest response was that PCPs will “sometimes” screen for UI (36%) and OAB (45%) but “hardly ever” screen for POP (43%) (Figure 2). Responses were evenly distributed among physicians who “always” screen (7% UI, 6% OAB, 4% POP) and “never” screen (6% UI, 7% OAB) for pelvic floor disorders, with the exception of 14.7% of respondents who “never” screen for POP (Figure 2). With regards to the management of UI and OAB, a majority of respondents will either treat (30% UI, 39% OAB) or start treatment then refer (53% UI, 49% OAB). For POP, 81% of respondents will immediately refer, while 17% will start treatment then refer (Figure 2). When consultation is necessary, there was not a statistically significant difference in referral to urology and urogynecology for UI (38% urology, 42% urogynecology) and OAB (54% urology, 31% urogynecology) nor a statistically significant difference

<table>
<thead>
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<th>Table 1. Demographics of Respondents.</th>
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<td><strong>Sex</strong></td>
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<tr>
<td>Male</td>
</tr>
<tr>
<td>Female</td>
</tr>
<tr>
<td><strong>Specialty</strong></td>
</tr>
<tr>
<td>Family Medicine</td>
</tr>
<tr>
<td>Internal Medicine</td>
</tr>
<tr>
<td><strong>Practice Type</strong></td>
</tr>
<tr>
<td>University</td>
</tr>
<tr>
<td>Private</td>
</tr>
<tr>
<td>Hospitalist</td>
</tr>
<tr>
<td>Community</td>
</tr>
<tr>
<td><strong>Years in Practice</strong></td>
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<tr>
<td>0-10</td>
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<tr>
<td>11-20</td>
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<tr>
<td>&gt;20</td>
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<tr>
<td><strong>Number of Patients Daily</strong></td>
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<tr>
<td>&lt;20</td>
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<tr>
<td>21-30</td>
</tr>
<tr>
<td>31-40</td>
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<td>&gt;40</td>
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Figure 2. Survey Results (UI=urinary incontinence, OAB=overactive bladder, POP=pelvic organ prolapse).
in referral to gynecology and urogynecology for POP (47% gynecology, 48% urogynecology). The few respondents who would refer to an “other” specialty, either specified physical therapy or did not specify a specialty (Figure 2). A majority of respondents reported being “somewhat familiar” (56%) with the subspecialty of urogynecology, while 27% were “very familiar”, 13% were “slightly unfamiliar”, and 3% were “very unfamiliar” (Table 2).

There was a significant difference between respondent sex and estimated prevalence of UI (P-value .01) and OAB (P-value .04). Males PCPs were more likely than female PCPs to underestimate the prevalence of UI (56% vs 30%) and OAB (57% vs 40%). There was also a significant difference between years in practice and management of UI (P-value .01). PCPs practicing >20 years had higher rates of immediate referral (15%) than those practicing 0-10 years (3%) and 11-20 years (5%). However, the rates of starting treatment then referring were similar regardless of years in practice (55% for PCPs practicing 0-10 years, 50% for PCPs practicing 11-20 years, and 54% for PCPs practicing >20 years). No statistically significant difference by specialty was observed.

**Discussion**

PCPs play a major role in patient access to appropriate healthcare. To date, there are only two published studies evaluating PCPs’ knowledge and treatment of female PFDs. In 2016, Mazloomdoost, et al, surveyed 108 internal medicine and family medicine physicians at a large academic community hospital system. The study found that PCPs were more familiar with UI and OAB than POP, and nearly one-fifth were unaware of urogynecologists in their system. In 2017, Mazloomdoost, et al, distributed surveys nationally via the American Medical Association internal medicine and family medicine residency database. The study received 391 responses from faculty physicians and found that nearly half of providers were unaware of urogynecologists to whom they could refer. Similar to the findings in Mazloomdoost, et al, 2016 and Mazloomdoost, et al, 2017, this large cross-sectional study of 150 PCPs in Hawai‘i found that PCPs were more familiar with UI and OAB than POP. This is supported by higher rates of correct estimated prevalence (34% UI, 38% OAB, 9% POP), “always” screening (7% UI, 6% OAB, 4% POP), and feeling comfortable treating UI and OAB compared to POP (30% UI, 39% OAB, 1% POP). While PCPs may perceive UI and OAB as more important than POP, in fact, the reported prevalence of POP (27%) is approximately that of UI (17%) and OAB (30%)12. A possible explanation for this phenomenon could be that increased knowledge, screening, and comfort level in treating UI and OAB could equate to a higher perceived importance than POP. In general, this study found that PCPs underestimate, under screen, and are unfamiliar with treatment of common pelvic floor disorders. This study also found that only 27% were very familiar with urogynecology and <50% would refer to urogynecology.

The prevalence of female PFDs has continued to increase over the years. Approximately 17%, 30%, and 27% of women in the United States suffer from UI, OAB, and POP, respectively. Not many physicians surveyed were able to correctly identify the prevalence of these disorders (34% UI, 38% OAB, 9% POP), with a majority underestimating the prevalence. While the survey’s question could have been further clarified as to the prevalence of which specific population, for example the general United States versus their personal practice, these results are still interesting. This large underestimation of the prevalence of female PFDs could suggest a minimization and/or lack of knowledge of these diseases that impede quality of life.

There was a significant difference between respondent sex and the estimated prevalence of both UI and OAB. Male PCPs were more likely than female PCPs to underestimate the prevalence of UI and OAB. Mazloomdoost found similar results and also found that male providers were less likely to have female patients report bothersome symptoms compared to female PCPs,16 which could explain why male PCPs perceive a decreased prevalence of UI and OAB. This phenomenon possibly stems from female patients feeling more comfortable with PCPs of the same gender. Moreover, females are more likely than males to experience UI and OAB. Therefore, one hypothesis could be that female PCPs are more likely than male PCPs to personally experience UI and OAB, which could increase their vigilance towards such disorders.

There was also a significant difference between years in practice and management of UI. PCPs who have practiced >20 years were more likely to immediately refer (15%) than those who have practiced 0-10 years (3%) and 11-20 years (5%). This may represent a higher level of confidence and/or competency associated with recent graduates from residency, or perhaps a heightened sense of self-awareness and skill-level as a seasoned physician. Additional follow-up questions would be necessary to further explore this association between years in practice and management of UI.

**Table 2. Survey Results: Are you Familiar with the Subspecialty of Urogynecology?**

<table>
<thead>
<tr>
<th>Familiarity</th>
<th>n</th>
<th>Percentage</th>
</tr>
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<tbody>
<tr>
<td>Very familiar</td>
<td>41</td>
<td>27%</td>
</tr>
<tr>
<td>Somewhat familiar</td>
<td>84</td>
<td>56%</td>
</tr>
<tr>
<td>Slightly unfamiliar</td>
<td>20</td>
<td>13%</td>
</tr>
<tr>
<td>Very unfamiliar</td>
<td>5</td>
<td>3%</td>
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Strengths of this study include identifying subjects by using the Hawai‘i Medical Service Association provider list, which is an up-to-date comprehensive list that includes 89% of all practicing PCPs in the state of Hawai‘i. Therefore, this study can be generalizable to the entire state. Unlike previous studies, surveys were distributed to not only academic but also community physicians.
Limitations of this study include selection bias. As with any survey-based study, selection bias is difficult to avoid, and it is possible that only providers familiar with and interested in female PFDs could have opted to participate in this study. The study’s largest limitation is its low response rate. Eliciting responses from busy physicians can be challenging. In the future, the response rate could be improved by distributing online surveys in addition to mailed surveys. Surveys could also be distributed multiple times to encourage participation. The sample size was further reduced by improperly completed surveys, such as skipping questions or choosing multiple answers for single-answer questions, which could be regulated and prevented with online surveys. Physicians practicing in the university (n=3) and hospitalist (n=3) settings were greatly underrepresented, which was probably associated with the study’s small sample size. Also, providers outside of the Hawai’i Medical Service Association are not represented in this study. Nonetheless, the study’s low response rate does not necessarily invalidate its results, and its response rate and sample size (22%, n=150) were similar to Mazloomdoost, et al, 2016 (30%, n=108), which highlights the difficulty in obtaining a large response rate.

Some surveys were noted to have unsolicited comments written in the margins. Comments generally referred to a lack of resources, particularly in rural Hawai’i. For example, “Not many urogynecologists around! Wish there were more!” “I refer to gyn first due to shorter referral wait time”, “No urogyn on Maui”, and “No local resources on Big Island”. Future directions include categorizing PCPs by island, thus distinguishing PCPs practicing on urban O’ahu and rural neighboring islands. Currently, there are six practicing urogynecologists on O’ahu to support a state population of 1,428,538 people (238,090 persons per urogynecologist), which is similar to the persons-to-urogynecologist ratio in the United States (283,639:1). However, a notable 31% of Hawai’i’s population resides on neighboring islands, geographically isolated from O’ahu. Expanding services to neighboring islands would help to serve people who are unable to travel to O’ahu due to the costs of travel, accommodations, and loss opportunities. This study could be the start of a larger discussion on the need for urogynecologic presence in rural Hawai’i.

In conclusion, most PCPs are not comfortable managing these common urogynecologic problems and would likely benefit from education on how to diagnose, treat, and refer for these conditions in order to optimize patient care. In the future, research could examine the effect of educational sessions on PCPs’ levels of comfort and competency in female PFDs.

Conflict of Interest
None of the authors identify a conflict of interest.

Acknowledgements
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References
A Case Report of Congenitally Absent Pericardium Masquerading as Recurrent Pericarditis

Tomoki Sempokuya MD; Corey J. Lum DO; Mahdi Veillet-Chowdhury MD; and Kahealani Rivera MD

Abstract
A 24-year-old female with a history of Swyer-James-MacLeod syndrome presented with acute onset of pleuritic chest pain and was initially diagnosed with acute pericarditis. The 12-lead electrocardiogram demonstrated typical diffuse ST-segment elevation and PR-segment depression. Symptoms resolved rapidly with anti-inflammatory therapy consisting of ibuprofen and colchicine. After completing a 3-month course of the latter, her symptoms rapidly recurred. Workup, including labs and cardiac imaging consisting of a transthoracic echocardiogram and cardiac magnetic resonance imaging, was initially interpreted as normal. Re-review of her cardiac imaging revealed the patient had signs of a congenitally absent pericardium, including a “Snoopy Sign” on her posterior-anterior chest X-ray, which is characterized by levoposition of the cardiac silhouette, a lucent area between the pulmonary artery and aorta because of the presence of lung tissue, a lucent area between the base of the heart and the left hemidiaphragm, loss of the right heart border, a prominent pulmonary artery, and a flattened and elongated left ventricular contour. The patient had a cardiac computed tomography scan, which confirmed the diagnosis. In conclusion, a congenitally absent pericardium is a rare disorder, often undetected or misdiagnosed. There are characteristic findings on imaging such as a “Snoopy Sign” on a posterior-anterior chest X-ray, which can be easily missed because of its rarity. Our goal of this report is to educate health care providers about this rare disorder.

Keywords
Congenitally Absent Pericardium; Snoopy Sign; Congenital Abnormalities

Abbreviations
EKG = Electrocardiogram
CT = Computed tomography
MRI = Magnetic resonance imaging
HIV = Human immunodeficiency virus
ANA = Anti-nuclear antibody
ANCA = Anti-neutrophil cytoplasmic antibody
TSH = Thyroid stimulating hormone
CRP = C-reactive protein
ESR = Erythrocyte sedimentation rate

Introduction
A congenitally absent pericardium is a rare disorder often found incidentally during thoracic surgery, imaging studies, or postmortem examination because it is generally asymptomatic, though has been reported to present with chest pain, prominent cardiac pulsation, or sudden death from herniation of cardiac tissue through partial pericardial defects. Although exact prevalence is difficult to determine, estimated prevalence ranges from 0.001% to 0.044%. Familial inheritance is rare and no association with medication exposure or underlying infection for pathogenesis has been identified. As majority of providers are not aware of this extremely rare disorder, symptomatic patients can be mistaken for other cardiac conditions such as ischemic heart disease, aortic dissection, pulmonary embolism, or acute pericarditis. This may lead to inappropriate treatments or diagnostic testing which can be problematic in the era of patient safety. Imaging studies including electrocardiogram (EKG), chest X-Ray, echocardiogram, cardiac computed tomography (CT) and cardiac magnetic resonance imaging (MRI) may aid in the diagnosis and timely treatment of such a condition, however currently no clear guideline for diagnosis or treatment exists. We present a case of congenitally absent pericardium which was initially mistaken for recurrent pericarditis. We aim to educate healthcare providers about this rare disease to reduce misdiagnosis and suggest a potential therapeutic option.

Case Report
A 24-year-old female with history of Swyer-James-MacLeod syndrome (characterized by alveolar hyperdistention and loss of pulmonary vasculature due to obliteration of small airways secondary to bronchiolitis) presented to our clinic for evaluation of recurrent pericarditis. She had pleuritic chest pain without identifiable triggers such as upper respiratory infections, new medications, previous radiation exposure, personal history of cancer, or Lyme disease. The patient denied any autoimmune disorder symptoms. Family history was non-contributory. Vital signs and full physical examination were unremarkable. Workup for infectious etiologies including tuberculosis, Coxsackie B, Parvo B19, human immunodeficiency virus (HIV) and, Hepatitis B and C were negative. Labs including anti-nuclear antibody (ANA), anti-neutrophil cytoplasmic antibody (ANCA), thyroid stimulating hormone (TSH), D-dimer, C-reactive protein (CRP), and erythrocyte sedimentation rate (ESR) were normal. A 12-lead EKG showed diffuse ST-segment elevations and PR-segment depression without any pathologic Q waves, T wave inversions, or ST-segment depressions. A posterior-anterior chest X-ray showed no infiltrates or pleural effusions. Imaging studies including electrocardiogram (EKG), chest X-Ray, echocardiogram, cardiac computed tomography (CT) and cardiac magnetic resonance imaging (MRI) did not reveal any pericardial effusion (Figure 1). Transthoracic echocardiogram showed normal left ventricular function without any pericardial effusion (Figure 2). The patient improved rapidly with ibuprofen and colchicine. However, her symptoms recurred soon after completing a 3-month course of colchicine. At this time, she was diagnosed with idiopathic recurrent pericarditis and was placed on an extended course of colchicine. A cardiac MRI did not reveal any pericardial gadolinium enhancement suggestive of pericarditis. Differential diagnosis included Familial Mediterranean Fever, Adult Onset Still’s disease, or very early systemic lupus erythematosus, though were not felt to be likely. Repeat echocardiogram showed preserved left ventricular function with right ventricular dila-
tion. However, review of the echocardiogram images suggested the final diagnosis of a congenitally absent pericardium. Re-evaluating the chest X-ray revealed a “Snoopy sign”, which is pathognomonic for a congenitally absent pericardium. Further review of her previous images, as well as performance of a cardiac CT confirmed the diagnosis (Figure 3-5).

Figure 1. Chest X-ray, posterior to anterior view. Leftward displaced heart, loss of right heart border, a lucent area between the left ventricle and left hemidiaphragm (white arrow), a lucent area between the pulmonary artery and aorta (blue arrow), and a flattened and elongated left ventricular contour (yellow arrow) are pathognomonic for a congenitally absent pericardium, previously described as the “Snoopy Sign.”

Figure 2. Transthoracic Echocardiogram, apical 4-chamber view. Teardrop-shaped appearance of the heart with elongated atria and a bulbous left ventricle. The imaging may be technically difficult due to unusual acoustic windows as a result of cardiac levoposition.

Figure 3. Cardiac CT shows area of pericardium (blue arrow) and area of absent pericardium (yellow arrow).

Figure 4. Cardiac CT shows absence of pericardium along the left ventricular free wall and leftward displacement of left ventricular apex (red arrow). There is the presence of pericardium along right atrium (yellow arrow).

Figure 5. Cardiac CT from a normal individual. Presence of pericardium along LV free wall (red arrow).
Discussion

A congenitally absent pericardium is a rare disorder often found incidentally while asymptomatic. 1 Failure of pleuropericardial membrane fusion is considered to be a cause of a congenitally absent pericardium. 8,9 This may occur when the heart enlarges before fusion of the pleuropericardial membrane. 8 Another potential cause can be a tear induced by traction contributing to a defect in the pericardium. 8,10 Lastly, if the cardinal veins (duct of Cuvier) prematurely atrophy, a defective pericardium may form as a consequence of reduced blood supply. 8,11

In symptomatic patients, clinical features differ by the type of defects. The localized defects of pericardium often manifest as syncope, palpitations, or sudden death. Delayed onset of symptoms is a key feature for a totally absent pericardium and it is often accompanied by postural or nocturnal stabbing, or angina-like pain with variable intensities, although pathogenesis of the pain is unclear at this time. 1,3,12–17 Dyspnea and tachypnea (Dyspnea associated with unilateral lateral recumbent position) may be other manifestations. 1,3,4

Physical examination may reveal displacement of the apical impulse to the axilla or posterior chest, systolic ejection murmurs and an absence of precordial heart sounds. 1,3,12,18,19 A 12-lead EKG may show a combination of an incomplete right bundle branch block, right axis deviation and a displacement of transition zone to the left in the precordial leads. 1,3,19,20

Transthoracic echocardiogram, typically, cannot directly visualize the defect of pericardium. Due to an atypical cardiac positioning and orientation, it may be necessary to obtain more lateral and superior echocardiographic windows. 8,21,22 Abnormal wall motion, such as cardiac hypermobility is commonly present. 5,21,22 In addition, systolic movement of the ventricular septum may be flat or paradoxical despite having normal systolic thickening. 8,21,22 Since the heart is not fixated in the mediastinum, the left ventricle may have a teardrop-shaped appearance with an elongated atria and a bulbous left ventricle, which can be prominently seen on an apical four chamber view (Figure 3). 5,21,22 Echocardiography may also detect associated congenital cardiac defects, such as Tetralogy of Fallot, patent ductus arteriosus, bicuspid aortic valve and atrial septal defect. 4,3 Unfortunately, echocardiogram is not always diagnostic. However, when echocardiography is performed in several positions, such as the left lateral decubitus, the right lateral decubitus and the dorsal decubitus position, in combination with a 12-lead EKG, it may be used as a diagnostic tool. 18,23

A posterior-anterior chest X-ray may be characterized by levoposition (leftward and posterior displacement) of the cardiac silhouette, a lucent area between the pulmonary artery and aorta and/or a lucent area between the base of the heart and the left hemidiaphragm because of the presence of lung tissue, loss of the right heart border, a prominent pulmonary artery, and a flattened and elongated left ventricular contour, previously described as a “Snoopy Sign” (Figure 2). 3,4,9,24–28

The diagnostic image modality of choice is cardiac MRI. 8,29 The absence of the pericardium or the pre-aortic pericardial recess are key findings. 4,8 A congenitally absent pericardium may have extra-cardiac associations such as bronchogenic cyst, pulmonary sequestration, Marfan’s syndrome, VATER syndrome, Pallister-Killian syndrome, and a syndrome of mental retardation, abnormal facies, and growth hormone deficiency. 4,24–26 There are several reported severe complications of a congenitally absent pericardium, such as myocardial ischemia, fatal myocardial strangulations and sudden death. 24,30

Since it is a rare disease, it may be easily missed or misdiagnosed. There are no standardized treatments but surgical reconstruction might be beneficial for controlling severe symptoms in patients refractory to medical therapy. 3 In our case, the use of a prolonged course of anti-inflammatory medications (>3 months) resulted in symptom resolution and may potentially be an alternative therapy prior to surgical reconstruction. As pathogenesis of pain associated with congenitally absent pericardium is unclear, the mechanism behind this treatment modality remains uncertain. Efficacy of treatment with anti-inflammatory medications suggests that underlying inflammatory process may be part of pain generation, though interestingly, CRP and ESR were normal. This may aid future research in pathogenesis of pain in congenitally absent pericardium.

This patient’s past medical history was significant for Swyer-James-MacLeod syndrome. However, in retrospect, this was an incorrect diagnosis and was due instead to cardiac levoposition.

Conclusion

In conclusion, a congenitally absent pericardium is a rare disorder, often undetected or misdiagnosed. There are characteristic findings on imaging such as a “Snoopy Sign” on a posterior-anterior chest X-ray, which can be easily missed because of its rarity. The goal of this report is to educate health care providers about this rare disorder.

Conflict of Interest and Disclosure

This case report was approved by Institutional Review Board of Queens Medical Center for publication. Informed consent could not be obtained due to loss of follow up after resolution of symptoms. There is no identifiable data in this case report. All of authors do not have any disclosure or conflict of interest.

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Reference


Girl Power: Providing Young Women with a Safe Space to Tackle the Tough Topics

Kameko M. Karasaki MS and Julie Crocker BS

In 1993, the Medical School Hotline was founded by Satoru Izutsu PhD (former vice-dean UH JABSOM), it is a monthly column from the University of Hawai'i John A. Burns School of Medicine and is edited by Kathleen Kihmm Connolly PhD; HJMPH Contributing Editor.

Introduction
The John A. Burns School of Medicine (JABSOM) strives to educate future physicians who are bright, driven, and most of all, dedicated to their jobs as community servants. The emphasis on community outreach and patient care is established early in the medical school curriculum, notably through the Community Health and Service Program. The major goal of this program is for first-year medical students to explore methods for promoting health and improving the quality of life for patients by working with a community organization throughout their entire first year. This column will focus on the Girl Power community health program and will provide an overview of the program as well as describe the insights gained from fostering mentorship between medical students and young women during its inaugural year.

The Girl Power Program
The Girl Power program was designed and implemented in 2017 by three medical students who grew up in Hawai'i and noticed a distinct lack of programming and mentorship targeted at girls in middle school. Girl Power is a weekly after-school breakout session for 6th-8th grade girls from local middle schools with medical student mentors through the YMCA of Honolulu. The goal of Girl Power is to develop female self-esteem and well-being through the development of interpersonal relationships and facilitating the introduction of positive female role models in the form of medical students.

The demographic subgroup of middle school girls is particularly well suited for mentorship from medical students. This is the age where most females will begin to undergo physical, emotional, and mental changes associated with puberty. The Hawai'i Department of Education’s Sexual Health Curriculum does not introduce any reproductive health education until the 7th grade, so a proportion of middle school girls experience menarche without any formal education on the topic. Medical students are able to provide scientifically accurate information about puberty from an approachable and non-intimidating (eg, not a figure of power such as a teacher, parent, or physician) source.

Additionally, the teenage years are a pivotal transition time in interpersonal development; Real Girls, Real Pressure: A National Report on the State of Self-Esteem shows that only 67% of girls ages 13 – 17 turn to their mother as a resource when feeling badly about themselves, compared to 91% of girls ages 8 – 12. A similar downward trend is seen with girls turning to their fathers. As teenage girls pull away from their parents, they begin to seek external validation from their peers and society as a whole. This becomes a problem when teenagers are surrounded by fashion and beauty as a for-profit industry, which influence their standards. The same study found that a girl’s self-esteem is strongly related to how she views her own body shape and weight, despite how much she actually weighs. Additionally, girls with low self-esteem are more likely to engage in negative behaviors such as disordered eating, self-harm, bullying, or substance abuse. By establishing a safe space where girls can discuss topics such as self-esteem, healthy relationships, and mental health with their peers and a knowledgeable facilitator, common ground can be found between individuals who may feel isolated, misunderstood, and deficient. Finally, through Girl Power, medical students are able to position themselves as older peers rather than adults and therefore may be able to introduce the girls to ideas such as healthy body image, self-esteem, and healthy relationships in a way that might be more relatable to the girls than the typical adult viewpoint provided through school or from their parents.

The Girl Power Curriculum
Girl Power sessions were held once per week at the YMCA of Honolulu with two JABSOM first year (MSI) students as facilitators. The sessions were divided into three blocks of eight sessions that roughly aligned to the JABSOM MSI academic schedule. Participation in Girl Power was open to all middle school girls enrolled in the Club Mid After School Program and day-to-day attendance was optional with the caveat that at the end of each block, a final wrap-up session would only be offered to those who had attended every session in the block. The number of attendees ranged from six to sixteen, with an average of eleven at each session. Since this was the inaugural year of Girl Power as a community health program, the curriculum was designed by the two MSI facilitators. Each of the three blocks followed a loose common theme: first block
emphasized bullying and self-expression; the second focused on mental and emotional health; and the third contained sessions pertaining to goal-setting and the pursuit of personal passions.

Each session was planned using a similar structure. The YMCA Club Mid program has students from multiple schools in the area so some of the participants knew each other and some did not. Each session began with team building exercise to foster communication and cooperation between the girls, especially those who are not friends outside of Girl Power. Because the goal of each session is to openly and honestly discuss difficult topics, trust and willingness to share is critical for the success of the curriculum. After the team building exercise, the topic of the day was introduced using a combination of socratic dialogue, examples from social media, and hypothetical scenarios meant to mirror real-life situations the girls may encounter.

Although each session covered a different topic, the underlying objective was to challenge the thought process of the girls and get them to critically examine not only cultural norms but also their own internalized thoughts and behaviors. One downfall of modern schooling when dealing with tough topics is that students are often rewarded for a correct answer without being pushed to explain or think through the issues (eg, being taught that drugs and alcohol are dangerous without discussion about the huge number of young celebrities who glorify party culture with seemingly no negative repercussions on their physical or mental well-being). Girl Power sessions aimed to combat this using a combination of scientifically accurate facts and open dialogue. Areas of confusion were identified and addressed in engaging conversations with age-relevant, pop-culture being used as a tie in as frequently as possible.

At the end of each Girl Power session, a short and anonymous written reflection was collected from each attendant and an exit survey was administered during the final Girl Power session of the school year.

**Participant Reflections**

Overall, the response to Girl Power sessions was overwhelmingly positive. Because participation was voluntary and girls were allowed to opt-out at any time, most participants were interested in being there and engaging with the topics that were being discussed. This was reflected in the responses to the exit survey, with all respondents agreeing that they enjoyed Girl Power and that they felt they learned something new every session. The majority of girls also felt that the topics covered in Girl Power were topics not usually discussed in school. This highlights the value of Girl Power since the topics covered were ones that teenage girls regularly have to engage with such as self-esteem, bullying, mental health, and healthy relationships. Additionally, the girls specifically mentioned that they enjoyed our open and in-depth discussions about puberty and menstruation, especially the 6th graders who hadn’t started health class in school yet.

One aspect of the program that can be improved upon was that two of the surveyed girls didn’t feel that Girl Power was a safe and non-judgemental environment. This was likely due to the fact that some of the girls knew each other from school and would occasionally bring outside situations or disagreements into Girl Power, especially as situational examples. Occasionally some of the more difficult topics (eg, healthy relationships, bullying, etc) would elicit oversharing of potentially private information from various friend groups. In the future, ensuring that girls only disclose information or situations that are theirs to share, and establishing further boundaries between outside friendships and the Girl Power space may alleviate some of those feelings.

Finally, the girls had some insight into how the Girl Power curriculum could be improved going forward. Some of the girls were there at every Girl Power session for all three blocks, while some only attended sporadically. In an attempt to keep the curriculum fresh, topics were not repeated. The physical, mental, and emotional changes associated with puberty and menstruation as a whole was covered during one Girl Power session, however, many of the girls who missed the lesson on puberty and periods were 6th graders who would have benefited from that lesson. The desire for more comprehensive reproductive education was evident in the reflections; a one-hour lesson from two medical students was seen as more informative than the in-school curriculum, and both 6th and 7th graders wished we had spent more time discussing puberty.

**Facilitator Reflections**

Kameko Karasaki

Facilitating Girl Power frequently made me feel as though I was playing an important role in helping the girls develop into young adults with confidence to make well informed and thought out decisions for themselves rather than blindly accepting the status quo. Before one Girl Power session, a group of the girls were singing lyrics to a song that came out when I was in middle school, albeit with a misogynistic twist. When I asked about why they were singing it like that, I discovered that a YouTube personality popular with teenage girls had sampled the song but drastically changed the lyrics. The original song is about the incredible potential and vast power of human beings, while the new version is sexually suggestive and filled with cliché imagery comparing women to motorcycles. The girls had absolutely no idea that the new version was sampled from anything and it led to a great discussion about the representation of women in media and how they are frequently reduced to objects.

The ability to market to kids and teenagers is endless, and also endlessly exploited, but so much can change if they’re encouraged to think critically about the type of media they choose to engage with. Encouraging the girls to begin examining the messages that they’re constantly bombarded with and decide if they align with their own developing values was my favorite part of Girl Power, and what I think will have the largest impact on the girls going forward.

Julie Crocker

I was excited to serve as a mentor for Girl Power and serve as a positive role model for young women. When I was young, I
struggled with my identity and self esteem because most of my interests were traditionally male dominated. I had no place to discuss why certain activities were more associated with one gender than another, and that it is okay to be different. As a leader in Girl Power I wanted to provide the students a space to think critically about societal expectations of them and encourage young women to pursue their dreams no matter what they are.

One of the most powerful moments came when we were discussing how products can be marketed to men or women. We showed them an ad by a pen company that produced a line of pens “For Her.” We challenged the girls that if it was ridiculous to think of pens as gendered, why were other products like nail polish or makeup gendered? One more talkative girl became quiet during that discussion. We later learned that she had a male friend outside of Girl Power whom she and her friends often teased for having female-associated interests. This moment was powerful for me because we could see that our discussions were having a real effect on the students and led them to critically think about their actions.

Conclusion
The Girl Power curriculum fills a critically important space in the education of teenage girls. By giving the girls a space to discuss tough and sometimes “taboo” subject matters with their peers, the girls can learn to think critically, defend their ideas in a well thought out and respectful manner, and relate to each other on a deeper level. Topics that are often shunned from mainstream education can begin to be normalized, and the girls are given a great resource in the medical student mentors. In return, the medical students are able to hone their leadership skills, were given the opportunity to discuss sensitive topics in an age-appropriate manner, and were able to advocate for the mental, physical, emotional health, and wellbeing of adolescents. Although the results are specific to the Girl Power program and cannot be generalized, the reflections and feedback from the students who participated show a potential important niche Girl Power can fill in adolescent education.

Acknowledgements
Girl Power is a Community Health Program that was created by Elizabeth Ferreira MD, Michele Kanemori MD, and Fanny Yeung MD when they were second year medical students at JABSOM. Many thanks to their perseverance in establishing Girl Power, as it demonstrates that medical students have the ability to contribute to the curriculum and community through their passions.

We would also like to extend our sincere gratitude to Keahi Kaawa, Program Director at the YMCA of Honolulu, for his continued investment in the success of Girl Power at the YMCA. Additional thanks to Monique Ani-Opiopio and Tiana Maruyama from the YMCA for their assistance.

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References
HAWAI'I JOURNAL WATCH

KAREN ROWAN MS

Highlights of recent research from the University of Hawai‘i and the Hawai‘i State Department of Health

HEALTH PROBLEMS IN INDIGENOUS PEOPLE MAY HAVE ROOTS IN HISTORICAL TRAUMA

Health problems among Indigenous people have been linked to Indigenous historical trauma (IHT), but the relationship is not straightforward. In a systematic review, researchers including Rachel L. Burrage PhD, of the Myron B. Thompson School of Social Work, analyzed 32 empirical studies of IHT and health outcomes in Indigenous people in the United States and Canada. Many studies found statistically significant direct and/or indirect associations between indicators of IHT and adverse health outcomes. However, study design, sample, measures, and analyses varied greatly, limiting the ability to make recommendations for health policy or professional practice at this time. Further research is needed to refine the measurement of IHT and to identify patterns of psychological harms that arise from IHT, the researchers concluded in their review (https://bit.ly/2SHRRkx) published in The American Psychologist.

A BETTER WAY TO TEST GONORRHEA BACTERIA FOR SUSCEPTIBILITY TO ANTIBIOTICS

The bacteria that cause gonorrhoea (Neisseria gonorrhoeae) are becoming increasingly resistant to antibiotics, and health care providers rely on laboratories to conduct antimicrobial susceptibility testing. Now, findings (https://bit.ly/2BKDRPZ) published in the Journal of Medical Microbiology show that Etest strips can reliably be used in susceptibility testing. Researchers including Norman P. O’Connor, with the Hawai‘i State Department of Health sent 100 pairs of N. Gonorrhoeae samples to eight labs for testing against three different antibiotics. The labs were in agreement within one dilution level on the minimum inhibitory concentration values of the antibiotics in 80% of tests. The traditional testing method, agar dilution susceptibility testing, is difficult to run for labs that do such testing only infrequently. Intra-laboratory correlation could be improved with more experience in using Estrips, the researchers wrote.

CAN A KETOGENIC DIET HELP CHILDREN WITH AUTISM?

Some children with autism who initiate a ketogenic diet may show improvement in the severity of their condition. The diet involves a low-carbohydrate and high-fat intake and is postulated to change neural cellular metabolism by promoting the use of ketones as an energy source. Researchers including Michael Corley PhD, of the John A. Burns School of Medicine, conducted an open-label trial with 3- to 13-year-old children in Honolulu. The 15 children who adhered to the diet for three months showed significant improvement in their social affect scores, and six showed substantial improvement in autism severity. Some children improved more than others, suggesting that other factors may influence individual responses to the diet, the researchers wrote in their study (https://bit.ly/2RQ6yuR) in Physiology & Behavior.

NATIVE HAWAI’IANS’ RISK OF LUNG CANCER

Native Hawaiians who smoke have a higher risk of lung cancer compared with people of other ethnicities who smoke at the same level. Researchers including Loïc Le Marchand MD, PhD, of the UH Cancer Center, analyzed data from 184,000 men and women who have been followed since 1996 in the Multiethnic Cohort study. Findings showed that among participants who smoked for 50 years at 10 cigarettes per day (25 pack-years), the estimated excess relative risk for lung cancer was 21.9 for Native Hawaiians, 19.1 for African Americans, 11.9 for whites, 10.1 for Japanese Americans, and 8 for Latinos. The racial and ethnic differences in lung cancer risk are more pronounced at low and moderate smoking intensities, the researchers noted in their findings (https://bit.ly/2STkX44) published in the Journal of the National Cancer Institute.

PUBLIC HEALTH RESEARCHERS SUPPORT CAPACITY-BUILDING EFFORTS IN BRAZIL

Locally-led public health research is essential to healthy communities. In a new paper, Catherine Pirkle PhD, and Tetine Sentell PhD, with UH Public Health, along with colleagues in Brazil detail an education program to help build a skilled public health workforce in an economically-disadvantaged region of Brazil. In the program, Brazilian students are trained to administer health surveys, interview study participants, and collect epidemiological data in the field. Students need a solid understanding of the social, economic, and psychological motivations of community, the researchers wrote in a paper (https://bit.ly/2En4TOZ) in the Journal of Global Health. The project is meeting its goals of increasing health research proficiency and capacity in the region.

MENTAL HEALTH SERVICES IN THE PERINATAL PERIOD: THE ROLE OF NURSE PRACTITIONERS

There is growing evidence of the impact of pregnancy-related mental health conditions on women, newborns, and families, according to a new paper from Lorraine Byrnes PhD, with the School of Nursing and Dental Hygiene. Pregnant women may need screening, diagnosis, and treatment for depression, anxiety, obsesive compulsive disorder, or posttraumatic stress disorder. Therefore, nurse practitioners (NPs) who provide care to women should have a comprehensive protocol for screening, diagnosing, and treating women with these conditions during pregnancy. In addition, NPs should assess women to determine how they are coping with pregnancy and the postpartum period, and whether they have sufficient social support, according to the paper (https://bit.ly/2SUunwF) published in The Journal for Nurse Practitioners.

COLLEGE STUDENTS IN HAWAI’I BELIEVE E-CIGARETTES HELP THEM QUIT

College students in Hawai‘i who use e-cigarettes tend to believe that these devices may help them to reduce or stop smoking regular cigarettes. Researchers led by Deborah Ann Taira ScD, with the Daniel K. Inouye College of Pharmacy, conducted in-depth, face-to-face interviews with 23 students. Results also showed that most believed that e-cigarette use had improved their health. Some said they used e-cigarettes to cut down on smoking marijuana and chewing tobacco. Interestingly, the students reported that non-e-cigarette users tend to show interest or seemed to become intrigued by their vaping. The students also said they would like more information on the long-term health impacts of e-cigarettes, according to the study (https://bit.ly/2El2FeA) is published in Health Behavior and Policy Review.
THE WEATHERVANE
RUSSELL T. STODD MD; CONTRIBUTING EDITOR

LET’S STOP KIDDING OURSELVES. IF WEED IS MEDICINE, SO IS BUDWEISER.
“Medical” marijuana is approved in 21 states and the District of Columbia for numerous conditions, including glaucoma, Crohn disease, post traumatic stress disorder, epilepsy, Alzheimer disease and chemotherapy-induced nausea and vomiting. Getting on the bandwagon, both the number of states and the number of approved indications for medical marijuana are expected to increase. Physicians must bear the responsibility for these prescriptions and have an obligation to understand the issues in “medicalization.” For most of these conditions evidence of marijuana benefit falls far short of standards required by the Food and Drug Administration (FDA). Actual medicines have research behind them, detailing benefits and possible harms. Marijuana does not. Evidence for use relies largely on testimonials and gossip not adequately controlled, double-blind randomized clinical trials. Tetrahydrocannabinol (THC), the primary ingredient in marijuana, has no clear optimal dose. It is in fact a toxin. It impairs judgment and driving ability, increases the risk of psychosis and schizophrenia. The fumes will damage the respiratory tract. The 2017 report from the National Academy of Medicine called the evidence for these harms as substantial. Claims that marijuana relieves pain may be true, but there are no clinical studies that compare it with known pain relievers like ibuprofen, only compared to placebo. If getting high relieves pain it follows that a bottle of Bud might be called medicine also. Marijuana belongs along with tobacco and alcohol, substances that adults can choose to enjoy and are willing to live with consequences. But please, stop calling it medicine.

GROUND BREAKING FOR GMO THERAPEUTICS.
The Food and Drug Administration gave the green light for Onpattro (Amylum Pharmaceuticals) to be prescribed to silence the gene that allows nerve damage that causes heart and digestive disease. It can be fatal. This is a rare disease affecting fewer than 5,000 people in the United States, so what’s the big deal? The treatment is based on the Nobel prize-winning research that shuts down a specific genetic process. This is the first such FDA approval, and its importance is that it opens a whole new therapeutic avenue. Gene silencing is the latest new technology that mobilizes the immune system replacing genes and weaponizing cells. This is one of the hottest areas of drug industry research, with hopes that it could yield a new class of drugs getting at the root causes of cancer, infectious disease, even age-related macular degeneration.

WHY WAIT FOR UBER? THE AIR TAXI TAKES FLIGHT.
Attempts to develop self-driving cars for use in cities have hit snags causing setbacks (eg, death of a pedestrian in Arizona) producing doubts about their readiness for public use. Aerospace companies are eager to fill the interurban gap. Boeing announced that the prototype for an autonomous air taxi took its first flight in Manassas, Virginia, in January. The autonomous airborne vehicles under development generally take off and land like a small helicopter. The concept is that they would shuttle to predetermined points, such as rooftops. Boeing claims that its electric powered demonstrator is designed to have a range of 50 miles. The 30 foot long by 28 foot wide craft only hovered and landed, but future flights will be forward. This flight heats up the race among companies that plan to transform urban transit. For the nonce the self-driving car is in the back seat.

PLEASE SPEAK UP. I CAN’T QUITE HEAR YOU.
Public officials and scientists are increasingly concerned about the effects of sound on our health. A World Health Organization (WHO) study in 2011 made the case that at least one million West Europeans could expect to lose about a year of good health over the course of their lives due to traffic noise. Such noises cause high blood pressure, interrupt sleep and increase stress. Auditory insult at street level in New York City was found to average about 73 decibels in a 2015 study published in Environmental Health. The Environmental Protection Agency (EPA) has found that outdoor noise levels above 55 decibels can be dangerous to one’s health. Chronic exposure to noise levels above 70 decibels can lead to hearing loss and health problems. In New York City where noise is one of the most frequent complaints on the city’s hot line, New York University’s Center for Urban Science and Progress (CUSP) measures noise levels in Manhattan, Queens, and Brooklyn using recording devices installed on buildings. A research scientist at CUSP says by the time the noise insult is sent in and an investigator is sent out the noise is often gone.

YES, THEY DO. THE AIRLINE WANTS YOU TO TIP. THE FLIGHTS GO UP, BUT THE SALARIES ARE GROUNDED.
Not only do they have to herd grumpy travelers, soothe nerves, apologize for delays, serve drinks, perhaps even save lives in an emergency, flight attendants are expected to collect tips to augment their meager airline salaries.

ADDENDA
- Want to ski a unique slope? Try taking the chair lift up Mt. Harmon on the Golan Heights, providing views of Syria and Lebanon. With a summit of 6,692 you can ski in the afternoon following a morning soaking in the Dead Sea, the lowest place on earth.
- For the first time in history, more than half of all members of US Congress are millionaires.
- The only state with no straight-line boundary is Hawaii.
- Eleven per cent of people admit to having had sex while driving.
- Men have become the tools of their tools.
- I am not young enough to know everything.

ALOHA AND KEEP THE FAITH
(EDITORIAL COMMENT IS STRICTLY THAT OF THE WRITER.)
The following guidelines are developed based on many common errors we see in manuscripts submitted to HJM&PH. They are not meant to be all encompassing, or be restrictive to authors who feel that their data must be presented differently for legitimate reasons. We hope they are helpful to you; in turn, following these guidelines will reduce or eliminate the common errors we address with authors later in the publication process.

**Percentages:** Report percentages to one decimal place (eg, 26.7%) when sample size is \( \geq 200 \). For smaller samples (<200), do not use decimal places (eg, 26%, not 26.7%), to avoid the appearance of a level of precision that is not present.

**Standard deviations (SD)/standard errors (SE):** Please specify the measures used: using “mean (SD)” for data summary and description; to show sampling variability, consider reporting confidence intervals, rather than standard errors, when possible to avoid confusion.

**Population parameters versus sample statistics:** Using Greek letters to represent population parameters and Roman letters to represent estimates of those parameters in tables and text. For example, when reporting regression analysis results, Greek symbol (\( \beta \)), or Beta (b) should only be used in the text when describing the equations or parameters being estimated, never in reference to the results based on sample data. Instead, one can use “b” or \( \beta \) for unstandardized regression parameter estimates, and “B” or \( \beta \) for standardized regression parameter estimates.

**P values:** Using \( P \) values to present statistical significance, the actual observed \( P \) value should be presented. For \( P \) values between .001 and .20, please report the value to the nearest thousandth (eg, \( P = .123 \)). For \( P \) values greater than .20, please report the value to the nearest hundredth (eg, \( P = .34 \)). If the observed \( P \) value is greater than .999, it should be expressed as “\( P > .99 \).” For a \( P \) value less than .001, report as “\( P < .001 \).” Under no circumstance should the symbol “NS” or “ns” (for not significant) be used in place of actual \( P \) values.

**“Trend”:** Use the word trend when describing a test for trend or dose-response. Avoid using it to refer to \( P \) values near but not below .05. In such instances, simply report a difference and the confidence interval of the difference (if appropriate), with or without the \( P \) value.

**One-sided tests:** There are very rare circumstances where a “one-sided” significance test is appropriate, eg, non-inferiority trials. Therefore, “two-sided” significance tests are the rule, not the exception. Do not report one-sided significance test unless it can be justified and presented in the experimental design section.

**Statistical software:** Specify in the statistical analysis section the statistical software used for analysis (version, manufacturer, and manufacturer’s location), eg, SAS software, version 9.2 (SAS Institute Inc., Cary, NC).

**Comparisons of interventions:** Focus on between-group differences, with 95% confidence intervals of the differences, and not on within-group differences.

**Post-hoc pairwise comparisons:** It is important to first test the overall hypothesis. One should conduct post-hoc analysis if and only if the overall hypothesis is rejected.

**Clinically meaningful estimates:** Report results using meaningful metrics rather than reporting raw results. For example, instead of the log odds ratio from a logistic regression, authors should transform coefficients into the appropriate measure of effect size, eg, odds ratio. Avoid using an estimate, such as an odds ratio or relative risk, for a one unit change in the factor of interest when a 1-unit change lacks clinical meaning (age, mm Hg of blood pressure, or any other continuous or interval measurement with small units). Instead, reporting effort for a clinically meaningful change (eg, for every 10 years of increase of age, for an increase of one standard deviation (or interquartile range) of blood pressure), along with 95% confidence intervals.

**Risk ratios:** Describe the risk ratio accurately. For instance, an odds ratio of 3.94 indicates that the outcome is almost 4 times as likely to occur, compared with the reference group, and indicates a nearly 3-fold increase in risk, not a nearly 4-fold increase in risk.

**Longitudinal data:** Consider appropriate longitudinal data analyses if the outcome variables were measured at multiple time points, such as mixed-effects models or generalized estimating equation approaches, which can address the within-subject variability.

**Sample size, response rate, attrition rate:** Please clearly indicate in the methods section: the total number of participants, the time period of the study, response rate (if any), and attrition rate (if any).

**Tables (general):** Avoid the presentation of raw parameter estimates, if such parameters have no clear interpretation. For instance, the results from Cox proportional hazard models should be presented as the exponentiated parameter estimates, (ie, the hazard ratios) and their corresponding 95% confidence intervals, rather than the raw estimates. The inclusion of \( P \)-values in tables is unnecessary in the presence of 95% confidence intervals.

**Descriptive tables:** In tables that simply describe characteristics of 2 or more groups (eg, Table 1 of a clinical trial), report averages with standard deviations, not standard errors, when data are normally distributed. Report median (minimum, maximum) or median (25th, 75th percentile [interquartile range, or IQR]) when data are not normally distributed.

**Figures (general):** Avoid using pie charts; avoid using simple bar plots or histograms without measures of variability; provide raw data (numerator and denominators) in the margins of meta-analysis forest plots; provide numbers of subjects at risk at different times in survival plots.

**Missing values:** Always report the frequency of missing variables and how missing data was handled in the analysis. Consider adding a column to tables or a footnote that makes clear the amount of missing data.

**Removal of data points:** Unless fully justifiable, all subjects included in the study should be analyzed. Any exclusion of values or subjects should be reported and justified. When influential observations exist, it is suggested that the data is analyzed both with and without such influential observations, and the difference in results discussed.
Guidelines for Publication of HJM&PH Supplements

The following are general guidelines for publication of supplements:

1. Organizations, university divisions, and other research units considering publication of a sponsored supplement should consult with the editorial staff of HJM&PH to make certain the educational objectives and value of the supplement are optimized during the planning process. It is important that the sponsoring editor is aware of all steps to its publication. Please contact Drs. Kalani Brady for further information.

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