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SURGICAL REPAIR OF ABDOMINAL AORTIC AND RENAL ARTERY ANEURYSMS IN TAKAYASU'S ARTERITIS

Paul J. Wetstein MD; Margaret E. Clark MD; Danielle E. Cafasso DO; Scott R. Golarz MD; Farhan S. Ayubi DO; and Dwight C. Kellicut MD

4

THE PARADOX OF DISCRIMINATION, THE "ALOHA SPIRIT," AND SYMPTOMS OF DEPRESSION IN HAWAI'I

Krysia N. Mossakowski PhD and Turro S. Wongkaren PhD

8

COLONOSCOPY SCREENING AMONG NATIVE HAWAIIANS AT QUEEN'S MEDICAL CENTER BETWEEN AUGUST 2011 AND JANUARY 2013

Jodie M. Kaalekahi RN; Krupa R. Gandhi MPH; John J. Chen PhD; and Scott K. Kuwada MD

13

MEDICAL SCHOOL HOTLINE

Cultural Competency in Serving the Homeless in Hawai'i at the John A. Burns School of Medicine

Jennifer W.H. Wong MSIV and Jill Omori MD

18

INSIGHTS IN PUBLIC HEALTH

Building Well-Being: Linking the Built Environment to Health

Sara Jensen Carr PhD

22

THE DANIEL K. INOUE COLLEGE OF PHARMACY SCRIPTS

Prescription Drug Pricing

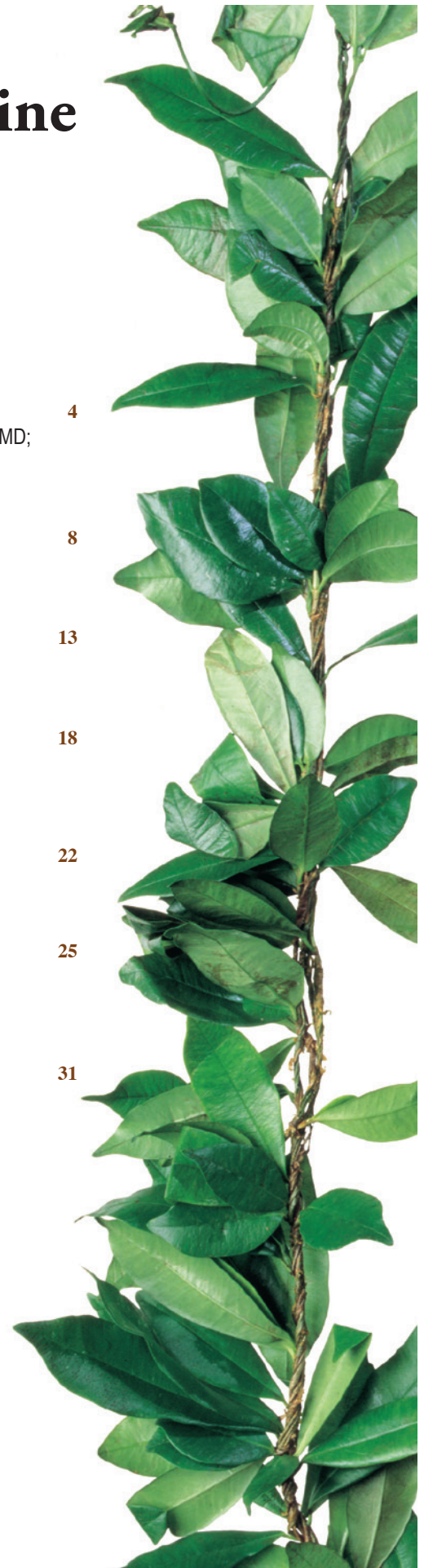
Wesley K. Sumida PharmD; Ronald Taniguchi PharmD; and Deborah Taira Juarez ScD

25

THE WEATHERVANE

Russell T. Stodd MD

31



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Surgical Repair of Abdominal Aortic and Renal Artery Aneurysms in Takayasu's Arteritis

Paul J. Wetstein MD; Margaret E. Clark MD; Danielle E. Cafasso DO; Scott R. Golarz MD; Farhan S. Ayubi DO; and Dwight C. Kellicut MD

Abstract

Takayasu's arteritis is a large vessel vasculitis that can be a challenging diagnosis to make and has a varied clinical presentation. Management largely depends on affected vessel disease severity and individual patient considerations. The diagnosis must be considered in a young patient with large vessel aneurysms. We present a case of a 30 year-old woman of Pacific Islander descent who presented to the Tripler Army medical Center Vascular Surgery Department in Honolulu, Hawai'i seeking repair of her abdominal aortic and renal artery aneurysms prior to conception.

A 30 year-old Pacific Islander woman with a history of a saccular abdominal aortic aneurysm and renal artery aneurysms presented to our clinic seeking vascular surgery consultation prior to a planned pregnancy. She had a renal artery stent placed at an outside institution for hypertension. She met the diagnosis of Takayasu's arteritis by Sharma's criteria. Physical exam was significant for a palpable, pulsatile, abdominal mass and CT angiography revealed a saccular irregular-appearing infra-renal abdominal aortic aneurysm, extending to the aortic bifurcation, with a maximum diameter of 3.3 cm. A right renal artery aneurysm was also identified proximally, contiguous with the aorta, with a maximal transverse diameter of 1.7 cm. The patient underwent a supraceliac bypass to the right renal artery with a 7mm Dacron graft, as well as excision of the right renal artery aneurysm. The abdominal aortic aneurysm was replaced using a Hemashield Dacron bifurcated 14mm x 7mm bypass graft. Intraoperative measurements of the renal artery aneurysm were 1.5 x 1.5 cm and the saccular appearing distal abdominal aortic aneurysm measured 3.6 x 3.3cm. The patient was discharged from the hospital 7 days post-operatively. At 1-year follow up, CT scan of the abdominal aorta revealed the repair was without any evidence of aneurysm formation, anastomotic pseudoaneurysm formation, or areas of stenosis. She has remained normotensive with a normal serum creatinine 18 months after her repair. She has since delivered her second child.

It is rare for Takayasu's arteritis to present with aneurysmal disease. It is much more common to present with stenosis or occlusion. It has yet to be proven that Takayasu's truly has a higher incidence in those of Asian descent. Takayasu's can be a difficult diagnosis to make but can be aided with the use of Sharma's criteria. Our particular patient posed unique considerations on the effects of the physiology of pregnancy on her aneurysms and repair.

Managing the active phases of disease is imperative, and though medical management is first line, surgical intervention may be necessary. Surgical intervention should be performed in a quiescent period of disease if possible given that biological inflammation at the time of intervention increases the complication rate. Repair of aneurysmal disease in a young female should also be considered prior to pregnancy.

Keywords

Arterial Aneurysms, Pregnancy, Abdominal Aortic Aneurysm, Renal Artery Aneurysm

Introduction

Takayasu's arteritis (TA) is a large vessel vasculitis. The current body of knowledge is varied, from the histopathology, diagnosis, and clinical manifestations. The histopathological

features vary from an extensive acute inflammatory process to extensive post-inflammatory mural fibrosis.¹ The most severe manifestations of Takayasu's arteritis are Takayasu retinopathy, secondary hypertension, aortic regurgitation, and aneurysm formation. The diagnosis is made clinically according to Sharma's criterion for diagnosing Takayasu Arteritis.² The gold standard for diagnosis is angiography exhibiting stenosis particularly of midsubclavian artery lesions.³

We report the case of a young Pacific Islander woman who presented with aneurysmal disease and was successfully managed with open surgical repair. This case is significant to the health care field in that our patient had an unusual presentation with aneurysmal disease and a complicated surgical history, including a prior renal artery stent placed across an inflammatory aneurysm that was freely floating. We also provide a review of the literature to aid clinicians in diagnosis and medical management and show that data supporting a racial predisposition is actually lacking. The surgical management of a young patient with complicated inflammatory aneurysms with a previously placed renal artery stent is unique and we hope to provide one method for consideration.

Case Report

A 30 year-old Pacific Islander woman (as defined as the areas within the Pacific Ocean encompassing Micronesia, Polynesia, and Melanesia) with a history of a saccular abdominal aortic aneurysm presented to our clinic seeking vascular surgery consultation prior to a planned pregnancy. She also had a proximal saccular renal artery aneurysm associated with a presumed distal renal artery stenosis, previously stented in Italy. The patient initially had her abdominal aortic aneurysm detected during her first pregnancy 4 years prior. Her first pregnancy was unremarkable. She delivered at term under high risk obstetric care. However, it was recommended by her subspecialist obstetrician at a US academic center, that if she were to consider pregnancy again she should seek repair of both aneurysms prior to conceiving. In the interim she developed refractory hypertension secondary to renal artery stenosis necessitating stent placement.

She reported having a history of fevers, chills, and rigors in her youth. By Sharma's diagnostic criterion for Takayasu's arteritis our patient met at least two major and three minor criteria. Her major criteria included characteristic signs and symptoms that were unexplained in her adolescence, and a documented discrepancy in systolic blood pressure in her upper extremities associated with a subclavian murmur (R 170/84 and L 151/99).

Her minor criteria included an abdominal aortic lesion, elevated ESR (28mm/hr at age 29), and hypertension. Physical exam was significant for a palpable, pulsatile, abdominal mass and CT angiography revealed a saccular irregular-appearing infra-renal abdominal aortic aneurysm, extending to the aortic bifurcation, with a maximum diameter of 3.3 cm (Figure 1). A right renal artery aneurysm was also identified proximally, contiguous with the aorta, with a maximal transverse diameter of 1.7 cm (Figure 2). Given the saccular nature of the aortic aneurysm, as well as the patient's desire to become pregnant, the decision was made to proceed with an open repair. The patient underwent a supraceliac bypass to the right renal artery with a 7 mm Dacron graft, as well as excision of the right renal artery aneurysm. The abdominal aortic aneurysm was replaced using a Hemashield

Dacron bifurcated 14mm x 7mm bypass graft. Intraoperative measurements of the renal artery aneurysm were 1.5 x 1.5 cm and the saccular appearing distal abdominal aortic aneurysm measured 3.6 x 3.3cm. There were no intra-operative or post-operative complications, and the patient was discharged from the hospital 7 days post-operatively. On attempted sectioning of her removed renal aneurysm, the tissue was extensively calcified without active inflammation. At 1-year follow up, CT scan of the abdominal aorta (Figure 3 and 4) revealed the repair was without any evidence of aneurysm formation, anastomotic pseudoaneurysm formation, or areas of stenosis. She has remained normotensive with a normal serum creatinine 18 months after her repair. She has recently conceived and will be monitored closely throughout her pregnancy.



Figure 1. Saccular irregular-appearing infra-renal abdominal aortic aneurysm, extending to the aortic bifurcation with a maximum diameter of 3.3 cm.



Figure 2. Right renal artery aneurysm contiguous with the aorta with a maximal transverse diameter of 1.7 cm. Stent is seen protruding into the proximal aneurysm cavity.



Figure 3. Supraceliac origin of right renal artery bypass graft.



Figure 4. Right renal artery aneurysm exclusion with thrombosis in the original renal artery aneurysm.

Discussion

In young patients with aneurysmal disease connective tissue disorders should be ruled out. TA more commonly presents with stenosis or occlusion than aneurysmal disease, and should also be included in the differential. Our patient had both stenosis and aneurysmal disease, requiring a stent placement for refractory hypertension. Aneurysmal disease is more common depending on the geographic location, with 71% of TA patients in South Africa having aneurysmal disease, versus only 32% in Japan.⁴ The aneurysms associated with TA are frequently multiple, saccular aneurysms that are associated with stenotic lesions.

TA is a large vessel vasculitis known for its propensity to affect women from childhood until the age of forty. TA is rare, with an annual incidence of 1.2-2.6 cases/1 million.⁵ Most series reveal that 85% of cases are women, although the gender association has been shown to vary with geographic location.⁶ While classically thought to be a disease with increased prevalence in Asians, no racial predisposition has been proven.⁶ Vessels most commonly involved are the aorta and its immediate branch vessels. TA presents pathologically as fibrous transmural thickening following necrotizing inflammation of the aorta and major vessels, similar to giant cell arteritis. The transmural intimal thickening results in weakening of the vessel wall, predisposing the patient to aneurysm formation.⁷ Clinical manifestations are dependent on the vessels involved; however, nonspecific and systemic complaints such as fever, malaise, weight loss, arthralgia, myalgia, and night sweats are well described.⁷ The transmural thickening often results in severe stenosis of major branch vessels, hence the term “pulseless disease.” Certain HLA haplotypes have been identified as being associated with TA, however, the pathogenesis is unknown.⁸

Diagnosis may be made with histology, revealing pan-arteritis of all three layers of the vessel wall, with skip areas along the length of the vessel.⁹ However, histology is usually not available, so historically the most widely accepted clinical diagnostic criteria were Ishikawa’s criteria (1988), which have since been modified by Sharma, et al, improving sensitivity to 92.5% while maintaining a 95% specificity when applied to their population.² Sharma’s criteria include three major and ten minor criteria (Table 1).² The presence of two major, or one major and two minor, or four minor criteria imply a high clinical suspicion for TA.

Treatment of TA is initially medical. However, approximately 20% of patients are resistant to medical treatment, which justifies an aggressive medical regimen and possible surgical intervention.^{10,11} Corticosteroids are used as first-line therapy to control the acute arteritis. If a patient is resistant to corticosteroids then treatment with cyclophosphamide, azathioprine, or methotrexate is started. Other proposed treatment modalities include mycophenolate mofetil and anti-tumor necrosis factor- α biological agents for those unresponsive to the other immunosuppressors.^{11,12}

It is important to control the acute inflammation and acute arteritis prior to surgery. A multicenter retrospective analysis of 79 patients with TA who underwent surgical or endovascu-

Table 1. Sharma’s Criteria. Characteristic signs and symptoms include limb claudication, pulse differences or pulselessness in limbs, difference of >10 mm Hg in systolic blood pressure between limbs, fever, pain, transient amaurosis, blurred vision, syncope, dyspnea, or palpitations.

10 Minor Criteria	3 Major Criteria
Persistently high ESR	Left mid-subclavian artery lesion
Carotid artery tenderness	Right mid-subclavian artery lesion
Hypertension	Characteristic signs and symptoms for at least one month’s duration
Aortic regurgitation or Annuloaortic ectasia	
Pulmonary artery lesion	
Left mid-common carotid lesion	
Distal brachiocephalic trunk lesion	
Descending thoracic aorta lesion	
Abdominal aorta lesion	
Coronary artery lesion in the absence of risk factors	

lar intervention revealed that biological inflammation at the time of revascularization was associated with the occurrence of arterial complications regardless of the method of repair, with biological inflammation defined as ESR >30mm/hr and CRP >6 mg/L.¹⁰ The most commonly encountered complication after endovascular intervention reported in this series was renal artery re-stenosis. Other post-intervention complications include bleeding, stroke, thrombosis, infection, and anastomotic failure.^{9,10}

The periarterial adventitial thickening of aneurysms with TA results in a lower rate of rupture compared to degenerative aneurysms.¹³ The life expectancy of these patients is expected to be nearly the same as healthy individuals. Over a longer time period, patients with long standing TA and aneurysm formation do have an increasing risk of aneurysm rupture. These patients may not suffer from the same medical comorbidities as patients with degenerative aneurysms and would be suitable candidates for surgical repair.

Hypertension with aneurysmal formation in TA is present in a significant portion of patients. In a paper by Sharma et al, of the 88 patients diagnosed to have TA, eight patients had aneurysms. Those eight patients all had long standing uncontrolled hypertension.¹⁴ The high prevalence of systemic hypertension and TA suggests the causative factor for aneurysm formation is high blood pressure. Stenotic disease is associated with aneurysm formation in TA patients. Isolated aneurysm formation occurs in only 2% of patients with TA.¹⁵ Surgically correctable stenotic lesions would prevent future aneurysm formation and progression.

TA with aneurysm formation in pregnant patients presents a unique challenge. The effects of hypertension during pregnancy on fetal demise are well known. The other concern is further

aneurysm growth during pregnancy. Under the age of 40, half of ruptured arterial aneurysms occur in pregnant women.¹⁶ Pregnancy related circulatory and endocrine changes may cause new aneurysm and further expansion of aneurysms already present.¹⁶ A ruptured aortic aneurysm during pregnancy could mimic benign disease processes leading to high mortality rates. Early repair of TA related aneurysms will potentially eliminate the potential for rupture and allow future pregnancies.

Conclusion

There is often a delay in diagnosis of TA given its varied presentation and nonspecific symptoms. Managing the active phases of disease is imperative, and though medical management is first line, surgical intervention may be necessary. Surgical intervention should be performed in a quiescent period of disease if possible given that biological inflammation at the time of intervention increases the complication rate. Repair of aneurysmal disease in a young women should also be considered prior to pregnancy. After endovascular treatment of renal artery stenosis, our patient successfully underwent open aortic and renal artery aneurysm repair and has delivered a second child by an uncomplicated repeat low transverse Caesarean section.

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 US Government.

Conflict of Interest

None of the authors identify any conflict of interest.

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The Paradox of Discrimination, the “Aloha Spirit,” and Symptoms of Depression in Hawai‘i

Krysia N. Mossakowski PhD and Turro S. Wongkaren PhD

Abstract

It remains to be determined whether the “aloha spirit” is a cultural resource that influences psychological well-being in Hawai‘i. Thus, the purpose of this study is to investigate whether the aloha spirit is associated with levels of psychological distress and the risk of depression, while taking into account various risk factors. Data for this study were drawn from an anonymous survey of undergraduate students (N = 1,028) at the University of Hawai‘i. Regression results revealed that having learned the aloha spirit was associated with significantly lower levels ($b = -1.76$; $P < .01$) of psychological distress and a reduced odds of depression ($OR = .69$; $P < .01$) over and above the effects of perceived discrimination, local identity, levels of ethnic identification, race/ethnicity, immigrant status, duration of residence in Hawai‘i, and other sociodemographic factors. In contrast, everyday discrimination was associated with significantly higher levels ($b = 0.41$; $P < .001$) of psychological distress and a greater odds of depression ($OR = 1.08$; $P < .001$). Together, these findings highlight the paradox of discrimination and the aloha spirit in Hawai‘i by documenting their distinct relationships with mental health. Overall, this study contributes to medical and public health research on mental health disparities during the transition to adulthood by delving into the social context of daily life in the understudied, multicultural location of Hawai‘i.

Keywords

aloha spirit, discrimination, symptoms of depression, the transition to adulthood, Hawai‘i

Introduction

The term “aloha spirit” has been thought to involve compassion, tolerance, and social harmony, which has contributed to Hawai‘i being considered a multicultural paradise.¹ Yet, this idealistic model of Hawai‘i has been critiqued and it has been argued that race and ethnic relations are not harmonious.^{2,3} In fact, social tensions exist among different racial minority groups as well as among ethnic subgroups of Asian Americans, and racial/ethnic discrimination is often experienced by those who are perceived as not “local” or belonging to the local community in the Hawaiian islands.²⁻⁸ For instance, Whites in Hawai‘i are both understood by some to be non-local, relatively recent arrivals, and agents of Native Hawaiian dispossession historically. Consequently, Whites are exposed to discriminatory treatment when they are racially marked as “haole” or foreigner regardless of how long they have resided in Hawai‘i.⁵ Therefore, the prevalence of discrimination across all racial/ethnic groups and the pervasiveness of the aloha spirit in Hawai‘i appear to be a paradox.

Research has revealed that discrimination is a public health issue because it not only has social consequences, but also has damaging psychological ramifications. For example, studies have documented a relationship between self-reported experiences of racial/ethnic discrimination and significantly higher levels of psychological distress, assessed with symptoms of

depression.⁹⁻¹¹ This growing literature has primarily examined African Americans, Latinos, and more recently Asian Americans.¹²⁻¹⁵ Our knowledge is limited about the mental health effects of discrimination as a stressor among Pacific Islanders and in the unique, ethnically diverse location of Hawai‘i.^{7,16} According to recent US Census estimates, Hawai‘i’s population has the following racial/ethnic distribution: Asian 38.3% (Filipino 14.4%; Japanese 13.6%; Chinese 4.1%; Other Asian 6.2%); White 25%; Native Hawaiian 6%; Other Pacific Islander 3.8%; Hispanic 9.3%; African American 1.8%; American Indian and Alaska Native 0.2%; and two or more races 23.8%.¹⁷

The purpose of the current study is to investigate Hawai‘i’s paradox of discrimination and the aloha spirit by evaluating each of their relationships with mental health. If the aloha spirit involves conveying warm feelings to others and a sense of inclusion, and it is regularly practiced in Hawai‘i,¹⁸ it is plausible that it could benefit mental health as a cultural and social-psychological resource. Alternatively, it has been contended that the aloha spirit has been transformed into a popular marketing tool to propel the tourist industry by promoting a welcoming and friendly atmosphere in hotels, stores, and restaurants,¹⁸ and perhaps it may not necessarily function as a cultural resource to enhance the psychological well-being of Hawai‘i’s population.

The present study addresses an unanswered research question: Is there a relationship between the aloha spirit and psychological well-being in Hawai‘i? More specifically, this study examines whether the aloha spirit is associated with significantly lower levels of psychological distress and a reduced risk of depression. The strength of the influence of the aloha spirit on these mental health outcomes is tested by controlling for self-reported experiences of discrimination, levels of ethnic identification, race/ethnicity, immigrant status, duration of residence in Hawai‘i, local identity, and other sociodemographic factors. Moreover, the focus of this study is on undergraduate students who are in a formative stage in the life course—the transition to adulthood—when symptoms of depression and anxiety are likely to manifest.¹⁹ Thus, examining this pivotal life stage is important for preventing psychological distress, which can lead to diagnosable depressive and anxiety disorders in adulthood.

Methods

Data were collected using anonymous surveys during 2012 to 2013. Participants consisted of 1,091 undergraduate students at the University of Hawai‘i at Manoa. Students completed surveys by writing their responses during class time (10 minutes on average) in undergraduate courses in the departments of Sociology, Women’s Studies, Nursing, Philosophy, Accounting, and

Engineering. The survey's procedures were approved by the university's Institutional Review Board (CHS # 20055). The survey questionnaire informed the students about the purpose of the research as well as the benefits and risks, and that their participation was voluntary and confidential. The final sample size was 1,028 after list-wise deletion of missing cases.

Measures

The two dependent variables were based on the 20-item Center for Epidemiologic Studies Depression scale (CES-D). The CES-D is a widely used, valid, and reliable measure for adolescents, young adults, and adults to assess symptoms of depression, also known as psychological distress.²⁰ The CES-D is a screening measure not intended to be a diagnostic tool. Respondents were asked how they felt in the past week, such as how often they had crying spells, and felt sad or lonely. The response categories were: (0) rarely or none of the time or less than 1 day, (1) some or a little of the time or 1-2 days, (2) occasionally or a moderate amount of the time or 3-4 days, and (3) most or all of the time or 5-7 days. Ordinary least squares (OLS) regression models were conducted for the summed scale, dependent variable measuring self-reported levels of depressive symptoms (Cronbach's alpha = .90) referred to as psychological distress, and logistic regression models were used for the dichotomous depression measure (1 = score > 15 as a proxy for clinical depression).²⁰

The focal independent variable was aloha spirit assessed with the following question: Have you learned the Aloha Spirit in Hawai'i? This question was open to the student's own interpretation. Responses ranged from (1) strongly disagree, (2) disagree, (3) agree to, (4) strongly agree. Other focal independent variables included perceived lifetime racial/ethnic discrimination (1 = yes) and everyday discrimination, which was Williams and colleagues' scale measuring day-to-day experiences of unfair treatment not necessarily due to race or ethnicity, such as receiving poorer service than others in restaurants and stores, being treated with less courtesy/respect, and being called names. The summed 9-item scale had high internal consistency (Cronbach's alpha = .89).⁹ Response categories were: (0) never, (1) less than once a year, (2) a few times a year, (3) a few times a month, (4) at least once a week, and (5) almost every day.

Control variables included local identity (whether you consider yourself to be a local or not) and Phinney's ethnic identity scale, which consisted of the average of 12 items (Cronbach's alpha = .89).²¹ According to Phinney, ethnic identity is a continuum of behaviors, feelings, attitudes, and knowledge about one's racial/ethnic group membership.²¹ Responses ranged from strongly disagree (0) to strongly agree (3). Other sociodemographic control variables included racial/ethnic group, gender, age, immigrant status, the number of years of residence in Hawai'i, and parental education. Parents' level of education are often used as a measure of family socioeconomic background among students who are in the early stages of status attainment.²¹

STATA v. 13 was used to conduct the statistical analyses, which included t-tests and regression models. Regarding the statistical power of the regression models for our sample size

and the number of control variables, the rule of thumb is that there should be a minimum ratio of 30 observations for each variable. With our sample size of 1,028 observations, we have enough cases for the number of variables we use in the models. For further verification, we calculated the statistical power of our models using G*Power 3 software that is designed to do so.²² The results showed that the fully adjusted regression models with the largest number of independent variables have the statistical power that is needed.

Results

Descriptive Statistics

The final study population consisted of 1,028 undergraduates at the University of Hawai'i. Overall, fifty-four percent were women (Table 1). Study participants self-identified as either Japanese (21%), White (19%), Filipino (16%), Native Hawaiian (14%), Chinese (10%), Other Asian (6%), Pacific Islander (4%), or Other Race (10%). The racial composition of the sample was commensurate with the university's diverse student body (Fall Semester 2012): Asian (40.4%), White (20.9%), Native Hawaiian or other Pacific Islander (17.4%), Other Race (18.2%). The one exception is that Asians were somewhat overrepresented in the sample: 53.0% versus 40.4%. Most students were born in the United States (14% immigrants) and the average duration of residence in Hawai'i was 13 years. The average level

Variables	n (%)	Mean	SD
Female	555 (54.0%)		
Race/Ethnicity			
White	195 (19.0%)		
Japanese	216 (21.0%)		
Filipino	164 (16.0%)		
Chinese	103 (10.0%)		
Other Asian	62 (6.0%)		
Native Hawaiian	144 (14.0%)		
Pacific Islander	41 (4.0%)		
Other race	103 (10.0%)		
Immigrant Status (Yes)	144 (14.0%)		
Identifies as local	668 (65.0%)		
Experienced lifetime discrimination	514 (50.0%)		
Age (years)		21.23	4.52
Years Living in Hawai'i		13.07	9.00
Parental education (years)		14.88	3.13
Everyday discrimination [range possible, 0 to 44]		12.04	8.16
Aloha spirit [range possible, 1 - 4]		3.41	0.64
Ethnic identity level [range possible, 0 - 3]		2.03	0.50
Psychological distress [range possible, 0 - 60]		13.28	10.12
Depression	339 (33.0%)		

N = 1,028. N (%), proportion; SD, standard deviation.

of parental education was more than high school (15 years) among these students with an average age of 21 years. Half of the students reported having experienced racial/ethnic discrimination in their lifetimes. The average score among students who reported experiencing everyday discrimination was 12 on a scale ranging from 0 to 44.

The average reported level of having learned the aloha spirit for the sample was relatively high (mean=3.4; range 1–4) (Table 1). Furthermore, the level of learning the aloha spirit was highest among Native Hawaiians (mean=3.8), which was significantly (*t*-tests, $P < .001$) different compared to all other racial/ethnic groups (Table 2). White students had fewer opportunities to learn the aloha spirit because they lived in Hawai‘i for only 5 years on average, while Native Hawaiian students had an average of 19 years of residence, followed by Japanese (18 years), Filipinos (16 years), Chinese (15 years), Other Asians (14 years), Pacific Islanders (8 years), and Other Race (5 years). Supplementary analyses (not shown) indicated that those who lived in Hawai‘i longer had significantly ($P < .001$) higher levels of having learned the aloha spirit and those who identified as local reported high levels of having learned the aloha spirit (3.6).

Ordinary Least Squares Regression Analyses for Psychological Distress

Table 3 presents two OLS regression models that examine the association between aloha spirit and levels of psychological distress. Model 1 (unadjusted model) shows that having learned the aloha spirit was associated with significantly lower levels of psychological distress ($P < .001$). The final multivariate model in Table 3 adjusts for additional risk factors: self-reported experiences of racial/ethnic discrimination in a lifetime, everyday discrimination not necessarily due to race/ethnicity, gender, age, parental education, race/ethnicity, levels of ethnic identification, immigrant status, years of residence in Hawai‘i, and local identity. In this model, the strength of the statistically significant effect of aloha spirit decreased only slightly ($b = -1.76$; $P < .01$). Female gender ($P < .01$), everyday discrimination ($P < .001$), and being an immigrant ($P < .01$) were significantly associated with higher levels of distress. In contrast, higher levels of ethnic identification were linked with less distress ($P < .01$). Years of residence in Hawai‘i ($P > .05$), local identity ($P > .05$), and race/ethnicity did not have significant mental health effects ($P > .05$).

Logistic Regression Analyses for Clinical Depression

Table 4 displays the unadjusted and fully adjusted logistic regression models that examine the association between aloha spirit and depression (>15 CES-D score cut-off as a proxy for clinical depression). Overall, aloha spirit has a protective effect on depression in the unadjusted (OR=0.70; $P < .001$) and fully adjusted models (OR=0.69; $P < .01$). Female gender (OR=1.33, $P < .05$) and everyday discrimination (OR=1.08, $P < .001$) were associated with higher odds of depression. Lifetime discrimination, age, parental education, race/ethnicity, ethnic identity level, immigrant status, years of residence

Table 2. Racial/Ethnic Differences in Learning the Aloha Spirit and Duration of Residence in Hawai‘i

Race/Ethnicity	Aloha Spirit [range possible, 1-4]	Number of Years Living in Hawai‘i
White	3.0	5
Japanese	3.5	18
Filipino	3.6	16
Chinese	3.3	15
Other Asian	3.4	14
Native Hawaiian	3.8	19
Pacific Islander	3.3	8
Other race	3.2	5

Table 3. OLS Regression Models of the Association Between Aloha Spirit and Levels of Psychological Distress

	Model 1 b (SE)	Model 2 b (SE)
Aloha spirit	-1.96*** (0.49)	-1.76** (0.54)
Lifetime discrimination		0.73 (0.65)
Everyday discrimination		0.41*** (0.04)
Female		1.56** (0.60)
Age		-0.08 (0.07)
Parental education		-0.18 (0.10)
Japanese ^a		0.02 (1.15)
Filipino ^a		0.87 (1.18)
Chinese ^a		-0.22 (1.33)
Other Asian ^a		2.07 (1.48)
Native Hawaiian ^a		1.08 (1.26)
Pacific Islander ^a		2.60 (1.62)
Other race ^a		0.68 (1.17)
Ethnic identity level		-1.51** (0.63)
Immigrant		2.41** (0.93)
Years in Hawai‘i		0.11 (0.07)
Identifying as local		-1.16 (1.21)
Intercept	19.95***	18.98***

* $P < .05$; ** $P < .01$; *** $P < .001$ (two-tailed tests). SE, standard error.

^aReference category is White.

in Hawai‘i, and local identity were not significantly associated with depression ($P > .05$).

Discussion

To our knowledge, this study is the first to document a relationship between the aloha spirit and mental health. Our results reveal that stronger agreement with having learned the aloha spirit is associated with significantly lower levels of psychological distress and a reduced risk of depression among undergraduate students in Hawai‘i. These statistically significant effects

Table 4. Logistic Regression Models of the Association between Aloha Spirit and Depression		
	Model 1 OR (95% CI)	Model 2 OR (95% CI)
Aloha spirit	0.70*** (0.57-0.85)	0.69** (0.54-0.88)
Lifetime discrimination		1.03 (0.77-1.40)
Everyday discrimination		1.08*** (1.06-1.10)
Female		1.33* (1.00-1.76)
Age		1.00 (0.96-1.03)
Parental education		0.97 (0.93-1.01)
White ^a		0.72 (0.47-1.09)
Ethnic identity level		0.75 (0.56-1.00)
Immigrant		1.34 (0.90-2.02)
Years in Hawai'i		1.03 (0.99-1.06)
Identifying as local		0.70 (0.40-1.23)

*P < .05; **P < .01; ***P < .001 (two-tailed tests). OR, odds ratio; CI, confidence interval.
^aReference category is racial/ethnic minorities.

are over and above the effects of self-reported discrimination, local identity, levels of ethnic identification, race/ethnicity, immigrant status, duration of residence in Hawai'i, and other sociodemographic factors. These findings suggest that the aloha spirit could be a cultural resource that is beneficial to psychological well-being in Hawai'i— a place often referred to as the “Aloha state” and known for having better levels of well-being than most other states.²³

Despite the relatively high levels of learning the aloha spirit reported by the students in the current study, everyday discrimination was associated with significantly elevated levels of psychological distress and a greater likelihood of depression. Moreover, everyday discrimination not necessarily due to race/ethnicity had a stronger association with symptoms of depression than having ever experienced racial/ethnic discrimination in a lifetime, which has been found among Asian Americans in prior studies.^{12,24} The relationship between the chronic stress of everyday discrimination and symptoms of depression in Hawai'i has been documented previously in a study of Filipino Americans in Honolulu.¹² Another relevant study found that among a sample of 94 adult Native Hawaiians, perceived racism increased the likelihood of self-reported hypertension, adjusting for age, gender, education, and degree of Hawaiian and American cultural identities.²⁵ More research is necessary on racial/ethnic differences in the effects of discrimination on different physical and mental health outcomes in Hawai'i. Results of the present study also indicate that having a salient ethnic identity is associated with significantly lower levels of depressive symptoms, which is consistent with prior research on Filipinos in Hawai'i and California.¹² In other words, a stronger sense of ethnic pride and knowledge about one's ethnic group is related to better mental health.

Limitations of the present study are worth noting, such as the cross-sectional survey design (N = 1,028), which cannot determine the causal ordering of the relationships. It is possible that symptoms of depression could predispose these college students to perceive that they are being discriminated against. Yet, there is longitudinal evidence in the literature that prior experiences of discrimination predict subsequent symptoms of depression, regardless of earlier mental health problems.^{11,26} Other limitations of this study are that self-reports were used and depression was the only mental illness measured. The self-reported symptoms of depression were not based on diagnosis, but a proxy was used for clinical depression using the cut-off for the CES-D and levels of psychological distress were examined. The CES-D is a screening measure not intended to be a diagnostic tool. Furthermore, the measure of the aloha spirit was a single question asking the degree to which the respondents strongly disagreed or agreed that they had learned it in Hawai'i. Thus, the aloha spirit was not defined in the survey and was open to the respondent's own interpretation. Our findings, however, suggest that this is a ripe area for future research. Qualitative research is especially needed to comprehensively define the different dimensions of the aloha spirit for each of the racial/ethnic groups in Hawai'i, ascertain how often it is practiced in daily life and whether certain aspects of it may be different than the commercialized renditions that the tourist industry exploits, and inquire whether the aloha spirit is a social-psychological resource for coping with stress. In essence, aloha is not simply a greeting used in Hawai'i. More research needs to uncover how it is a way of life that has implications for social relations, health, and well-being.

In conclusion, this study draws attention to the paradox of discrimination and the aloha spirit in Hawai'i by highlighting their distinct relationships with mental health. Overall, future research should expand the population of study beyond college students to other age groups, use a representative probability sample of the state of Hawai'i, assess temporal ordering using longitudinal data, and examine more mental health outcomes. This would bring us closer to establishing whether the high levels of psychological well-being in Hawai'i are due in part to the aloha spirit—a cultural asset that should no longer be overlooked by the research literatures in medicine and public health.

Conflict of Interest

None of the authors identify any conflict of interest.

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Colonoscopy Screening among Native Hawaiians at Queen's Medical Center between August 2011 and January 2013

Jodie M. Kaalekahi RN; Krupa R. Gandhi MPH; John J. Chen PhD; and Scott K. Kuwada MD

Abstract

A retrospective chart review in the Endoscopy Department at Queen's Medical Center identified 358 Native Hawaiian patients who had completed a colonoscopy screening procedure between August 2011 and January 2013, through either the Direct Referral Colonoscopy program or its Traditional Referral program. The differences in the characteristics of Native Hawaiian patients were summarized and compared between the two referral programs to identify potential barriers for future interventions and increase colorectal cancer screening. The combined colonoscopy screening rate among Native Hawaiians was 13%. Younger patients and those with private insurance were found to be undergoing colonoscopy screening through the Direct Referral program. The findings of this study underscore the need to reduce disparities in colonoscopy screening among Native Hawaiians.

Keywords

Colonoscopy, Colorectal Cancer Screening, Direct Referral program, Traditional Referral program, Native Hawaiians

Introduction

Colorectal cancer (CRC) is the third leading cause of cancer death in both men and women in the United States (US), with approximately 5% of the population affected.¹ In 2015, there were an estimated 132,700 new cases of CRC and 49,700 deaths in the US.² In Hawai'i, approximately 12 percent of annual cancer incidence and 10 percent of cancer mortality is attributed to colorectal cancer, which is the second leading cause of cancer death in the state.³ Although mortality rates associated with CRC have declined over the past 30 years among most racial/ethnic groups in Hawai'i due to increased screening and improvements in treatment, similar gains have not been observed for Native Hawaiians.^{3,4} Studies report poor survival and unchanged life expectancy for Native Hawaiian CRC patients with a majority diagnosed at advanced stages.⁴⁻⁶ Native Hawaiian men show an increased risk for CRC and higher mortality rates than Native Hawaiian women.^{3,7,8}

The United States Preventive Services Task Force (USPSTF) recommends persons aged 50-75 years with an average risk for CRC to be screened by the following different modalities: fecal occult blood testing (FOBT) every year, or sigmoidoscopy every 5 years with FOBT every 3 years, or colonoscopy every 10 years.⁹ Several studies have shown colonoscopy to be a very effective method for reducing colorectal cancer mortality.¹⁰⁻¹⁵ The popularity of colonoscopy is reflected in the Behavioral Risk Factor Surveillance System (BRFSS) survey which indicated that the most commonly used CRC screening test was colonoscopy, with 61.7% of all respondents in the US.¹⁶ In 2013, an estimated 66.4% of adults in Hawai'i reported being up-to-date with CRC screening, an increase from 61.1% in 2012. Of those individuals, the ethnicity with the highest completion rate was

Japanese (74.2%), followed by Chinese (70.7%), Caucasians (68.6%), Native Hawaiians (62.8%) and Filipinos (52.8%).¹⁷

CRC screening rates have increased significantly in the US. However, low screening rates are consistently seen among minority populations,¹⁸⁻²⁴ particularly among Hispanics and African Americans.²⁵⁻³¹ Native Hawaiians have also been found to have low screening rates.³² Prior studies conducted on Native Hawaiians with CRC mainly focused on assessment of risk factors, incidence and mortality rates, cancer staging, cancer survival and public health perspectives of CRC screening.^{4-8,22} Only a couple of studies have been conducted on targeted interventions among Native Hawaiians.^{33,34}

Traditionally, in order for a patient to be screened, a primary care provider must refer the patient to a gastroenterologist who sees the patient in their outpatient clinic. The clinic staff then preauthorizes the procedure with the patient's insurer, schedules the colonoscopy, and reviews the preparation instructions with the patient. In 2011, a Direct Referral Colonoscopy (DRC) program was developed by Queen's Medical Center in Honolulu, Hawai'i to facilitate and streamline screening colonoscopy procedures. The DRC program allows primary care providers (PCP) a means to directly refer a patient for colonoscopy without a pre-consultation office visit with a gastroenterologist. In the DRC program, Gastroenterology (GI) nurses receive the colonoscopy referrals and then carry out pre-authorization of the colonoscopy, patient education (on the procedure and preparation), and scheduling. The intent of the DRC program is to increase screening colonoscopy rates through ease of use for PCPs, who often wait several weeks for new GI clinic appointments, and decrease the costs by eliminating the need for a pre-colonoscopy office visit.

List of Abbreviations	
CRC	Colorectal Cancer
US	United States
USPSTF	United States Preventive Services Task Force
FOBT	Fecal Occult Blood Test
BRFSS	Behavioral Risk Factor Surveillance System
DRC	Direct Referral Colonoscopy
PCP	Primary Care Providers
GI	Gastroenterology
RN	Registered Nurse
ICD	International Classification of Diseases
TRC	Traditional Referral Colonoscopy
N.H.	Native Hawaiian

The purpose of this study was to investigate differences in the characteristics of Native Hawaiian patients who completed direct versus traditional referral colonoscopy (TRC) screening procedures. This comparison will help to identify system barriers and inform potential interventions to improve colonoscopy screening among persons in the Native Hawaiian population.

Methods

A retrospective chart review was conducted in the Endoscopy Department at Queen’s Medical Center. All patients who completed a screening colonoscopy procedure between August 2011 and January 2013, either through the DRC program or the TRC program, were identified. The study was approved by Queen’s Medical Center’s Institutional Review Board. Since the study was a retrospective chart review, informed consent from the patients and patient contact was not needed.

Queen’s Medical Center developed a DRC program in the spring of 2011, with the first patients being screened in August of 2011. An eligibility checklist, based on a patient’s medical history and presence of gastrointestinal symptoms, was completed by the referring physician and sent to the DRC program to be reviewed by a Registered Nurse (RN) (Table 1). Only patients with no items checked on the checklist were eligible for the DRC program, while patients with one or more items checked were referred to a GI specialist for a pre-consultation visit.

A RN contacted eligible patients to review medical history, schedule a colonoscopy procedure date, and provide education. The RN maintained communication with referring physicians to provide updates on the status of the referral and to obtain any other necessary paperwork. A RN contacted the patient 3-7

days prior to their scheduled procedure date to review bowel prep instructions and provide support and education. On the procedure day, the patient met with the gastroenterologist performing the procedure to review their medical history and sign consent.

The DRC program was first advertised to the Queen’s Clinics in Hawai’i Kai and Kapolei. Shortly after the program started, DRC was advertised to PCPs and private practices located in the Queen’s Physician Office Buildings, community health centers, and PCPs in private practice on O’ahu.

The inclusion criteria for the study were: (1) Native Hawaiian (self-reported), (2) age 50-75 years, (3) pre-op diagnosis of screening colonoscopy or ICD (International Classification of Diseases) 9 code V76.51. Exclusion criteria were: (1) pre-op diagnosis or indication for procedure did not indicate ‘screening’ or ICD-9 code V76.51 as purpose for procedure and, (2) patient received a screening colonoscopy within 10 years.

Demographic variables were collected as follows: age (50-54 years, 55-64 years and 65-75 years), gender, ethnicity (Native Hawaiians and Part-Hawaiians), marital status (single, married, and divorced/widowed/separated), and type of medical insurance (public and private). Patients were categorized based on the type of referral (direct referral or traditional referral).

Descriptive statistics were used to summarize demographic characteristics. Bivariate analysis was performed to evaluate the relationship between the demographic variables and use of colonoscopy screening procedures using Chi-square test or Fisher’s exact test as appropriate, for categorical variables. Two-sided *P*-values of less than .05 were considered statistically significant. Statistical analyses were conducted using SAS version 9.3.

Is the patient or does the patient have ...	Yes	No
Age 75 or older		
Pregnant		
Cardiac disease including Congestive Heart Failure (CHF), valvular heart disease, pacemaker/Automatic implantable cardioverter-defibrillator (AICD)		
On anti-platelet or anticoagulation medication (including over-the-counter medication such as aspirin) and cannot safely stop prior to procedure		
Severe lung disease including Chronic Obstructive Pulmonary Disease (COPD), emphysema, asthma requiring supplement oxygen		
Sleep apnea requiring Continuous Positive Airway Pressure (CPAP) machine		
Significant kidney/liver disease		
A history of difficulty with previous sedation/anesthesia		
Drug or alcohol abuse (males: >16 drinks/week, females: >10 drinks/week)		
Use of antidepressants, antipsychotic, anti-seizure, benzodiazepines, narcotics, sedatives, or sleeping pills (frequent/regular use ie, >3-4 times/week)		
Diabetes on insulin		
Morbid Obesity (Body Mass Index (BMI) >40 or BMI >35 w/co-morbidities)		
Current GI symptoms		

Note: Patients with no item checked on the checklist will be referred to the DRC program directly, while patients with one or more items checked will be referred to a GI specialist.

Results

Between August 2011 and January 2013, there were a total of 2,738 patients who had completed colonoscopy screenings at Queen's Medical Center, 592 through the DRC program and 2,146 through the TRC program. Among 592 patients screened through DRC program, 71 (12%) were Native Hawaiians, whereas 287 out of 2,146 (13%) screened through TRC program were Native Hawaiians (Figure 1). Overall, patients in the direct referral program were younger with 59% aged 50-54

years compared to 44% for the traditional referral program ($P=.002$) (Table 2). Also, 20% of patients in the traditional referral program were 65 years and above, compared to just 4% in the direct referral program. Although the majority of patients in either referral program had private insurance, the DRC program had a significantly higher proportion of privately-insured patients compared to those in the TRC program (87% vs 67%, $P<.001$). No significant differences were observed for gender ($P=.38$), ethnicity ($P=.65$), or marital status ($P=.28$).

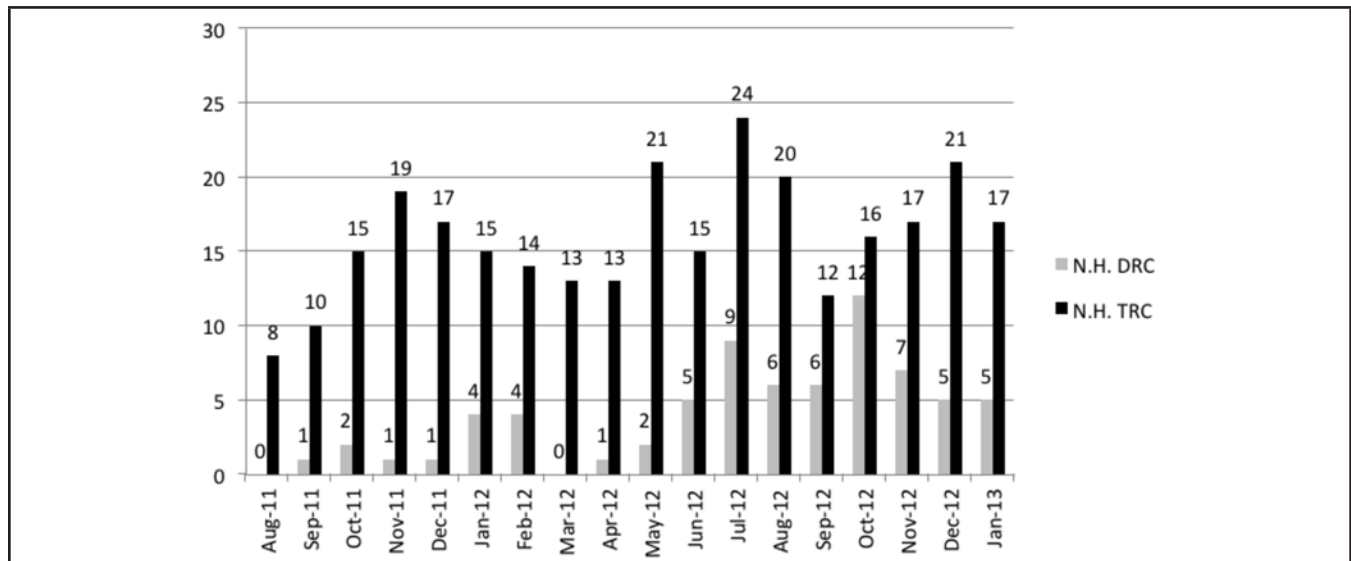


Figure 1. Summary of monthly counts of colonoscopy screenings (Native Hawaiians only) at Queen's Medical Center completed between August 2011 and January 2013, by referral types

DRC = Direct Referral Colonoscopy (n=71 Native Hawaiians); TRC = Traditional Referral Colonoscopy (n=287 Native Hawaiians); N.H. = Native Hawaiians

Variable	Total (n=358)	By Type of Referral		P-value*
		Direct Referral (n=71)	Traditional Referral (n=287)	
Age (n, %)				
50-54 years	167 (47%)	42 (59%)	125 (44%)	.002
55-64 years	132 (37%)	26 (37%)	106 (37%)	
65-75 years	59 (16%)	3 (4%)	56 (20%)	
Gender (n, %)				
Male	170 (47%)	37 (52%)	133 (46%)	.38
Female	188 (53%)	34 (48%)	154 (54%)	
Ethnicity (n, %)				
Hawaiian	250 (70%)	48 (68%)	202 (70%)	.65
Part-Hawaiian	108 (30%)	23 (32%)	85 (30%)	
Marital Status (n, %)				
Single	97 (27%)	14 (20%)	83 (29%)	.28
Married	221 (62%)	49 (69%)	172 (60%)	
Divorced/Widowed/Separated	40 (11%)	8 (11%)	32 (11%)	
Type of Medical Insurance (n, %)				
Private	255 (71%)	62 (87%)	193 (67%)	<.001
Public	103 (29%)	9 (13%)	94 (33%)	

n = number of patients. % = percentage of patients. *: Significance at alpha=0.05, based on Chi-square or Fisher's exact tests.

Discussion

The results obtained reveal a bias towards private insurance for Native Hawaiian patients undergoing screening colonoscopy via either the direct referral or traditional referral processes. Possibly, this reveals an underlying tendency for providers to favor patients with private health insurance.^{35,36} The interpretation of why the direct referral system reached a smaller proportion of patients with public insurance than the traditional referral systems is unclear. Since patients in the direct referral program were significantly younger on average than those in the traditional referral system, the finding could simply reflect the smaller proportion of Medicare patients in the former group.

The lower average age of patients in the direct referral program than the traditional referral system needs further exploration. This is most likely not related to insurance coverage issues since in Hawai'i, public and private insurance provides similar coverage for colonoscopies for people over 50 years of age.^{37,38} Possibly, the finding that patients in the direct referral program were significantly younger could be a result of the strict eligibility criteria for the direct referral program. Eligibility criteria were developed to identify those at increased risk for procedural complications who would benefit from a pre-consultation office visit with a gastroenterologist.³⁹ The eligibility criteria may have resulted in older patients being considered ineligible because they may have more co-morbidities.⁴⁰

Studies report 90% 5-year survival rates after early diagnosis and treatment of colorectal cancer at a localized stage, with eventual decrease in survival rates as the cancer spreads to distant organs.² In Hawai'i, only about 44% of the colorectal cancer cases were diagnosed at an early stage between the years 2000 and 2005. Several studies have reported older age to be a risk factor for developing colorectal cancer.⁴¹⁻⁴⁴ Screening rates are increasing with the aging population in Hawai'i³; however, Native Hawaiians (62.8%) still have lower uptake of screening procedures compared to Japanese (74.2%).¹⁷ Preventive efforts made by Queen's Medical Center through the DRC program are aimed to increase uptake of colonoscopy screening procedures. The overall screening rate among Native Hawaiians at this facility appeared to be generally low in both the programs. However, there was no information available on the distribution of Native Hawaiians or other races/ethnicities in the population from which patients were referred for colonoscopy screening. As a result, it is not known whether there were disparities in colonoscopy screening among Native Hawaiians. Future studies are recommended with more baseline data on all races/ethnicities and those with complete and incomplete colonoscopy screenings to assess and compare completion rates of Native Hawaiians with non-Native Hawaiians in both the referral programs at the Queen's Medical Center. In the current study, the completion of direct referral colonoscopy was found to be lower among those aged 65-75 years than younger age groups and higher completion of direct referral colonoscopy was found among those with private insurance compared to public insurance.

The study has several limitations. First, the use of convenience sampling can lead to selection bias. The DRC eligibil-

ity criteria were designed to capture healthy patients with less co-morbidities, which may have deemed many older patients ineligible and resulted in selection bias. Second, receipt of a screening colonoscopy was identified with a diagnostic code or use of the word "screening" in the pre-operative diagnosis, so patients could have been missed if the procedure was coded differently or misspelled. However, differential misclassification bias is not expected, because coding and misspelling would not occur more in one group than the other as all patients in both groups were scheduled by the same schedulers. Third, use of a single site center could minimize generalizability. Fourth, Native Hawaiian ethnicity was self-reported, and was not verified. Fifth, the study only compared screening rates among Native Hawaiians between the two referral programs, ignoring potential differences among other racial/ethnic groups. Lastly, the direct referral program underwent restructuring in Spring 2013, which led to changes in eligibility criteria that would allow more patients to be eligible for the current direct referral program; this change may have influenced the proportion of patients eligible for DRC, but would not be expected to result in differential misclassification by race-ethnicity.

Our study reveals a tendency for younger and privately insured Native Hawaiian patients at a single facility to be directly referred for screening colonoscopy and future studies should be performed to determine the reason for this. Perhaps the strict criteria used for the DRC program discouraged the referral of older individuals as they had more co-morbidities. In addition, the rate at which various colorectal cancer screening modalities, as recommended by the USPSTF, are being offered to eligible Native Hawaiians needs to be compared with rates offered to non-Native Hawaiians. Much work needs to be performed to improve colorectal cancer screening rates in Native Hawaiians in order to reduce colorectal cancer mortality but the barriers to screening must first be identified.

The findings of this study will be helpful in further restructuring and expanding the current DRC program at the Queen's Medical Center. Although the study was unable to identify specific patient barriers, differences between patients in the two referral programs helped to reveal system barriers that need to be explored. The first major system barrier that warrants further investigation is the eligibility criteria for the DRC program. The DRC program will be staffed with an Advanced Practice Registered Nurse (APRN) that will allow for thorough screening of all referrals, scheduling pre-consultation office appointments with patients who may have otherwise been deemed ineligible for the program, and will also allow the gastroenterologist to focus on more complex patients. Through staffing with an APRN, the DRC program should be able to capture older populations as these patients can now be seen in the office by the APRN to review medical history and complete a physical assessment. Secondly, although DRC welcomed all referrals irrespective of the coverage offered by the patients' health insurance plans, the bias towards privately-insured patients likely occurred at the level of referring physicians' offices. Most of the state of Hawai'i's Medicaid patients were seen in local community

clinics, whereas, most of the privately-insured patients were seen by private practitioners. However, it is unknown if there were significant differences in colonoscopy referrals between community clinic providers and private practitioners. These findings underscore further studies to determine the causes of variability in referrals for colonoscopy screening among Native Hawaiians.

Among Native Hawaiians, the overall colonoscopy rate at Queen's Medical Center was only around 13% when both the referral programs were combined. Although younger patients and those with private insurance were captured by the DRC, future studies including all racial/ethnic groups and incomplete colonoscopy screenings are recommended to assess completion rates among Native Hawaiians compared to non-Native Hawaiians and to identify patient barriers for screening. An overall DRC program evaluation is recommended, including an evaluation of patient satisfaction and the financial impact of the program. Identification of screening barriers and overall evaluation of the program would be important to determine if interventions are needed in the current DRC program to further reduce disparities in colonoscopy screening among Native Hawaiians at Queens Medical Center.

Conflict of Interest

None of the authors identify a conflict of interest.

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MEDICAL SCHOOL HOTLINE

Cultural Competency in Serving the Homeless in Hawai'i at the John A. Burns School of Medicine

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The Medical School Hotline is a monthly column from the John A. Burns School of Medicine and is edited by Satoru Izutsu PhD; HJMPH Contributing Editor. Dr. Izutsu is the vice-dean of the University of Hawai'i John A. Burns School of Medicine and has been the Medical School Hotline editor since 1993.

Homelessness in Hawai'i has gained a tremendous amount of attention over the past year. National and international newspapers have been highlighting Hawai'i's issue of homelessness, as the state's rapidly growing homeless population has reached a five-year high of 7,620 individuals (Figure 1),¹ leaving Hawai'i with the unfortunate distinction of having the highest homeless rate per capita in the nation (487 homeless/100,000 people).² In October 2015, the City and County of Honolulu conducted its largest homeless sweeps on the streets of Kaka'ako neighboring the University of Hawai'i John A. Burns School of Medicine (JABSOM). These sweeps displaced over 200 homeless individuals, and with limited shelter space available many were left with no place to go. The fact that the number of unsheltered homeless individuals (3,843) is greater than the number of sheltered homeless individuals (3,777) demonstrates the need for more social services and better housing policies.¹ In response, politicians have proposed ideas to allocate additional resources for the homeless, such as providing temporary housing communities on Sand Island and in Kaka'ako.^{3,4}

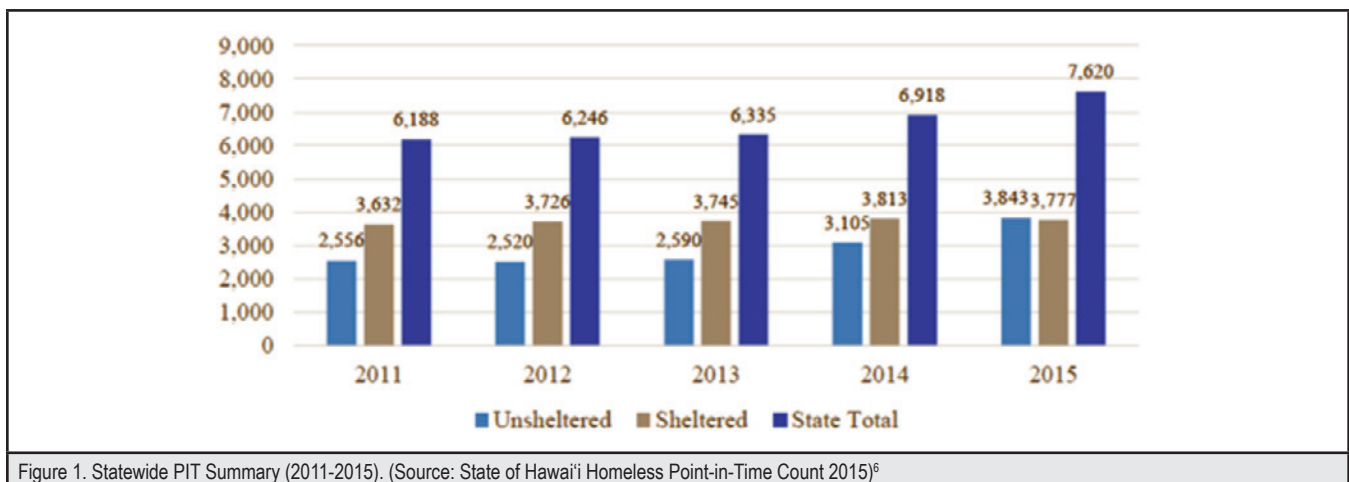
While Hawai'i's politicians are working to create safe environments for these individuals, medical students at JABSOM have been addressing this statewide issue since 2005 through the Homeless Outreach and Medical Education (H.O.M.E.) Project,⁵ which provides four student-run free clinics each

week and teaches future physicians to provide high quality and effective healthcare in an environment of limited resources. By caring for both homeless and non-homeless patients, students refine their skill in addressing cultural issues—an art that is arguably as important as the science behind the medicine.

Cultural Competency

Social determinants of health, such as social status, employment, education, and wealth, have been examined closely in attempts to improve the healthcare system.⁷ These social factors must take culture into account in order to be fully understood and before potential solutions can be proposed.^{8,9} For example, most Western societies define wealth as monetary and material gain, whereas the Hawaiian word for both “wealth” and “fresh water” is *wai*, which reflects the precious significance of fresh water to the Hawaiian culture.¹⁰ Even though the social determinants of health are universal processes, they have unique meanings in each society. Healing is not always solely dictated by evidence-based medicine. It also incorporates the patient's cultural values, personal principles, goals, and aspirations.⁹

The Oxford English dictionary defines “culture” as *the distinctive ideas, customs, social behaviour, products, or way of life of a particular nation, society, people, or period*.¹¹ Culture is a complex collection of identities, including but not limited to



race, gender, religion, sexual orientation, education, disability, and homelessness. The purpose of cultural competency is to make healthcare services accessible, acceptable, and effective for all people, regardless of their cultural background.¹² For decades, the importance of cultural competency in healthcare has been emphasized in response to the nation's growing healthcare disparities amongst racial groups. According to the United States Census Bureau, the number of racial minorities is increasing at a rapid rate with racial minorities becoming the population's majority in five states.¹³ Racial minorities comprise 75% of the population in Hawai'i, which is the largest minority population of any state in the nation.¹³

Hawai'i is often thought of as one of the most culturally diverse places in the world. The state attracts a wide range of people from across the globe and is comprised of an irreproducible mixture of native Hawaiian, intranational, and international cultures. Commonly referred to as a "cultural melting pot," Hawai'i embodies the importance of cultural competency in medicine. It is an excellent place for medical students to learn to care for patients of various backgrounds. By training at the University of Hawai'i, future physicians are able to interact directly with and learn from these individuals, thereby preparing them to provide comprehensive care for their patients that includes addressing cultural issues.

Learning by Caring for the Homeless

Homelessness is a unique type of culture. Some of the special healthcare needs of the homeless community result from higher rates of cardiovascular disease,¹⁴ infectious diseases,^{15,16} cancer,¹⁷ and mental illness¹⁸ than in the general public. As a result of their poor health outcomes, homeless individuals are often victim-blamed for being inattentive to their personal health. However, these accusations fail to take into account homeless culture and the many barriers they face. The lack of adequate healthcare among homeless individuals can be attributed to poor finances, lack of knowledge of the healthcare system, language and cultural barriers, lack of transportation, and other priorities that take precedence over health (ie, shelter, safety, food).^{19,20} These factors must be taken into consideration when physicians create individual treatment plans to enhance feasibility and optimal patient adherence. Healthcare providers must remember to approach patients holistically and to practice culturally competent care, so that false assumptions are not reached and do not perpetuate existing disparities within the healthcare system.

The mission of the Hawai'i H.O.M.E. Project is to improve quality and access to healthcare for Hawai'i's homeless while increasing student and physician awareness and understanding of the homeless and their healthcare needs.⁵ The H.O.M.E. Project touches the lives of both patients and students, as it mentors future physicians to advocate for personal and systemic changes that may effectively address healthcare disparities. Through the H.O.M.E. Project, medical students gain intimate exposure to the various obstacles that homeless individuals face and obtain a better understanding of how socioeconomic factors drive public health.

By understanding and targeting the multiple sources of their clients' health problems, the H.O.M.E. Project is able to propose solutions that are feasible and sensible for homeless patients. For example, a major problem among the homeless community is the inability to obtain affordable meals, particularly affordable healthy meals, which results in a diet consisting primarily of inexpensive processed foods. This mass consumption of high calorie, high fat, nutrient-deficient foods leads to increased rates of obesity, diabetes, hyperlipidemia, and the many complications associated with these diseases. While the homeless are often judged for their poor lifestyle and non-adherence to treatment plans, the reality of their situation is that consuming cheap, unhealthy food is a more realistic alternative to starving or spending their limited funds on expensive medications and healthy foods.

Finances and accessibility limit preventive healthcare. When patients finally present to a physician, their medical problem list is the by-product of longstanding untreated disease that has accumulated over many years. Personal priorities of the homeless often differ from those of the general public as a result of their economic situation. Students at the H.O.M.E. Project take these social determinants of health into account and have created easy-to-read educational pamphlets, such as "Eating Healthy on a Budget." Additional services include providing healthy refreshments, free medications, and personal items such as socks, shoes, sleeping mats, and hygiene products. Through these activities, JABSOM students are taught to become empathetic leaders within the community.

Each patient has his or her own story. Medical students are encouraged to obtain detailed histories to better understand each person's background — What is important to them? How did they become homeless? How are they struggling with homelessness? What are some of the barriers they face in trying to overcome homelessness? At the clinics, medical students not only care for, but also befriend many of the patients. One very memorable patient was a pleasant middle-aged woman who presented to H.O.M.E. clinic with a severe headache. Her headache began earlier that day, after she had gotten into an argument with her ex-husband who was an unmedicated schizophrenic, polysubstance abuser. She had a long history of domestic violence, but consistently declined protection at the local women's shelter because of the shelter's no pet policy. She refused to surrender the dog that she had rescued as a stray puppy that had remained faithfully by her side through her job loss, divorce, and eventual eviction. This dog was her only family and companion. After treating her headache with acetaminophen, her enraged ex-husband came to the H.O.M.E. clinic and demanded that she leave with him. Concerned for her safety, she was asked privately if she would permit us to call the police. She politely declined and departed with him. It was difficult to understand why she would decline help. The attending physician enlightened me that unfortunately, helping victims of domestic abuse can often do more harm than good, especially if they are not ready or hesitant to receive assistance.^{21,22} Moreover, for victims who have gathered the strength to seek help, police have traditionally

been reluctant to make arrests for “minor assaults”, discouraging and further endangering victims of domestic abuse.²² The attending physician also reassured me that in these types of situations, providing emotional support is often more powerful than actual medicine.

Homelessness is more than a lack of finances. It is often complicated by other underlying issues such as domestic abuse, substance abuse, and mental illness. The “drift hypothesis” is a longstanding theory regarding the relationship between mental illness and social class.²³ It argues that mental illness causes a downward shift in social class, thus explaining the disproportionately high rate of schizophrenia among the low income population.²³ The H.O.M.E. Project has helped students to realize that many of these individuals are victims of unfortunate circumstances and that cultural competence is necessary to treat the whole person, rather than just the disease.

Nurturing Culturally Competent Physicians at the John A. Burns School of Medicine

All physicians, regardless of their specialty, will encounter patients from various backgrounds and, therefore, should be proficient in providing culturally competent healthcare. The nation’s top professional organizations, including the American Medical Association and Association of American Medical Colleges, have called for medical education to address the needs of culturally diverse patient populations.²⁴⁻²⁷ However, according to the 2015 Association of American Medical Colleges Graduation Questionnaire, only 64.2% of medical students nationwide reported any formal education experience related to cultural awareness and cultural competence.²⁷ This translates into a significant number of doctors who are inadequately prepared to provide comprehensive healthcare to a large percentage of their patients.

The H.O.M.E. Project was established 10 years ago in response to growing healthcare disparities. Today, over 49 US medical schools operate at least one student-run free clinic.²⁸ JABSOM introduces its students to the issue of homelessness early in their medical careers and continues to revisit this topic throughout their medical education. Curriculum highlights include a panel of homeless persons that provides students with an opportunity to listen to personal stories of homelessness, along with several problem-based-learning (PBL) cases that revolve around a homeless teenager and his family. The issues discussed challenge students to think critically about accessibility to healthcare, underlying systemic problems, and potential solutions.²⁹ Students are engaged in both class lectures and small group discussions about the basic healthcare management of homeless patients and clinical “pearls” such as treating gout attacks with indomethacin, rather than colchicine, since the latter causes diarrhea and homeless patients often lack quick access to restrooms—a luxury that most people take for granted. After three years of instruction and working with the H.O.M.E. Project, student knowledge, skills, and empathy are evaluated through Objective Structured Clinical Exams (OSCEs).²⁹ With

this rigorous curriculum, JABSOM graduates are molded into exceptional physicians who are well prepared to address the needs of Hawai‘i’s homeless.

Compared to the 64.2% of medical students nationwide that reported any formal education experience related to cultural awareness and cultural competence, for the last five years 82.8 – 94.9% of JABSOM students reported having these educational experiences.²⁷ In addition to addressing the issues of the homeless, JABSOM excels at training students to understand the cultural needs of other underserved communities. The following are some examples of experiences addressing cultural competency that are available to JABSOM students:

- First year community health rotations addressing under served populations: Native Hawaiian health,³⁰ low income clinics (Kalihi-Palama Health Center, Waimanalo Health Center), at risk youth (School Health Education Project,³¹ Hawai‘i Youth Program for Excellence, Healthy Keiki Can, Kuaola Program), individuals with intellectual disability (Sunny Buddies Program), and senior citizens (Wellness Initiative for Seniors in Hawai‘i)
- PBL on the neighbor islands
- Clinical rotations in rural health: neighboring Hawaiian islands, Pacific Islands (Philippines, Guam, American Samoa, Pohnpei, Chuuk, Yap, Palau), Southeast Asia, and Japan
- Student organizations: Partnership for Social Justice,³² LGBT Health Interest Group³³, Global Health Interest Group, Rural Health Interest Group
- Student projects in medical education: student-written PBL cases addressing the special needs of Muslim³⁴ and LGBT³⁵ patients

The JABSOM curriculum is a collaboration amongst faculty, administration, and students to promote cultural competence through hands-on training and real world experience. The school’s student body reflects the state’s diversity and the essential characteristics of a highly effective doctor—empathy, activism, compassion, and cultural competence. It is no surprise that JABSOM is currently ranked among the top 20 United States medical schools for primary care.³⁶ With continued experiences like those provided at the H.O.M.E. Project clinics, we will not only be able to provide more culturally competent care to the growing homeless population in Hawai‘i, but we are preparing our future physicians to better care for all of the people in our community.

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INSIGHTS IN PUBLIC HEALTH

Building Well-Being: Linking the Built Environment to Health

Sara Jensen Carr PhD

Insights in Public Health is a monthly solicited column from the public health community and is coordinated by HJMPH Contributing Editors Tetine L. Sentell PhD from the Office of Public Health Studies at the University of Hawai'i at Manoa and Donald Hayes MD, MPH from the Hawai'i Department of Health in collaboration with HJMPH Associate Editors Ranjani R. Starr MPH and Lance K. Ching PhD, MPH from the Hawai'i Department of Health.

Background

The World Health Organization's Alma-Ata Declaration of 1978 redefined health as not simply the absence of disease, but a state of physical, mental, and social well-being, and declared this to be a fundamental human right.¹ This signified a major shift from looking at internal causes of disease to including the external aspects that shape our everyday lives. While many other factors influence health defined broadly, including genetics, behavior, and nutrition, an important and growing interdisciplinary field of research and policy highlights the particular role of the built environment in creating and fostering health.

The built environment encompasses the design of buildings and urban landscapes, land use, and transportation systems.² In the 1970's and 1980's, researchers such as Robert Ader, who traced lines from environmental influence and individual perception to the manifestation of disease,³ and Roslyn Lindheim and Leonard Syme, who connected the social and spatial conditions of neighborhoods to health outcomes,⁴ provided seminal evidence of the important relationship of the built environment to well-being. While related areas of research consider the role of economic, social, and political environments in health,⁵ the realm of the built environment has been of particular interest in the past decade. A recent literature review found that between 1993 and 2002, there were only 39 studies examining built environment and health, but between 2003 and 2013, there were 675.⁶

This field of study has delineated important and specific connections between certain health-related behaviors, health outcomes, and the correlating dimensions of the built environment. For instance, safe sidewalks providing access to daily destinations such as schools, grocery stores, and retail can encourage daily walking,^{7,8} which in turn can decrease obesity and associated diseases. Being in the presence of, or even just viewing trees and green, lush landscapes, can reduce stress and aggression.^{9,10} Accessible and well-designed public spaces can encourage neighborhood interaction, which in turn builds social capital.¹¹

In the United States, it has become clear that the traditional separation of the fields of urban planning, architecture and design, and public health combined with several decades of fast and cheap development without health in mind have left

us in a vast landscape that inhibits healthy habits.¹² To quote the recent publication *Making Healthy Places* (2011): "The modern America of depression and loss of community has not 'happened' to us; rather we legislated, subsidized, and planned it."¹³ While this poor community planning takes a toll on all Americans, it disproportionately impacts minorities and immigrants, who often have less access to safe walkable areas, parks, and grocery stores.¹⁴⁻¹⁶ As sprawling neighborhoods are increasingly deemed unhealthy, they become cheaper, and as a result, are increasingly occupied by these often economically disadvantaged populations.¹⁷

Along with the improved evidence base on this topic there is increasing interest and political will to address this issue. The growing importance of this issue has been recognized by the United States Surgeon General, Vivek Murthy, who recently issued a call to action to build more walkable communities.¹⁸ With a broad body of evidence and increasingly innovative technologies for spatial analysis, the diverse areas of expertise of designers, planners, and public health professionals are well-positioned now more than ever to work together to implement interventions. What comes next?

The Next Era of Built Environment and Health

As we continue to specify the connections between aspects of the built environment and health outcomes, there remain several challenges to coordinating transdisciplinary practice. Chief among them is surmounting the differences in foundational concepts and language, as well as reconciling quantitative and qualitative methods from each sphere. The heterogeneity of study methods in evaluating the built environment, not only within the field of public health but across fields, makes it difficult to draw common conclusions across studies.¹⁹ Additionally, given the multiple genetic, biologic, and environmental contributors to chronic disease, the pathways from health origins to outcomes can be murky. While the role of the built environment in human well-being has become much more expansive in the past several years, it remains difficult to prove its direct "causality," so understanding its impact may be difficult on an epistemological level for many to accept.^{20,21}

That said, as research on health and the built environment proliferates the public sphere, more states, counties, and cities are starting to integrate health as a priority in development and including design guidelines to build sustainably and safely, re-orient the public realm to the pedestrian, and ensure equitable access to healthy foods and parks.²² Here in Hawai‘i, a Complete Streets bill, which seeks to “reasonably accommodate convenient access and mobility for all users of the public highways... including pedestrians, bicyclists, transit users, motorists, and persons of all ages and abilities” was signed into law in 2009.²³ The law tasks the state and each county with adopting Complete Streets policies, which, to date, all of the counties have done through either resolution or ordinance. These policies are in various stages of implementation, with Kaua‘i leading the way and Honolulu close behind. In Honolulu, the City and County Department of Transportation Services (DOTS) is taking advantage of widespread construction related to the new rail transit project and the anticipated launch of a large bikeshare system in urban Honolulu to implement their Complete Streets policy and principles.²⁴ The state Department of Health (DOH) has supported policy implementation by partnering with state and county agencies and advocacy groups (such as the Hawai‘i Bicycling League and American Association of Retired Persons) to encourage safer, multimodal streets that provide opportunities for physical activity.

It will take years, if not decades, to truly see how these policy changes will affect building and planning, and even longer to gauge population health impacts. However, studies have already shown that both existing and new walkable neighborhoods are also more expensive than auto-oriented ones.^{25,26} While the higher property values signify widespread public support for pedestrian-friendly environments, it also limits access for the economically disadvantaged. As more neighborhoods change, provisions for affordable housing must be made to ensure healthful environments for those who need it most.

Lastly, professionals in all fields must realize that simply building better is not enough. Built environment change is most effective when it comes hand in hand with coordinated educational programs aimed at behavior change. An example is Walk with a Doc, a nonprofit program which has medical doctors prescribe walks to patients and then meet them at a designated site to join them in the activity. Walk with a Doc programs can now be found in over 160 locations, including Hilo, Hawai‘i.²⁷ Programs like this not only institute healthy habits, but build awareness of the neighborhood environment, increase social capital by helping residents connect to their neighbors, and increase stewardship of streets and parks for sustained community investment.

Now is a crucial time to move forward with innovative environmental interventions. To apply the adage, “If we want more evidence-based practice, we need more practice-based evidence,”²⁸ only by literally building on the current body of research and detailed post-occupancy analyses can we begin to hone in on best practices for building healthy places. A few professional organizations in the architecture and planning fields

have begun to take up this mantle. The American Institute of Architects (AIA) has recently launched a 10-year Design and Health initiative that aims to educate architects about the effect of buildings and urban design on human well-being, as well as bring schools with joint health, planning, and architecture programs together in a research consortium to share projects and findings.²⁹ The Urban Land Institute, a real estate-focused research and education organization, has similarly started their Building Healthy Places initiative, and recently published a toolkit for developers and planners.³⁰ It will be important for both public health researchers and the designers utilizing these guidelines to evaluate their impact.

Action on the Built Environment and Health in Hawai‘i

Beyond the transdisciplinary partnerships around Complete Streets mentioned above, Hawai‘i has a number of innovative initial efforts to confront health issues related to the built environment supported by diverse partners including the Office of Public Health Studies and the School of Architecture at University of Hawai‘i, Manoa and the State DOH. For instance, the DOH has been instrumental in supporting small programs like the Kalihi Valley Instructional Bike Exchange (KVIBE), a youth earn-a-bike outreach program promoting bicycle riding, safety, and repair in a traditionally disadvantaged community. It also recently coordinated the second Pacific Northwest Mobile Study Tour to the Seattle and Portland areas, taking 55 people representing all four county transportation planning and public works departments, the state transportation department and other public and private sector partners to meet with peers and see innovative best practices for the built environment. Participants were able to see not only what Complete Streets and walkable environments looked like, but ask questions about how project leaders found funding, built community support, and maintained projects. DOH also recently helped coordinate a special panel on Health and the Built Environment at the Hawai‘i Public Health Association annual conference, held on October 9, 2015. Topics presented included enhancing pedestrian and bicycling street environments in O‘ahu and Kaua‘i, reconnecting communities to local healthy food sources, and the Hawai‘i Medical Service Association’s (HMSA) Blue Zones effort to branch outside of the healthcare setting into community-based programs. The Office of Public Health Studies (OPHS) at the University of Hawai‘i at Manoa, in conjunction with the Department of Health, is conducting a follow-up study on a significant statewide assessment of the walking and biking accessibility of Hawai‘i’s streets, engaging the Department of Transportation in the research. They are also looking at food environments and related health disparities across the state. A joint position between the School of Architecture (75%) and OPHS at the University of Hawai‘i at Manoa was created to solidify the link between these two traditionally distinct research areas. The first cross-listed course between the departments will commence in Spring 2016, and will bring together graduate students in Public Health and Architecture to critically engage transdisciplinary issues and

learn how to evaluate the built environment for health. They will also work with the Native Hawaiian Health Program at Queen's Medical Center to learn about traditional Hawaiian gathering spaces and survey neighborhood residents to design an outdoor community center for the traditionally underserved west side of O'ahu.

In a national effort to bring these disciplines together fruitfully, the Association of Collegiate Schools of Architecture (ACSA) and the Association of Schools and Programs of Public Health (ASPPH) will come together for the first time in Fall of 2016 to co-sponsor a conference, "Building Well-Being: Buildings Cities Systems," at the University of Hawai'i at Manoa. The academy is in a unique position to advance the health and built environment agenda. Rigorous empirical research will be central to thoughtful interventions to accomplish this, but government agencies and design and planning professionals often lack time or resources to conduct research or analyze data. The goal of the ACSA/ASPPH conference is to connect practitioners and policymakers to academics in order to form transdisciplinary partnerships to build healthy communities. Hawai'i's delegation also plans to showcase relevant efforts in Hawai'i including the state plan for aging, resilience planning in the face of sea level rise, and new pedestrian and transit-oriented developments surrounding Honolulu's planned rail project.

Conclusion

The past decade has seen an exponential expansion of publication and discussion regarding the built environment's influence on health. Given the long timeframe required to make changes in the public realm, the time to act on that research is now. Yet doctors, public health professionals and researchers, architects, landscape architects, urban designers, and planning professionals have several challenges to face, including but not limited to building a shared vocabulary, testing tools and measures, and ensuring equitable environments in the face of change. However, it is still imperative to come together and thoughtfully employ evidence to build healthy places and programs, as only then can we truly evaluate impacts and hone best practices. The current conversation on health and the built environment overwhelmingly focuses on it as a source of illness. We should equally concentrate on its vast potential to prevent disease, and improve population health.

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THE DANIEL K. INOUE COLLEGE OF PHARMACY SCRIPTS

Prescription Drug Pricing

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Abstract

Prescription drugs have reduced morbidity and mortality and improved the quality of life of millions of Americans. Yet, concerns over drug price increases loom. Drug spending has risen relatively slowly over the past decade because many of the most popular brand-name medicines lost patent protection. In the near future, there will be fewer low-cost generics coming into the market to offset the rising prices of brand-name drugs. Drug expenditures are influenced by both volume and price. This article focuses on how drug prices are set in the United States and current trends. Drug prices are determined through an extremely complicated set of interactions between pharmaceutical manufacturers, wholesalers, retailers, insurers, pharmacy benefit managers (PBMs), managed care organizations, hospitals, chain stores, and consumers. The process differs depending on the type of drug and place of delivery. Rising drug prices have come under increased scrutiny due to increased cost inflation and because many price increases come as a result of mergers and acquisitions of generic drug companies or changes in ownership of brand name drug manufacturers. Other countries have reigned in drug prices by negotiating with or regulating pharmaceutical manufacturers. The best long-term solution to rising drug prices is yet to be determined but the United States will continue to debate this issue and the discussions will get more heated if drug expenditures continue to rise at a rapid rate (ie, increasing 13% in 2014 from the previous year).

Introduction

In an unprecedented occurrence, a prominent oncologist recently spoke out about over-priced drugs at the annual meeting of the American Society of Clinical Oncology. Dr. Leonard Saltz said, "These drugs cost too much. Cancer-drug prices are not related to the value of the drug. Prices are based on what has come before and what the seller believes the market will bear."¹

Americans spent \$329.2 billion on prescription drugs in 2013, which accounted for approximately 11% of health care costs. A decade ago, prescription medications were the fastest growing component of health care costs, and as such, received a lot of attention from policy makers. Since the year 2000, the annual percent change in prescription drug costs was moderate, with pharmaceutical costs rising less than 3 percent every year until this past year when drug expenditure increases reached 13 percent, the highest level since 2002 (Figure 1).² These falling rates of inflation over the past decade were caused by some common brand name drugs ending their patent protection and through insurers' efforts to control costs.² In the ten-year period between

2003 and 2012, generic drugs generated \$1.2 trillion in savings to the US health care system.³ Recently, however, both generic and brand name drug prices have been increasing resulting in higher rates of increase in pharmaceutical expenditures.

This article focuses on how drug prices are determined in the United States and current trends.

Drug Pricing Process

In a perfectly competitive market at equilibrium, price equals the marginal cost of production. With many pharmaceuticals, however, there is a large gap between marginal cost of production and price. Drug prices are determined through an extremely complicated set of interactions between pharmaceutical manufacturers, wholesalers,retailers,insurers,pharmacy benefit managers (PBMs), managed care organizations, hospitals, chain stores, and consumers.

Part of the complexity arises from the high cost of research and development (R&D) of pharmaceuticals. Costs of developing a new drug in the United States include basic research and development, testing, and meeting the requirements of a

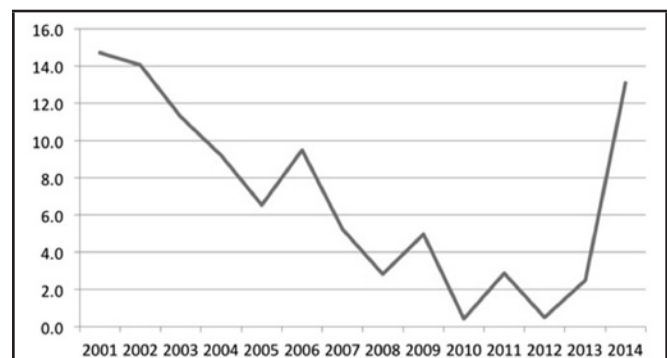


Figure 1. Annual Percentage Change in Prescription Drug Expenditures, 2001-2014

CDC/NCHS, Health, United States 2013, Figure 29. Data from the Centers for Medicare & Medicaid Services, Office of the Actuary, National Statistics Group, National Health Expenditures Accounts. IMS Health Analytics 2015.

complex regulatory system and are estimated at between \$161 million and \$2.6 billion, depending on the study methodology.^{4,5} For pharmaceutical manufacturers to receive a return on investment from these developmental costs, they are given patents which ensure their exclusive rights to produce these drugs for a limited time. These patents intentionally create a lack of competition and enable manufacturers to set prices for newly developed drugs determined to be of value to society.

Drug prices are set differently depending on how prescription drugs are dispensed: (1) through retail pharmacies, including independent pharmacies, chains, pharmacies in supermarkets or mass merchandisers, and mail-order pharmacies; and (2) from physicians or hospitals for drugs administered in those settings.

Medications Distributed at Retail Pharmacies

In retail pharmacy, prices are set through a series of negotiations and market transactions between manufacturers and various wholesalers, mail order pharmacies, hospitals, and managed care organizations (Figure 2).^{6,7}

(1) In the first transaction of the purchase chain, the manufacturer sells the drug to a wholesaler, mail order pharmacy or nonretail pharmacy at a price that varies by the dosage form and strength. The manufacturer's price is negotiated and depends on both the cost of producing the drug and a share of the manufacturer's R&D costs, taxes, and profits and depends upon the level of competition in a market. Competition depends upon whether a brand-name drug has patent protection and the availability of generic (multi-source) versions of the drug. In addition, even brand name drugs under patent protection can face competition from other drugs that are therapeutic equiva-

lents. Wholesalers may receive manufacturer discounts based on volume or prompt payment and a manufacturer of a multi-source drug may offer a discount to incentivize wholesalers to promote their generic version of the drug.⁷ The average price wholesalers pay to manufacturers is called the Average Manufacturer Price (AMP). For institutions that operate their own outpatient pharmacies, such as hospitals and clinics, charges to the pharmacies may reflect negotiated discounts arranged by buying groups (Figure 2).

(2) In the second transaction, the wholesaler sells the drug to a retail pharmacy at a price reflecting the price paid to the manufacturer plus a markup. This price is commonly referred to as the average wholesale price (AWP, Table 1). The AWP, however, is more of a "list price" and not the average of the amounts that retail pharmacies actually pay wholesalers. A wholesaler may sell specific drugs to all pharmacies at prices below the AWP or may give discounts to certain pharmacies based on their relative purchasing power.⁷

(3) In the third transaction, the retail pharmacy sells the drug to a patient. For patients paying without drug benefit coverage, the price includes the cost of acquiring the drug from the wholesaler plus a retail markup that varies by pharmacy and is dictated by that pharmacy's purchasing power. Pharmacies may set a lower markup for chronic medications and a higher one for drugs used for acute conditions. These markups typically range from 20% to 25% above the pharmacy's acquisition price and include both the fixed operating costs of the pharmacy as well as taxes and profit margins.⁷ Pharmacies may also offer discounts on drugs to certain groups of cash customers, such as senior citizens.

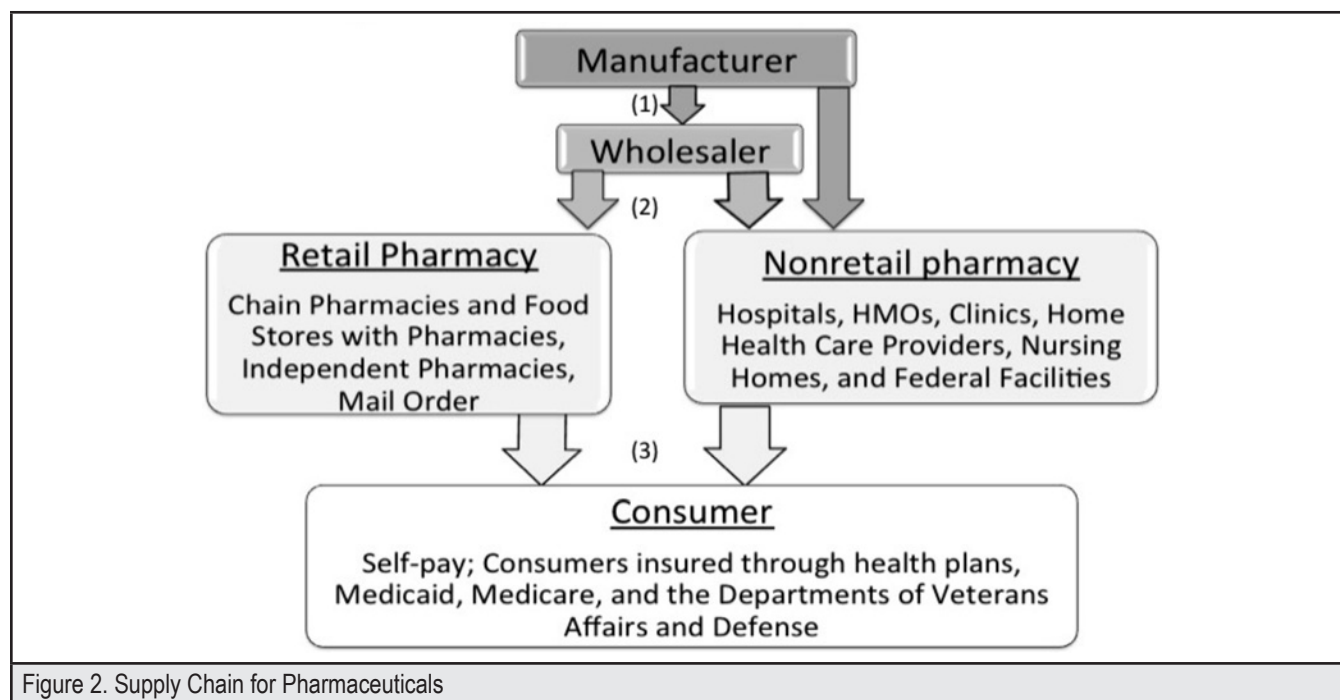


Figure 2. Supply Chain for Pharmaceuticals

For patients with drug benefit coverage, drug prices are typically negotiated between the health plan or pharmacy benefit manager (PBM) and individual pharmacies. The health plan or PBM will usually reimburse a pharmacy a preset rate for the drug plus a dispensing fee. Since some health plans or PBMs have a large market share in their service area, a pharmacy will often accept a reimbursement that is less than it would charge cash customers in order to be included in the health plan's network of pharmacies available to its membership.

Medications Administered at the Physician's Office

The process differs for medications administered in a physician's office. These include drugs which are injected subcutaneously, intramuscularly, or intravenously as well as selected orally administered chemotherapeutic and anti-emetic agents and drugs administered via nebulizers. The manufacturer or wholesaler sells the medication directly to the provider and the physician is reimbursed under the third party payer's medical benefit rates.

Under the Medicare Prescription Drug, Improvement, and Modernization Act of 2003, reimbursement for these types of medications is set as the average sales price (ASP) plus a 6 percent margin to cover overhead costs for drugs administered in physician offices. The prices of the drugs paid by providers to manufacturers or wholesalers are negotiated without any involvement of CMS. If the reimbursement is greater than the cost paid to the manufacturer, the physician can make a profit from dispensing these drugs.

Current Trends

Generic Medications

Acquisition prices depend in part on the type of prescription medication. Approximately 86% of medications sold in the United States are generic and have several different manufacturers (ie, multi-source).⁸ By definition, generic medications are not under patent protection so prices tend to be significantly lower than for brand name medications because they are available from multiple sources.

For generic drugs, about 75% are reimbursed to pharmacies using limits known as maximum allowable cost (MAC). These MAC limits are established by insurers or PBMs and the federal government, based on the lowest estimated acquisition cost for any of the generic equivalents of a given drug. The MAC tends to be 50 to 60% below AWP for brand-name drugs.⁷ The remaining 25% of generics are reimbursed like brand-name drugs. The dispensing fee for generics tends to be the same as for brand name drugs, but, as a way to encourage generic substitution by pharmacies, often times a prescription may cost 25%-50% more. Historically, generic medications have benefited everyone: patients save money, health insurers save money, and the pharmacy makes the same or a little more money than it would on the brand name product.

Recently, the cost of some generic medications has increased markedly, drawing the attention of policy makers. In November 2014, the US Senate held a hearing on why the prices of some generic products have been skyrocketing while MAC payment

Table 1. Drug Pricing Terminology	
Term	Definition
Average manufacturer price (AMP)	The AMP is the average price paid to manufacturers for drugs distributed through retail pharmacies. It includes all forms of discounts given to wholesalers and to pharmacies, but it does not include rebates paid by manufacturers to third-party payers. The AMP is used to calculate the rebates that manufacturers of brand-name drugs are required to give to federal and state governments for sales to Medicaid beneficiaries.
Average wholesale price (AWP)	A publicly available list price for sales of drugs by wholesalers to pharmacies or other providers, the AWP is not the actual price that wholesalers charge but is more like a sticker price in the automobile industry. The AWP is used as the basis for setting payment rates to pharmacies. AWP is publicly available (e.g. Thomson Micromedex's Red Book).
Biosimilars	A biosimilar product is a biological product that is approved based on a showing that it is highly similar to an FDA-approved biological product, known as a reference product, and has no clinically meaningful differences in terms of safety and effectiveness from the reference product. Only minor differences in clinically inactive components are allowable in biosimilar products. (Source: FDA)
Brand name drug	One that has received a patent on its chemical entity, formulation, or use; has been approved by the Food and Drug Administration after clinical testing; and is sold under a brand name. It is a single-source drug while it is still protected by its patent and becomes a multi-source drug once generic versions become available
Generic drug	A copy of a brand-name drug, containing the same active ingredients that the Food and Drug Administration judges to be comparable in terms of therapeutic effectiveness. Generic copies may be sold after the patent on a brand-name drug has expired. Generic drugs are usually sold under their chemical name rather than under a brand name.
Maximum allowable cost (MAC)	A MAC is an upper payment limit on the ingredient costs for a multiple source drug. PBMs set MACs for the purpose of reimbursing pharmacies and medical practices. All generic drugs with the same active ingredients, strength, and dosage form will have the same MAC.
Multi-source drug	A multiple-source drug is one available in both brand-name and generic versions from a variety of manufacturers.
Orphan drugs	The Orphan Drug Act (ODA) provides for granting special status to a drug or biological product ("drug") to treat a rare disease or condition.
Pharmacy benefit manager (PBM)	PBMs administer drug benefits on behalf of health plans and employers. They negotiate with both pharmacies and manufacturers or lower prices. By adopting formularies, PBMs obtain discounted prices on many brand-name drugs in the form of rebates from manufacturers, which are shared with health plans.

Source: CBO report on drug pricing.

rates have remained the same. Sixteen states have passed MAC reform legislation and H.R. 4437, the Generic Drug Pricing Fairness Act, was introduced in Congress.¹⁰ According to a report, out of a research sample of 4421 drug groups, 222 generic drug groups more than doubled in price, with some prices increasing over 1000% between November of 2013 and November of 2014.⁹

There are several reasons for the increasing generic drug prices. Due to mergers and acquisitions, there are fewer manufacturers of generic drugs to keep costs low.³ Second, there are drug shortages due to quality issues and increased Food and Drug Administration (FDA) regulations which can also drive up prices. FDA inspects and monitors every facility that is used for production and issues notices to manufacturers when issues arise, temporarily halting production and/or initiating drug product recalls. For instance, in the case of generic drug doxycycline, price increases stemmed from a temporary shortage. Hikma Pharmaceuticals stopped making the drug in November 2012 after the FDA issued a notice for inadequate quality controls at one of its plants.¹⁰ This was compounded by the fact that the government issued an authorization of emergency use (EUA) and began stockpiling doxycycline in order to be prepared in case of an anthrax emergency.¹¹ Under the EUA, doxycycline may be dispensed by the government in emergency situations without individual patient prescriptions. Due to this combination of events, the price of doxycycline increased 6000% in one year.

Innovative New Medications

When medications are innovative and represent a significant improvement in care, pharmaceutical manufacturers have a lot of leverage in price setting, as physicians want to be able to prescribe these drugs and patients want to have access to them. Manufacturers engage in intense discussions and analyses to determine how best to price these often called "breakthrough" drugs.¹² Increasingly, pharmaceutical manufacturers are setting prices for these innovative new drugs equal to an estimate of the total benefit of the drugs to patients and the costs that third party payers save by using the medicines. This may be determined by calculating the cost of hospitalizations and other medical care utilization involved in currently treating the disease the drug targets.

For example, sofosbuvir (*Sovaldi*), a treatment for hepatitis C, has received a lot of attention because it costs \$1000-per-pill or \$84,000 for 12 weeks of treatment.¹³ Since the drug must be taken in combination with other drugs and some patients need retreatment, full treatment can exceed \$100,000. Following the release of sofosbuvir, manufacturer Gilead released Ledipasvir/sofosbuvir (*Harvoni*), a combination drug that does not require administration with other drugs, priced at \$1125 per pill or \$94,500 for 12 weeks. The drug cured more than 90 percent of patients with hepatitis C type 1 after 12 weeks of treatment. These costs might be lower than treatment with sofosbuvir, because it is taken without companion medications and many patients will only require eight of the 12 weeks of therapy.

Drug pricing for multiple sclerosis (MS) treatments, all of which currently are brand name drugs, provide another example. Unlike the hepatitis C drugs, MS medications are intended for long-term use, thus creating a substantial financial burden due to duration and high costs.

The new drug dimethyl fumarate (*Tecfidera*, Biogen) came to market priced at \$54,900 per patient year which was competitive with existing alternative therapies fingolimod (*Gilenya*, Novartis) at \$60,000 per patient per year and teriflunomide (*Aubagio*, Sanofi) at \$51,000 per patient year.¹⁴

Interestingly, as new MS drugs come to market with higher prices, the prices of older drugs also increase.¹⁵ In the 1990's, several MS drugs were initially priced between \$8,000-\$12,000 per year have now have increased in price to between \$50,000-\$65,000 per year in order to keep up with the prices of the new MS drugs. This seems contrary to the theory of market competition, which suggests that increased supply would decrease price. It is as if the pharmaceutical manufacturers are using the launch of new drugs to gauge what price the market will support.

Biosimilars

Biological agents which are commonly found on the United States top drug expenditure lists are medical products made from a different source such as human, animal, or microorganisms.¹⁶ A biosimilar product is a biological agent that receives FDA approval based on its ability to demonstrate highly similar safety and effectiveness to an FDA-approved biologic originator product.¹⁷ Examples include filgrastim (*Neupogen*), an agent used to stimulate the production of white blood cells, and rituximab (*Rituxan*), a monoclonal antibody used to treat non-Hodgkin's lymphoma and other diseases. These products have complex molecular structures compared to traditional generic medications, are much larger molecules, and require complex manufacturing.¹⁸

Biosimilar manufacturers do not have to bear the research and development costs of the originator biological agents, thus production becomes less costly. However, due to their complex nature, they are more expensive than your typical generic pills or capsules. The European experience has seen a 30% price reduction with biosimilar agents compared to 70%-80% price reduction for traditional generic medications.¹⁹

The first biosimilar agent approved by the FDA under the changes brought about by the Biologics Price Competition and Innovation Act (BPCIA), was filgrastim-sndz (Table 2, *Zarxio* injection, Sandoz Inc.). This product is a biosimilar to the currently licensed originator product *Neupogen* and was approved on March 6, 2015. The new product differs from the original product in only one inactive ingredient.²⁰ Table 2 depicts currently available filgrastim WAC pricing. The Sandoz biosimilar product and pricing is still pending release. TBO-filgrastim is a follow-on preparation that was approved under the previous and lengthier biologics approval process. Additional biologic agent patent expirations are anticipated in 2015.¹⁶

Once approved by the FDA, Medicare Part B payment

covers new biologicals under the abbreviated biological approval pathway into the Average Sales Price (ASP) payment methodology. Once the manufacturer's wholesale acquisition cost (WAC) is available, Medicare will pay 106 percent of the WAC for the product until ASP information is available. Once ASP information is available for a biosimilar, Medicare will pay ASP plus six percent of the ASP for the reference product.²¹

Orphan Drugs

Orphan drugs are used to treat rarely occurring diseases. Without government subsidy, these drugs would be too costly and risky for drug manufacturers to develop.^{22,23} With the FDA approving an all-time record number of orphan drugs in 2014, the pricing of these treatments has drawn increased attention.

In 1983, Congress introduced the Orphan Drug Act which encouraged the development of treatments for rare diseases affecting fewer than 200,000 individuals within the United States. Prior to this legislation, 34 drugs were approved between 1967 and 1983.²⁴ Since legislation, more than 400 medications have been approved for rare diseases and over 400 medications and vaccines are in development. Experimental therapies receiving orphan drug status by the FDA become eligible for various incentives including tax credits and additional market exclusivity (reduced market competition) once the product successfully receives FDA approval. A 2014 report estimated that the median orphan drug cost was \$98,534 per patient year. The most costly orphan drug for an ultra-rare indication costs in excess of \$500,000 per patient per year.²⁵

Drug Company Ownership Related to Drug Pricing

An often-overlooked factor affecting drug prices is ownership changes. A recent article noted that after 2015 Valeant Pharmaceuticals International, Inc. bought the rights to two life-saving heart drugs.²⁶ According to a study, the list price of a one-milliliter vial of isoproterenol hydrochloride (*Isuprel*, Valeant), jumped from \$215 to \$1,346, while a two-milliliter vial of nitroprusside (*Nitropress*, Valeant) increased from \$257 to \$805. Ascension Health System, which operates 131 hospitals across the country, estimates the increases will triple its spending on these drugs this year to \$8 million.²⁶ Cleveland Clinic says the price hikes for the two Valeant drugs are unexpectedly adding \$8.6 million, or 7%, to this year's budget for medicines administered at its hospitals.

These high price increases are troubling in that the companies that are buying these drugs have not incurred any of the R&D costs. Pharmaceutical manufacturers are buying drugs that they see as undervalued and are then drastically raising the prices to cover their investment. For instance, Mallinckrodt PLC paid \$1.4 billion for Cadence Pharmaceuticals, even though the *Ofirmev* (acetaminophen) pain injections that were the main products in the deal were projected to have just \$110.5 million in 2013 revenue.²⁶

Discussion

Prescription drugs have reduced morbidity and mortality and improved the quality of life of millions of Americans. Yet even though the overall value of prescription medications is not in question, increases in cost continue to generate growing concern. This concern extends to Hawai'i where in 2013 the cost of each of three drugs was over \$8M for Medicare Part D beneficiaries: (1) fluticasone/salmeterol, for asthma and chronic obstructive pulmonary disorder, at \$8.8M; (2) memantine hcl, for dementia, at \$8.1M; and (3) sitagliptin phosphate, for diabetes, at \$8.0M.

At the national level, policy makers are increasingly inclined to take action to curb these high drug prices, particularly because many seem to have nothing to do with recouping R&D expenditures. Many large price increases are coming in the area of generic drugs. Calls for policy change occur when manufacturers announce extraordinarily high earnings figures. For its two hepatitis C drugs described earlier, Gilead had \$4.55 billion in sales revenue for the first quarter of 2015. Recently released information revealed that nine out of 10 big pharmaceutical manufacturers spend more on sales and marketing than on R&D.²⁷

A contributor to higher US per capita drug spending is faster uptake of new and more expensive prescription drugs in the United States relative to other countries.^{28, 29} Prices in the United States for brand-name patented drugs are 50 to 60 percent higher than in France and twice as high as in the United Kingdom or Australia.³⁰ In Canada, Australia, and the United Kingdom, a single per-unit price list is published by a national payer. Currently, the whole world is benefitting from United States investment in higher priced drugs.

In an attempt to control rising drug expenditures, the United States could implement some form of drug price regulation. Under current law, Medicare (Part D) is explicitly prohibited from

Generic Name	Brand Name	Strength	WAC	Comments
Filgrastim	Neupogen	300mg	\$319.50	
TBO-Filgrastim	Granix	300mg	\$246.17	Not a biosimilar. Approved under biologics license application.
Filgrastim-sndz	Zarxio	300mg		First drug approved through new biosimilar pathway. Cost not available. Product has not been released due to litigation.

<http://www.wsj.com/articles/court-blocks-novartis-copy-of-amgen-cancer-care-drug-1431018258>

negotiating or setting drug prices so policy makers would need to change this restriction. A study by the RAND corporation, which is a nonprofit institution that helps improve policy and decision-making through research and analysis, warns of the possible dangers of this approach.^{31,32} According to their study, there is a “trade-off between benefiting the current generation (with lower prices) and benefiting future generations (with greater pharmaceutical innovation and access to new drugs).” The argument is that drug price regulation will inhibit development of new potentially life-saving medications. One approach, suggested by RAND is cutting consumer copayments without reducing revenue to pharmaceutical manufacturers. This would entail higher cost to the government and employers but greater access for patients.

The best long-term solution to rising drug prices is yet to be determined but the United States will continue to debate this issue and the debate will get more heated if drug price inflation remains as high as it was in the past year. Despite the recent escalation of drug prices, there is reason to believe that there may be some pressure to limit increases on prices in the near future. Mergers and acquisitions among PBMs may keep medication prices down.³³ Novartis Chief Executive Officer Joe Jimenez was quoted as saying, “With a consolidated payer base as well as consolidated providers, you have to assume going forward that price increases in the United States are going to be quite limited.”³³ As a result, Novartis is proposing an innovative pay-for-performance approach to drug pricing. Under the proposed approach, PBMs would initially pay a low cost for their new drug Entresto (sacubitril and valsartan), followed by a subsequent payment by the PBM if the medication reduces hospitalizations. This type of new payment arrangement, encouraged by the Obama administration, may be the means by which drug prices are controlled in the future.

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REDEMPTION: DRINK COFFEE AND LIVE LONGER.

Historically coffee (caffeine) has been considered a bad drug. Medical science tried to relate coffee consumption to high blood pressure, heart disease, and as a growth retardant. Some were pleased when an erroneous 1970s report suggested that coffee bore cardiac risks. But in the 1980s a report from a Norwegian research team found that coffee seemed to fend off liver disease. Following that report the positive attributes of caffeine have been arriving at a steady drip. Caffeine reduces liver fibrosis, slows heart and liver damage, boosts feel-good dopamine and may counter Parkinson's disease, dementia and depression. (On the down side: it is mildly addictive, pregnant women should go easy since excess caffeine has been linked to miscarriage, caffeine can disturb sleep or make a person jittery, and it can increase heart rate despite the lack of a link to chronic high blood pressure.) Adding up the whole, the most astonishing finding is people who drink two or more cups of coffee a day live longer according to a US team in 2012. Research studies in Japan, Finland and Scotland agree. The old chronic worries about stomach ulcer, acid reflux and atrial fibrillation, fail to show up in large population studies. Still, acceptance is slow and that may be because scientists do not know just how coffee works. There are so many individual components in the bean that work together, nutritional epidemiologists struggle to tease out various effects.

TOO MUCH OF ANYTHING CARRIES A THREAT.

Public health officials say exercise is medicine, but unlike other medications prescribed in doses, exercise simply carries a "more is better" label. Additional benefits are believed to accrue with increases in physical activity. This study along with a small but growing number of others are saying, it ain't necessarily so. British physicians sought to evaluate the importance of extreme compared with moderate exercise. The data included 169 veteran competitive endurance athletes against a control group of 171 active but relatively sedentary subjects. This study found that athletes who ran beyond thirty five miles or cycled more than 150 kilometers a week had higher coronary artery calcium than did the control group. The potential cause of greater coronary calcium in extreme athletes could be inflammation, changes in cardiac structure or an excess secretion of hormones or vital proteins. Who knew the old adage regarding moderation in all things also applied to human exercise?

IT'S TIME FOR A SCRUTINY MUTINY.

Smart phones have introduced a special set of problems for doctors in discussing disease or injuries with patients and family. Until recently it was technologically impossible for most patients to surreptitiously record conversations with their physician. A doctor's exact words could not be recalled, scrutinized and dissected for whatever use at a later date. No longer. Often, without knowing, the physician is being recorded. This might be very useful when telling a family the diagnosis, therapy and prognosis if the patient is unable to communicate. The family can later repeat portions that they failed to note, but it may open ethical questions, especially if someone elects to place a matter on Facebook or other social media. The information may not all be beneficial to patients or family physicians. Some may disagree with the advice or are upset with the physician for whatever reason and can easily take comments from recordings out of context and disseminate them. Moreover when a physician learns that a conversation was secretly recorded he/she may believe the right to consent to a recording has been violated. The integrity of the physician/patient relationship is threatened or perhaps destroyed. Unless laws change, physicians may ask if a smart phone is in action, but irrespective of the reply, proceed as if it were. The electronic generation has us all under constant watch.

WOULD YOU LIKE CHOCOLATE SAUCE ON YOUR MENINGITIS?

You would think that a company that recklessly kills a few customers would at least change the product name. Blue Bell Ice Cream already had evidence of *Listeria* bacteria in its Oklahoma manufacturing plant in March 2013. The Food and Drug Administration stated that inadequate cleaning was apparent, but the Texas-based company continued to ship ice cream from the plant. Three deaths from listeria were reported in Kansas and seven illnesses in Texas, Oklahoma and Arizona were linked to the ice cream. Violations in the Oklahoma plant include dirty equipment, inadequate food storage, food held at improper temperatures and employees not washing hands appropriately. The FDA found violations in the Texas and Alabama plants as well. Blue Bell shut down all its plants and recalled all its products. The company is slowly bringing its products back in stores, following cleaning and sanitizing its four plants and new training for employees. Blue Bell joins General Motors and Takata air bag company in saying, "There is nothing like killing your customers to make you focus on safety." That and the huge fines.

HOW CAN I STUDY WITHOUT MY WOMBAT?

Service animals, mostly guide dogs, are specially trained to assist the owners in activities of daily living. By law, they can accompany college students everywhere. Attempting to be "inclusive," college campuses are also beset with requests for comfort creatures for students with anxieties, depression, panic attacks, or insecurities. The New York Times reported in October that besides dogs and cats, students have requested permission for pot-bellied pigs, tarantulas, lizards, ferrets, guinea pigs, and even sugar gliders (nocturnal flying six-ounce Australian marsupials). Justice Department guidelines ban only animals that are aggressive or destructive or provoke allergies.

THE OPHTHALMOLOGY BOARD EXAM — HALF A CENTURY AGO.

In the 1960s oral exams for the American Board of Ophthalmology were conducted for two days (or three?) at the Palmer House Hotel in downtown Chicago. One of my examiners had been a professor at my post-graduate course at Colby College in Waterville, Maine. We reminisced about clambakes, lobster dinners, and summer weather in Maine. He asked one question about the course of the sixth cranial nerve and remarked about the perspiration on my palm when we shook hands. Fifty years later that is all I can recall about my Boards, plus returning home to worry until receiving a positive response in the mail. It was a gentler and kinder world than our current electronic vortex and I miss it.

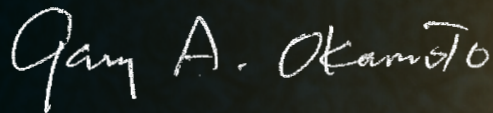
ADDENDA

- In 2012, 421,000 people were injured in motor vehicle crashes involving a distracted driver. About one in five drivers was using a cell phone.
- There is a Belgian resort town named Spa and an English one named Bath.
- Men skip around the television more than women. Men watch briefly and move on, but women wait to see if something will develop. This is because men are hunters and women are nesters.
- Curiosity killed the cat, but for awhile I was a suspect. The evidence was entirely circumstantial.
- Easy Street is a blind alley.
- There are a number of mechanical devices that cause sexual arousal in women. Chief among these is a Mercedes Benz SL500.

ALOHA AND KEEP THE FAITH *rts*

(Editorial comment is strictly that of the writer.)

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